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Controlled Release Solid Dosage Forms by Melt-Extrusion

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Für meine Eltern
Für meine Frau Iris

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IV Abbreviations

Ø	**Diameter**
°C	**Degree(s) Celsius (unit)**
CAP	**Cellulose Acetate Phtalate**
CR	**Controlled Release**
DSC	**Differential Scanning Calorimetry**
EC	**Ethylcellulose**
ER	**Enteric Release**
FDA	**(United States) Food and Drug Administration**
FF	**Flat Face**
g	**Gram (unit)**
GI	**gastrointestinal**
GDB	**Glyceroldibehenate**
GPS	**Glycerolpalmitostearate**
GTS	**Glyceroltristearate**
HEC	**Hydroxyethylcellulose**
HPC	**Hydroxypropylcellulose**
HPLC	**High Performance Liquid Chromatography**
HPMC	**Hydroxpropylmethylcellulose**
HPMCAS	**Hydroxypropylmethylcellulose Acetate Succinate**
HPMCP	**Hydroxpropylcellulose phthalate**
IR	**Immediate Release**
J	**Joule (unit)**
kN	**Kilonewton (unit)**
µm	**Micrometer(s) (unit)**
mg	**Milligram(s) (unit)**
Mg	**Magnesium (atomic symbol)**
MPa	**Mega Pascal (unit)**
MaPT	**Maximum processing temperature**
MiPT	**Minimum processing temperature**
min	**Minute(s) (unit)**
mm	**Millimeter(s) (unit)**
%	**Per cent**
per cent[m/m]	**Mass per cent (unit)**
MPa	**Megapascal (unit)**
MR	**Modified Release**
ml	**Milliliter(s) (unit)**
Mm	**Milimetre(s) (unit)**
N	**Newton(s) (unit)**
Nm	**Newtonmeter (unit)**
P	**Permeability**
pH	**Negative logarithm of proton concentration**
Ph. Eur.	**Pharmacopée Européen = European Pharmacopoeia**

PTFE	**Polytetrafluorethylen (Teflon)**
PVA	
PVP	**Polyvinylpyrrolidone**
PXRD	**Powder X-Ray Diffraction**
RTS	**Radial Tensile Strength**
s	**Second(s) (unit)**
SD	**Standard Deviation**
SEM	**Scanning Electron Microscopy**
SME	**Specific Mechanical Energy**
SRC	**Standard Round Concave**
STE	**Specific Thermal Energy**
USP	**United States Pharmacopoeia**
V	**Volume**
WHO	**World Health Organization**

1 Introduction

1.1 Solid Oral Dosage Forms

Solid dosage forms for oral application can be divided into two clusters, (i) immediate release (IR) dosage forms and (ii) modified release (MR) dosage forms. The latter includes dosage forms providing controlled, slow, enteric or delayed drug release.

1.1.1 Immediate Release Dosage Forms

Immediate Release Dosage Forms generally speaking allow for rapid dissolution of the active from the dosage form. The term "rapidly dissolving" can be applied when "no less than 85% of the labelled amount of drug substance dissolves within thirty minutes, using U.S. Pharmacopoeia (USP) apparatus I at 100rpm (or Apparatus II at 50rpm) in a volume 900ml or less in each of the following media: (i) 0.1N HCl or Simulated Gastric USP fluid without enzymes; (ii) a pH 4.5 buffer; and (iii) a pH 6.8 buffer or simulating intestinal fluid USP without enzymes" (FDA 2000, WHO 2006).

The European Pharmacopeia does not set specifications for drug release (Ph.Eur. 2007). While dissolution has to be appropriate for the tested oral dosage form, for coated and uncoated tablets general disintegration times of thirty minutes and fifteen minutes are specified (Ph.Eur. 2007a, Ph.Eur. 2007b).

In the case of immediate release oral dosage forms, fast dissolution of drug substance is intended to result in a fast therapeutic response to administration of the drug substance. This can only be achieved if the drug is rapidly dissolved and rapidly absorbed leading to speditious attainment of levels in the target receptor or organ. This is desired for acute indications such as pain relief, for which a rapid improvement in the patient´s status is highly desirable (Marzo A., et al (2000)).

Administration of immediate release dosage forms often leads to not only a rapid rise in plasma concentrations, but after cMax is reached, also a fast decrease of plasma levels. This phenomenon is most pronounced for compounds with a short half-life due to fast metabolism and/or excretion. In such cases, maintaining therapeutic plasma levels requires multiple daily dosing of IR dosage forms and is consequently inconvenient for the patient. Therapeutic failure can easily result when doses are missed, due to subtherapeutic plasma levels. Modification of drug release from oral dosage forms is one successful approach to overcome these therapeutic issues. Therapy of hypertension with β-receptor blockers, such as propranolol or metoprolol, is a classic example of improvement of therapy by dosage form design (Menard J. (1993), Mishriki A.A., et al. (1983)).

1.1.2 Modified Release Dosage Forms (MR)

The term modified release (MR) dosage form has often been used to summarize a variety of oral dosage forms with various release patterns. According to a FDA guidance (FDA 1997b), modified release is comprised of dosage forms "whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products". FDA further regards the terms extended release (ER) and controlled release (CR) as interchangeable for formulations that do not release active drug substance immediately after oral dosing and that also allow a reduction in dosage frequency (FDA 1993). Similarly, according to the European Pharmacopeia, modified release oral dosage forms comprise a modification of drug release rate or site of drug release by means of formulation of tablets or capsules (Ph.Eur. 2007a, Ph. Eur. 2007b).

Controlled release dosage forms aim to continuously release drug over a certain period of time, enabling therapeutic plasma levels to be maintained over an extended period of time and thus reducing dosing frequency. With CR dosage forms, once-daily dosing regimes may be possible even for drug substances with short half-lives. Again taking the example of hypertension treatment, reducing the pill burden is viewed as a way to improve patient compliance with the therapeutic regimen (Mishriki A.A., et al. (1983))

Modified release dosage forms can also be used as a drug delivery strategy. For example they have been used to (i) improve bioavailability of compounds with narrow absorption window, (ii) deliver drugs locally to desired sites of action within the GI tract and (iii) reduce toxic side effects for drugs with narrow therapeutic windows.

Improved bioavailability has been attempted by gastroretentive design of modified release dosage forms. Increasing the gastric residence time of the dosage form allows an increased share of compound dissolution to occur within the upper part of the gastrointestinal tract. Two approaches to prolong upper GI transit time are mucoadhesive systems with prolonged transit through the gastrointestinal tract and expandable single-dose systems. Increased residence time in the stomach or proximal parts of the intestine have been used to enhance bioavailability of compounds with narrow absorption window in proximal parts of the gut. The suitability of gastroretentive systems and mucoadhesive systems has been discussed in various publications (Streubel A., et al. (2006), Davis S.S. (2005), Moes A.J. (1993)).

Colonic delivery represents one example of site specific delivery of pharmaceutical actives. In order to achieve maximum benefit from the therapy, the drug has to be protected from absorption and degradation in the gastric and upper intestinal environments. Diseases such as Morbus Crohn, Colitis Ulcerosa or colorectal cancer demand specific sites of drug release from oral dosage forms (Chourasia M.K., et al. (2003)). Several approaches have been applied to obtain drug release specifically into the colon. Delayed drug release has for example been achieved by time-dependent, pH-dependent or microflora dependent release control (Gazzaniga A., et al (2006), Khan M.Z., et al. (1999), Liu H., et al (2006)).

As well as increasing therapeutic response, timed and site-specific controlled release after oral administration can lead to better tolerability of the drug therapy. Reduced exposure of compounds to irrelevant parts of gastrointestinal tract and organs, tighter control of plasma levels and improved patient compliance are all factors in improving therapy.

1.2 Design and Release Mechanism of CR Oral Dosage Forms

In general three approaches to control drug release from solid oral dosage forms can be distinguished. Drug release can be controlled by (i) a functional coating, (ii) a functional matrix or (iii) osmotic controlled functionality of the dosage form. A further technological distinction of CR dosage forms concerns the design as single or multiple unit dosage forms.

1.2.1 Coated Systems

Coated systems usually consist of coated tablets, granules in the form of coated pellets, or coated granules compressed into tablets (Ph.Eur. 1997a, Ph.Eur.1997b). Fig. 1.2.1 schematically depicts the release controlling principle of coated systems. In case of a coated tablet, the drug is dispersed as a solid within a compressed core. The core consists of drug and excipients such as fillers, binders or glidants and is surrounded by a thin coating made of water-insoluble excipients or a mixture of water-insoluble with water-soluble excipients. After administration, water diffuses through the coating into the tablet core. During dissolution the coating keeps the tablet core intact, preventing disintegration. The drug is dissolved within the tablet core resulting in a saturated concentration, cS. Drug diffuses through the coating along the concentration gradient, (cS-c)/d, where c is the drug concentration outside the dosage form and d represents the coating thickness.

Parameters affecting drug release rate from a coated system are summarized in equation 1.1, in which dc/dt gives the drug release per time (t). It is proportional to the permeability of the coating material (P), the surface area of the coating (A) and the concentration gradient (cS-c) through the diffusion barrier. An inversely proportional relationship exists between drug release rate and the thickness of the coating (d).

$$\frac{dc}{dt} = P \times A \times \frac{(c_S - c)}{d} \tag{1.1}$$

It can be seen that several parameters directly affect the drug release rate. As surface area and coating thickness are limited to certain ranges, the permeability (P) of the coating is an important determinant of the rate of drug diffusion through the coating (Lippold B.C. (1991)). It is governed by the physical and chemical properties of coating material. The glass transition temperature is a measure of the mechanical stiffness of the coating. Coating materials tend to highly restrict permeation of drugs through the film coat since strong intermolecular forces result in a rigid network of polymer molecules.

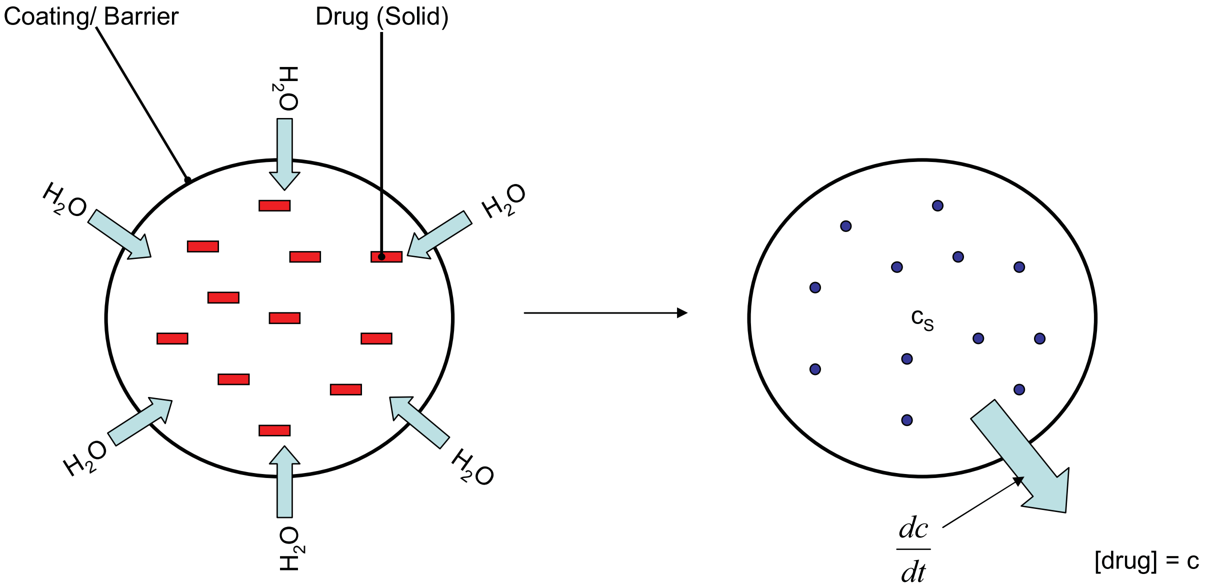


Fig. 1.2.1: Control of drug release from coated controlled release (CR) oral dosage forms

Adjuvant excipients - so called plasticizers – are usually added to the coating to reduce the intermolecular bonds between polymer molecules and thus increase the flexibility of the coating. Increased flexibility not only improves permeability but also the processing properties of film coatings. Further, plasticizers can induce an increased uptake of water into the coating, which can in turn further enhance mobility of molecules within the film.

Two types of plasticizers are commonly distinguished, internal and external plasticizers. The latter are commonly used in pharmaceutical industry. The most frequently used pharmaceutical plasticizer is triethylcitrate (Zhu Y., et al. (2006a), Bando H., et al. (2006), Fiedler H.P. (1989), Kojima M., et al. (2002)). Glycerol or sorbitol are further excipients used as plasticizers in film coatings (Krogers K., et al. (2002), Bauer K.H., et al. (1997)). In contrast to these external plasticizers, which are simply added to the coating dispersion, internal plastification infers a chemical modification of the coating polymer. By means of co-polymerization a decreased trend to form intermolecular bonds or an increased water uptake and swelling of the coating material in contact with dissolution medium can be achieved. Internal plastification is not as common for pharmaceutical applications (Bauer K.H., et al. (1997)). Combinations of different methacrylates or PVA with PVP are pharmaceutical examples of internal plastification.

Formation of pores during dissolution is a further example of modifying drug release from coated systems. Dissolution of water-soluble excipients out of the coating results in formation of a porous structure. Typical examples are sodium chloride, water soluble cellulose derivates, e.g. HPC, and low molecular weight polyethyleneglycols ((Lippold B.C. (1991)).

pH-dependency of polymer solubility can be used to modify drug release from dosage forms. By suitable selection of coating materials, dissolution of the film coating or a change in its permeability is observed with a change in pH of the dissolution medium. Introduction of acidic functions into a polymer results in pH-dependent physicochemical properties of the film. In an acidic environment, the coating is protonated, uncharged and hydrophobic. After deprotonation in a less acidic or neutral environment, the film either dissolves or adsorbs water rapidly, resulting in drug release. This approach has been used to develop enteric (gastro-resistant) dosage forms. Commonly applied enteric coats consist of hydroxypropylmethylcellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP) and certain poly(meth)acrylates (Lamprecht A., et al. (2004),), Thoma K., et al. (1999)). Enteric coated systems have been applied to protect drug substance from degradation or hydrolysis in the gastric environment (Qi R., et al. (2004)). A more pronounced delay in drug release can be used to deliver drug substance to distal parts of the intestine for the therapy of lower intestinal and colonic diseases such as Colitis Ulcerosa and Morbus Crohn. In these cases, site-specific drug delivery allows high local exposure at the inflamed sites and hence effective therapy (Prakash A., et al. (1999)). In the case of mesalazine, used for therapy of Colitis Ulcerosa, site specific drug delivery also reduces undesired systemic bioavailability (Christensen L.A., et al. (1990)). Colonic delivery has also been suggested for administration of biomolecules (Bourgeois S., et al. (2005), Gupta V.K., et al (2001)).

Coming back to equation 1.1, film thickness is an additional measure to control drug release rate from a coated system. Due to well controlled processing of modern film coatings, the desired thickness of the coating can be achieved with good reproducibility. The use of swellable polymers offers an additional approach to control drug release. After administration, water is adsorbed into the film coating. The presence of water results in a swelling of the film for certain polymers and, as a result, the thickness of the diffusion barrier is increased. On the one hand, the greater thickness of the film should lead to a decreased rate of release. However, the uptake of water into the coatings increases the mobility of molecules within the film coatings or may even form aqueous channels, both of which increase the release rate.

According to the Fickian principle of diffusion, the concentration gradient between the two sides of the film determines the drug release rate from coated systems. Equation 1.1 highlights that drug release rate increases with the concentration of dissolved drug within the core. This further implies that drug release rate is constant as long as the core is saturated, assuming sink conditions. Therefore drug release rate from coated systems also depends on the solubility of the pharmaceutical active and how this might be affected by excipients. In conclusion, each combination of active, excipients and release-controlling film coating can result in an individual drug release profile. This highlights the ability to create tailor-made release profiles for each individual compound during the pharmaceutical development process.

1.2.2 Matrix/ Embedded Systems

Dosage forms with matrix controlled drug release rate are usually tablets. In a few cases beads, pellets or granules have been developed (George M., et al. (2006), Siepmann F., et al. (2006)). These are considered with other multiparticulate forms in section 1.2.4.

In the literature, the term “matrix device” is commonly used. The term matrix has been used to describe an embedding of pharmaceutical active into an excipient carrier phase. Drugs can be embedded as dispersed particles or dissolved in the excipient matrix. Over the years pharmaceutical research has yielded various types of matrices. They differ mostly according to the aqueous solubility of the matrix forming excipient used and consequently its behaviour upon contact with water. Three different mechanisms of release control have been identified: (i) (Fickian) diffusion, (ii) swelling and (iii) erosion. In many cases one of these mechanisms dominates, but combinations have also been employed often. As a fourth principle, ion exchange resins can also be used as matrices for CR dosage forms (Lippold B.C. (1991), Bauer K.H., et al. (1997)). All matrices have in common that the matrix itself determines the kinetics of drug release from the dosage form. The mechanisms of drug release from the various matrices are now described in more detail.

Fig. 1.2.2 schematically depicts drug release from an “inert” matrix dosage form. Prior to administration, the drug is dispersed or dissolved in a carrier phase consisting of excipient(s) that are insoluble in aqueous media. Upon contact with gastric juice or dissolution medium, water enters the matrix via surface pores and cracks. After water penetrates, the diffusion of drug molecules through water-filled pores commences. Drug release is controlled by Fickian diffusion.

The matrix itself stays inert, i.e. it does not further influence the diffusion process. After the drug has been released, the matrix remains in its original configuration.

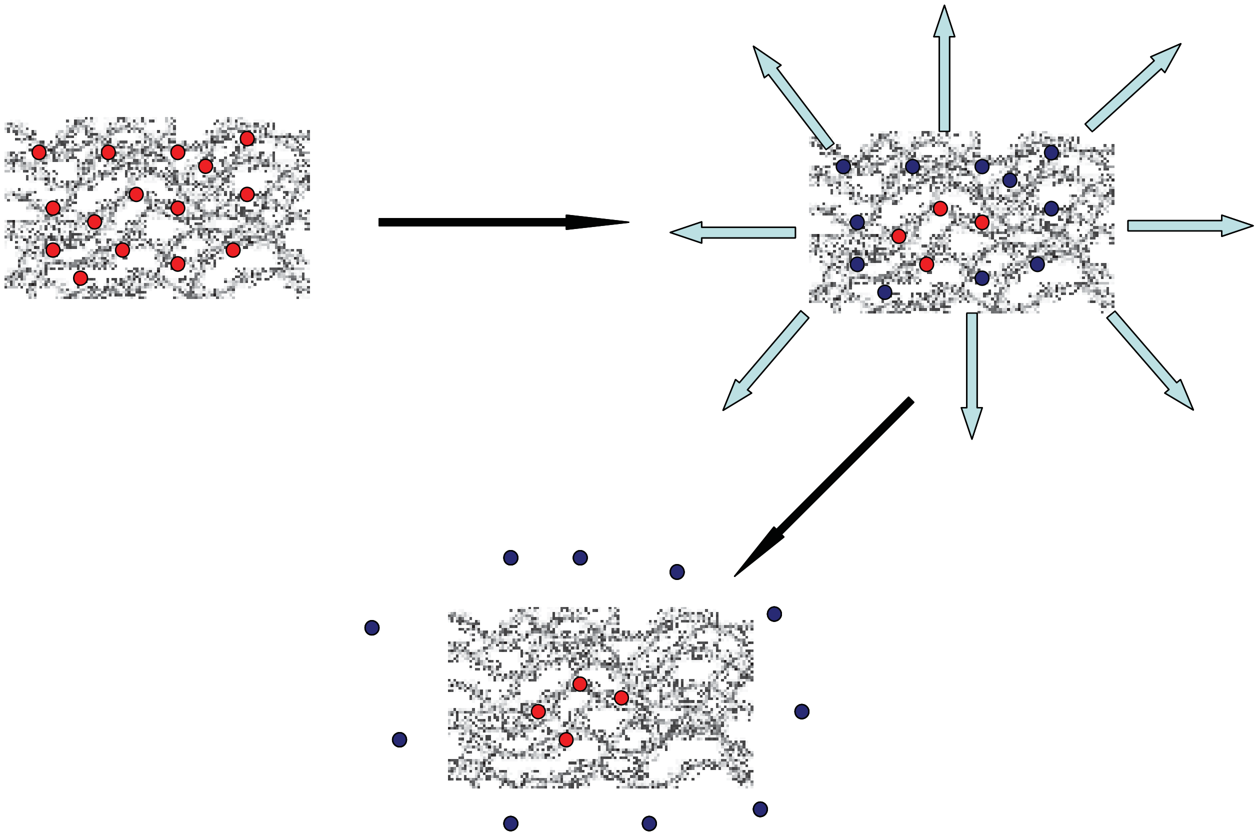


Fig. 1.2.2: Schematic description of diffusion controlled drug release from inert matrices (Case I)

A theoretical approach to describe drug release kinetics from inert matrices was proposed by Higuchi T. (1961). Eq. 1.2 shows the $\sqrt{t}$ -law for inert matrices, in which Q represents drug released into sink conditions at time t. D is the diffusion constant of the drug into the external phase, A is the concentration of the drug in the matrix and cS is the solubility of the drug in the aqueous medium.

$$Q = 2ADc_S\sqrt{t} \qquad (1.2)$$

Looking at Higuchi´s theory, several potential measures to manipulate drug release become apparent: control (i) water intrusion into the matrix by appropriate selection of excipients (ε), (ii) the availability of routes out of the matrix (ε and τ) and (iii) drug loading of the matrix (c0).

Selection of excipients is the most powerful tool to manipulate drug release. Changing the physicochemical properties of matrices such as varying the hydrophobicity of a matrix will affect the kinetics of water intrusion and drug release (Van Veen B., et al. (2005). The number, size and shape of capillaries also determines the kinetics of water intrusion into matrices. The more water entering due to hydrophilicity and porosity, the higher drug release rate becomes. Water soluble excipients which dissolve upon contact with dissolution medium, enabling pore formation can be added to the matrix composition. These “pore formers” represent a technological approach to increasing the rate drug release from inert matrices (Donelli G., et al. (2006)).

As already mentioned, the size of single unit oral dosage forms is limited by patient compliance. Due to the geometric relation between surface and volume of dosage forms, modification of surface area offers only limited potential to modify drug release kinetics from single unit matrices. To substantially increase drug release rate by means of surface area, multiparticulate dosage forms can be used.

For hydrocolloid matrices various release mechanisms can prevail. Fig. 1.2.3 schematically depicts drug release mechanisms for hydrocolloid systems. In these systems the pharmaceutical active is dispersed or dissolved in a hydrophilic excipient network. Upon contact with dissolution medium (or gastric juice) the matrix absorbs water. Water molecules interact with the hydrophilic polymer matrix, forming a hydrogel and thus swelling the dosage form. The drug molecules partly dissolve in the aqueous phase. The hydrogel functions as a diffusion barrier for the drug molecules and the drug release rate depends on the properties of the gel. In particular the viscosity determines the mobility of drug molecules. Essentially drug release is diffusion-controlled for non-eroding systems (CASE 1 kinetics) (Lippold B.C. (1991)).

However, gels tend to erode under physical stress such as gastric motility. Upon water absorption a gel structure is formed on the surface of the dosage form, creating a phase interface within the dosage form. The interface continuously moves towards the core of the matrix while the outer gel layers are eroded (dissolved). Drug diffuses through the gel phase, the width of which is controlled by water penetration and erosion. Gelation and erosion kinetics control the drug release rate of these matrices. These considerations also imply that drug release might be affected by external factors that affect swelling, e.g. pH or ionic strength or erosion, e.g. changes in hydrodynamics or motility patterns. The term “CASE II” kinetics has been established to describe drug release due to swelling/ erosion of dosage forms. For hydrocolloid matrices, a combination of Fickian diffusion and Case II controlled drug release is often observed (Gurny R., et al. (1982), Ritger P.L., et al. (1986), Collins R. (1998)).

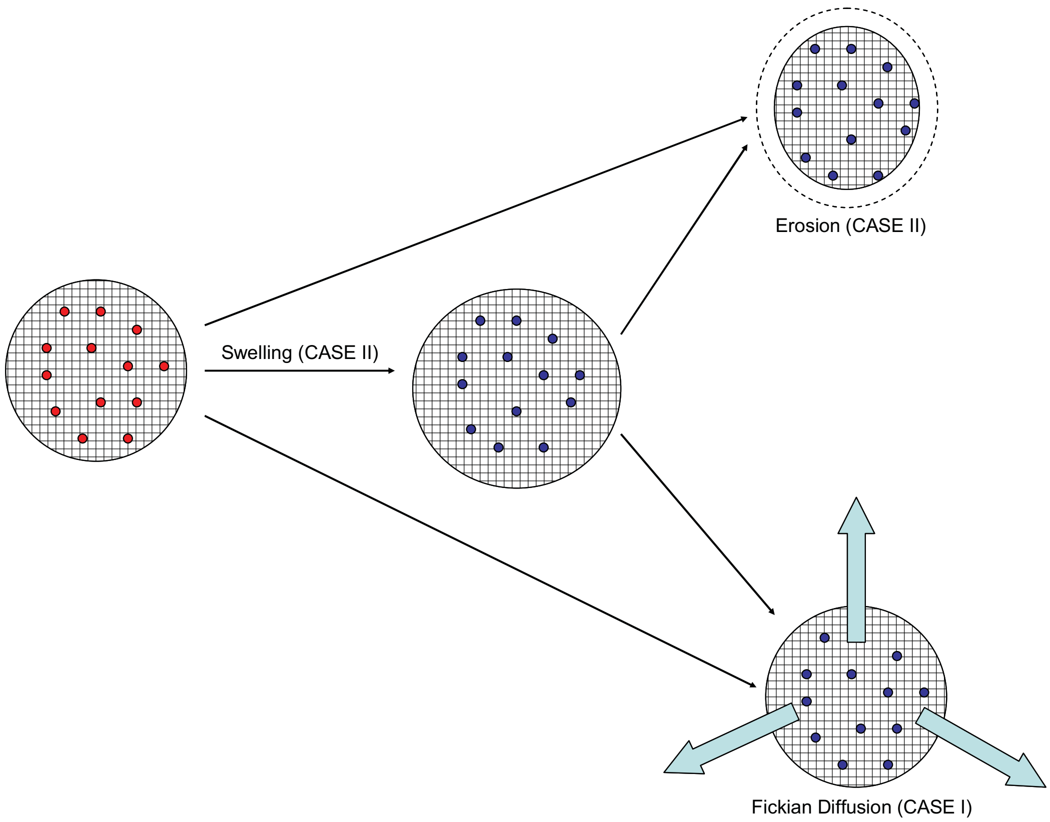


Fig. 1.2.3: Case I and Case II drug release from hydrocolloid matrices

Similar to inert matrices, Higuchi´s Square Root law is applicable for release from hydrocolloid matrices if this is controlled by pure diffusion. Therefore similar considerations also apply when considering technological approaches to modify drug release. Drug release is proportional to the surface area exposed to the dissolution medium as well as the drug loading and solubility of the active.

Moreover, the diffusion coefficient can be manipulated in hydrocolloid matrices: choice of excipients affects the kinetics and quantity of water uptake and hence the viscosity of the gel formed. Therefore, suitable selection of the matrix-forming excipient is a key parameter when developing CR dosage forms based on hydrocolloid matrices.

To complete this overview, the principle of ion exchange matrices should be mentioned. In using this principle pharmaceutically, drugs are physically bound to the side chains of the excipients. The drug-polymer interaction is based on the formation of ion pairs within the matrix. Matrices are formed by cross linked polymer chains. Upon contact with the GI fluids, the matrix gradually swells and the drug is released due to its substitution from the ion pair bond by physiological ions. A common example is the protonation of acidic functions of the excipient side chains in acidic environment and release of basic drugs (Lippold B.C. (1991)). Acidic drugs, such as diclofenac, can be released due to displacement by chloride anions (Voltaren®-Resinat).

Key parameters controlling drug release kinetics from exchange resins are (i) the strength of drug-excipient bond and (ii) the concentration of ions required for expulsion of drugs. First order kinetics have been reported due adherence of water on the surface of the dosage forms, but the order of release kinetics seems difficult to predict.

1.2.3 Osmotic Devices

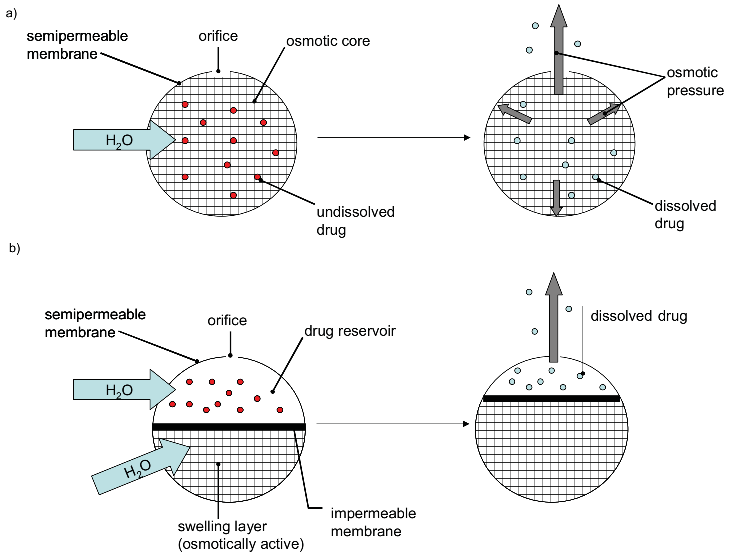


Fig. 1.2.4: Working principle of osmotic devices for oral controlled release dosage forms: a) osmotic pump, b) oral osmotic system (OROS)

1.2.4 Multiparticulates

Multiparticulate dosage forms for oral controlled release dosage forms consist of a few to many discrete particulates such as mini-tablets, beads, or pellets. For administration, particulates are usually compressed to tablets or filled into gelatine capsules (Lecomte F., et al. (2003), Mohamad A., et al. (2006)), though it is also possible to pack them into sachets. After administration, the single dosage form disintegrates and the discrete particles are released. Particulates usually consist of either coated sugar beads or coated matrix pellets. The principle of osmotic devices is usually not applied to multiparticulates due to the practical difficulties of reproducibly drilling the holes on the surface of particulates.

Multiparticulates offer several advantages over single unit dosage forms. First, they provide a high flexibility in dosing. Dose adjustment is simply achieved by variation of the number of particulates within the dosage form. Second, modification of drug release pattern can be easily achieved by combinations of different particulates within the dosage form. Third, their gastric residence time is less dependent on food intake because of their small size, typically between 0.5 and 1.5mm (Tuleu C., et al. (1999)). A further effect of their small size is that they are freely dispersible within the GI tract. Therefore formulation as particulates leads to inter-individual variability in gastrointestinal transit times of the particulate. This results in a minimized effect of gut transit on drug release from the dosage forms.

1.3 Excipients for drug release control from oral dosage forms

In pharmaceutical development, selected excipients can be used in either coated systems or matrix devices to control drug release. Film coatings are usually prepared by spraying aqueous or solvent-based suspensions or solutions of the coating excipient(s) onto a solid dosage form. Matrix dosage forms are mostly generated by compression of powder blends or granulates containing drug and matrix forming excipients. Matrix pellets may also be obtained from extrusion/spheronization processes. This section provides a general summary of commonly used excipients for controlling drug release from oral dosage forms.

1.3.1 Cellulose derivates

Cellulose derivatives are probably the most commonly used type of excipient used as release controlling agents in pharmaceutical technology. Cellulose is a water-insoluble polysaccharide formed by repeated β-(1,4)-glycosidic bonding of β-glucose molecules. A cellulose molecule typically consists of 3000-10000 monomers (Fiedler H.P. (1989), Bauer K.H., et al. (1997)). Chemical derivation is accomplished by esterification and etherification of the three β-glucose hydroxyl groups with aliphatic alcohols and acids. The properties of the polymers obtained are influenced by a number of chemical characteristics: "(i) the nature of the substituent group, (ii) the proportion of substituted hydroxyl groups, (iii) the uniformity of substitution in the repeating unit and along the polymer chain and (iv) the average length and molecular mass distribution (viscosity)" (Doelker E. (1993)).

Commercially available cellulose esters and ethers are commonly characterized by the degree of substitution and the viscosity of defined solutions or suspensions. Fig. 1.3.1 gives the monomer structure of cellulose and highlights the sites of esterification and etherification.

One of the most commonly used cellulose derivates is the water soluble hydroxypropylmethyl cellulose (HPMC) or hypromellose (Ph.Eur. 1997c). In order to obtain HPMC, cellulose molecules are modified by partial etherification of the glucose hydroxyl-groups with methyl- and 2-(O)-hydroxypropyl side chains. Different grades of HPMCs are distinguished according to the criteria mentioned above. In addition the ratio between methyl- and 2-(O)-hydroxypropyl side chains governs the characteristics of the HPMC grade.

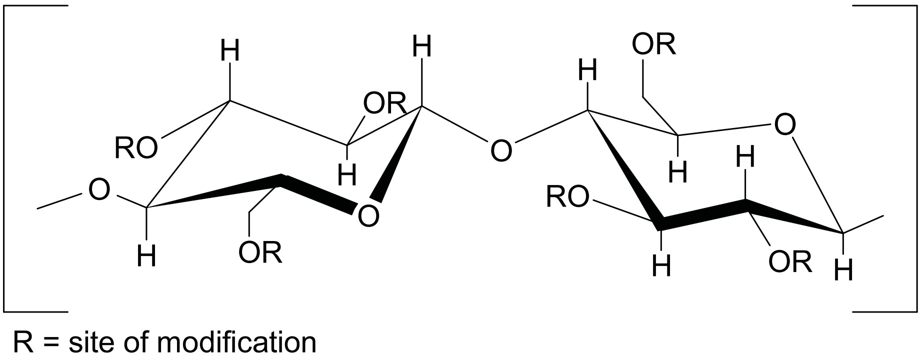


Fig. 1.3.1: β-(1,4)-glycosidic glucose dimer: generic structure of cellulose (R=H) and its derivates (R≠H)

HPMC has proven its value and flexibility for CR dosage forms as a release controlling excipient. Matrices can be prepared by either direct compression of powder blends (Khanvilkar K.H., et al. (2002)) or compressed from granulates (Cao Q.R. (2005), Huang Y., et al. (2003)). Saravanan M., et al. (2003) reported the suitability of HPMC for both dry and wet granulation techniques. Due to its swelling properties it has also been applied in push-pull osmotic devices. In this case, control of drug release is achieved by application of a HPMC-based swelling layer in combination with a semipermeable coating (Zhang Y., et al. (2003)).

As a film coating, HPMC is not suitable for retarding drug release due to its high water solubility. Low viscosity grades of HPMC can in fact be applied as a pore former to accelerate drug release from poorly soluble polymer coatings (Frohoff-Hulsmann M.A., et al. (1999), Sadeghi F., et al. (2003)). However, high viscosity HPMC grades have been used occasionally as release controlling film coatings. For this purpose, high viscosity HPMC is sprayed onto solid dosage forms, from as solution or dispersion in water, ethanol or combinations thereof (Cao Q.R., et al. (2004)).

HPMC-based matrix formulations show time-dependent drug release. Depending on the viscosity of the HPMC gel formed after administration, either swelling or erosion release control mechanisms can dominate (Zema L., et al. (2006), Cao Q.R., et al. (2004)). Applications of HPMC therefore range from rather fast drug release all the way to colonic delivery systems. The latter application has been extensively investigated over the last years (Qui M., et al. (2003), Ofori-Kwakye K., et al. (2003), Turkoglu M., et al. (2002)).

Water soluble cellulose polymers less frequently used to obtain controlled release are hydroxypropylcellulose and methylcellulose. Their mechanisms of release are similar to HPMC based formulations, but they generally release too quickly to meet the requirements of oral CR products.

Modification of cellulose by substitution with ethyl side chains results in an inert, water-insoluble, non-degradable polymer. Ethylcellulose (EC) is the most commonly used water-insoluble cellulose derivate. It has been applied in film coatings for both single and multiple unit dosage forms (Lippold B.C., et al. (1999), Lecomte F., et al. (2004), Rohera B.D., et al. (2002)). EC is also known as a matrix forming excipient for CR dosage forms. Comparable to HPMC, EC is suitable for various formulation processes. It has been processed by wet granulation (Fukui A., et al. (2002), Agrawal A.M., et al. (2003)) and melt extrusion processes (Verhoeven E., et al. (2006), DeBrabander C., et al. (2003)). Coating processes are usually performed with EC dispersions in water/ethanol mixtures or from organic EC solutions. Due to its low water solubility, drug release from EC-based dosage forms is mainly diffusion controlled. Constant drug release from EC film coated systems may be achieved under sink conditions. However, swelling and non-Fickian diffusion may also contribute to drug release mechanisms from EC-based formulations in some cases (Verhoeven E., et al. (2006), DeBrabander C., et al. (2003)). Due to its insolubility in aqueous media, water-soluble pore formers are often used in conjunction with EC to obtain useful release rates.

Plasticizers can be used to modify the rate of drug release from EC-based dosage forms. Per definition, plasticizers are described as liquids with high boiling points. Triethylcitrate (TEC), diethylphtalate (DEP), dibutylphtalate (DBP) and dibutylsebacate (DBS) are classical examples of plasticizers used in pharmaceutical applications.

Frohoff-Hulsmann M.A., et al. (1999) reported differences in drug release patterns depending on the aqueous solubility of the plasticizers used. In combination with water-soluble plasticizers such as HPMC and TEC, approximate zero-order drug release was obtained for coated pellet systems. Addition of low solubility plasticizers, such as DBP or DBS resulted in a two-phase release profile. In contrast, Rohera B.D. (2002) reported a zero-order release profile from EC coated tablets plasticized with dibutylsebacate (DBS). These conflicting observations suggest the importance of other (processing) parameters on the drug release profile, such as coating level, film thickness and grade of EC.

Cellulose derivates also offer the possibility of pH-dependent drug release. Hydroxypropylmethylcellulose-acetate-succinate (HPMCAS), Cellulose-acetate-phtalate (CAP) and Hydroxypropylmethylcellulose- phthalate (HPMCP) are the most commonly used cellulose derivates providing pH-dependent release control. Both derivates are anionic cellulose derivates, obtained by partial esterification of cellulose with acids. HPMCAS is obtained by partial semiesterification with the diprotic succinic acid. Deprotonation of the free acid function in weakly acidic aqueous environment results in a negative charge. Further modification of the cellulose structure is achieved by esterification with acetic acid and formation with methyl- and propylethers. Similarly HPMCP is formed by semiesterification with phthalic acid. Fig.1.3.2 depicts the functionality of acidic groups for HPMCAS.

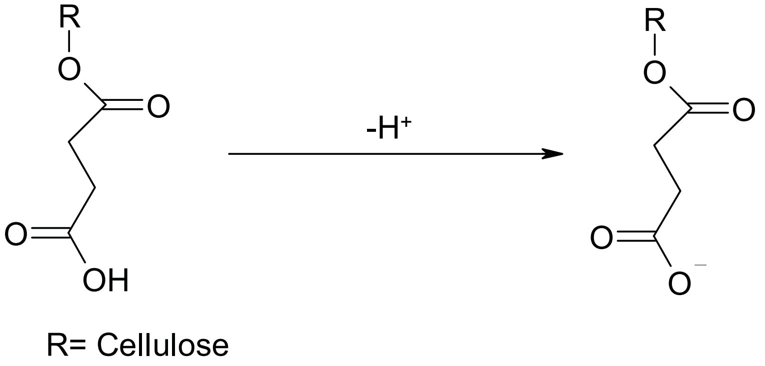


Fig. 1.3.2: Deprotonation of HPMCAS acidic substitutes

In its uncharged, protonated state, i.e. in acidic environments such as gastric juice, the polymer is insoluble. After deprotonation, the cellulose derivative immediately becomes water soluble. Depending on the degree of substitution, HPMCAS and HPMCP dissolve between pH 4.5 and pH 6 (Bauer K.H., et al. (1997)). In the uncharged state, drug release is slow and governed by Fickian diffusion. After deprotonation, polymer dissolution and dosage form erosion come into play. In this state they contribute quantitatively to drug release (Streubel A., et al. (2000)). Drug release rate is significantly faster with the water-soluble, ionized form of the polymer.

Processability of HPMCAS and HPMCP is comparable to other cellulose derivates. Hence they can be used as film coatings prepared by standard coating processes from aqueous solutions (Siepmann F., et al. (2006), Bechtold K., et al. (1999)). They are also used in matrix dosage forms prepared by various processes (Kojima M., et al. (2002), Palmieri G.F., et al. (2000), Hilton A.K., et al. (1993)). They function as release modifiers in enteric formulations. Colonic delivery of drugs represents a further application for HPMCAS and HPMCP based formulations (Fukui E., et al. (2001)).

1.3.2 Acrylate polymers

Polymethacrylates are a second class of polymers very commonly used to control drug release from oral dosage forms. The backbone consists of copolymers of methacrylic acid with methacrylate-esters (Bauer K.H., et al. (1997)). Characteristics of polymethacrylates are modified by introduction of functional groups into the polymer. Analogous to cellulose derivates, they can be differentiated by water solubility, charge and acidity/basicity. The monomer, methacrylic acid, is modified by esterification with different alcohols comprising acidic, basic, neutral or quaternary ammonium side chains. Fig.1.3.3 shows a generic structure of methacrylate monomers and polymers. Depending on the type and grade of the polymer, polymethacrylates are available as granulates or dispersions in water and/or ethanol.

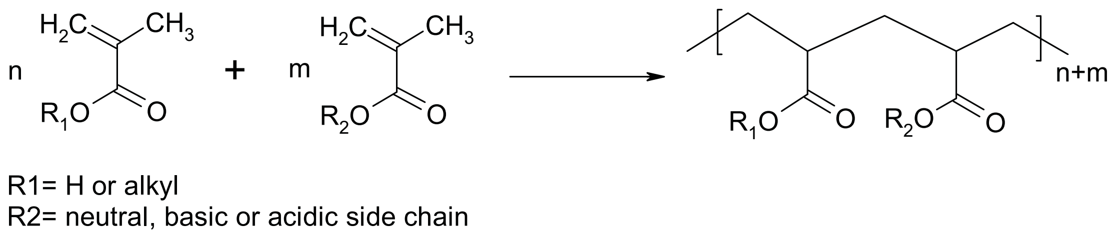


Fig. 1.3.3: Generic structure of monomers and polymers of methacrylates

Polymethacrylates are widely applied as carriers in matrix formulations, in which they contribute to the integrity of the matrix and control drug release after administration. Matrix formulations can be prepared by wet granulation (Abbaspour M.R., et al. (2005), Lee S., et al. (2005), Metha K.A., et al. (2001)), followed by compression. Polymethacrylate matrices can also be prepared by direct compression (Rey H., et al. (2000) and Gohel M.C., et al. (2003)), e.g. quarternary polymethacrylates. Alternatively, they can be used as carriers in melt extrusion processes due to their thermoplastic properties (Zhu Y., et al. (2006), Young C.R., et al. (2003)).

Spheronization is often used to form small single units such, as pellets or beads, for use in multiparticulate dosage forms (Young C.R., et al. (2005), Rudolph M.W., et al. (2001)). Polymethacrylates can also be applied as coatings to multiparticulates to control release. When used as dispersions, they are suitable for commonly applied coating processes such as fluidized-bed coating (Furst T., et al. (2005), Maejima T., et al. (2001)).

For controlled release applications acidic, polymethacrylates with acidic, neutral and quarternary side chains have been used. Polymers with neutral side chains such as methyl or butyl groups show low water solubility. Polymers substituted with quarternary functions, such as trimethylammoniumethyl, also possess low aqueous solubility. When used in CR dosage forms, they function as inert film coatings or matrices. Drug release is mainly diffusion controlled and pH-independent.

Enteric polymethacrylates are prepared by substitution with acidic side chains. Depending on the degree of substitution with carboxylic acids, they dissolve between pH 5 and pH 7.5.

1.3.3 Lipophilic excipients

A third category of excipients for controlling drug release from oral dosage forms consists of the heterogenous group of lipophilic excipients. These include fats and oils, diglycerides, monoglycerides, fatty acids and waxes.

Chemically, fats are defined as triacetylglycerides, i.e. a triester of glycerol with three fatty acids. Liquid fats are called oils. Fiedler H.P. (1989) defines lipids as mixtures of mono-, di- and triglycerides and fatty acids. Lipids for pharmaceutical purposes should be precisely defined with respect to their chemical composition. During purification, natural lipids often undergo modifications such as hydration of unsaturated fatty acids. Typical examples are hydrogenated castor, stearic acid and glyceroldistearate type I (USP (2003a/ 2003b), Ph.Eur. (2001)). (Semi)synthetic glycerides are derived from natural fats or oils. Fig.1.3.4 shows the generic structures of glycerides. Instead of fatty acids, glycerol can be (partially) esterified with polyethyleneglycols. A typical example is Gelucire® 55/15, a mixture of hydrogenated palm oil and glycerolmono- and –diglycerides with PEG1500 substitution.

By contrast, waxes are defined as fatty alcohol monoesters of fatty acids. A typical wax applied in pharmaceutical formulations is White Wax (Ph.Eur (1997c)).

Melting points of excipients are an important parameter for lipophilic excipient selection and formulation design. Unsuitable selection or combination of excipients will result in physical instability of the dosage forms, in particular when exposed to elevated temperatures. Therefore, rather high melting solid lipids and lipophilic excipients are often used for preparation of oral dosage forms, whereas oils play only a subordinate role in solid oral dosage form design.

Typically, solid dosage forms containing oils consist of soft gelatine capsules filled with liquids or semisolids (Jantratid E., et al. (2007), Avramoff A., et al. (2007)).
Melting points of lipids and lipophilic materials rise with increasing length of the carbon chains of fatty acids. This is due to an increased number of intra- and intermolecular bonds (Hart H. (1989)). Introduction of double bonds results in misalignment of the carbon chains and reduced chemical order of molecules. As a result the energy required to break these forces is reduced and melting point is lowered.

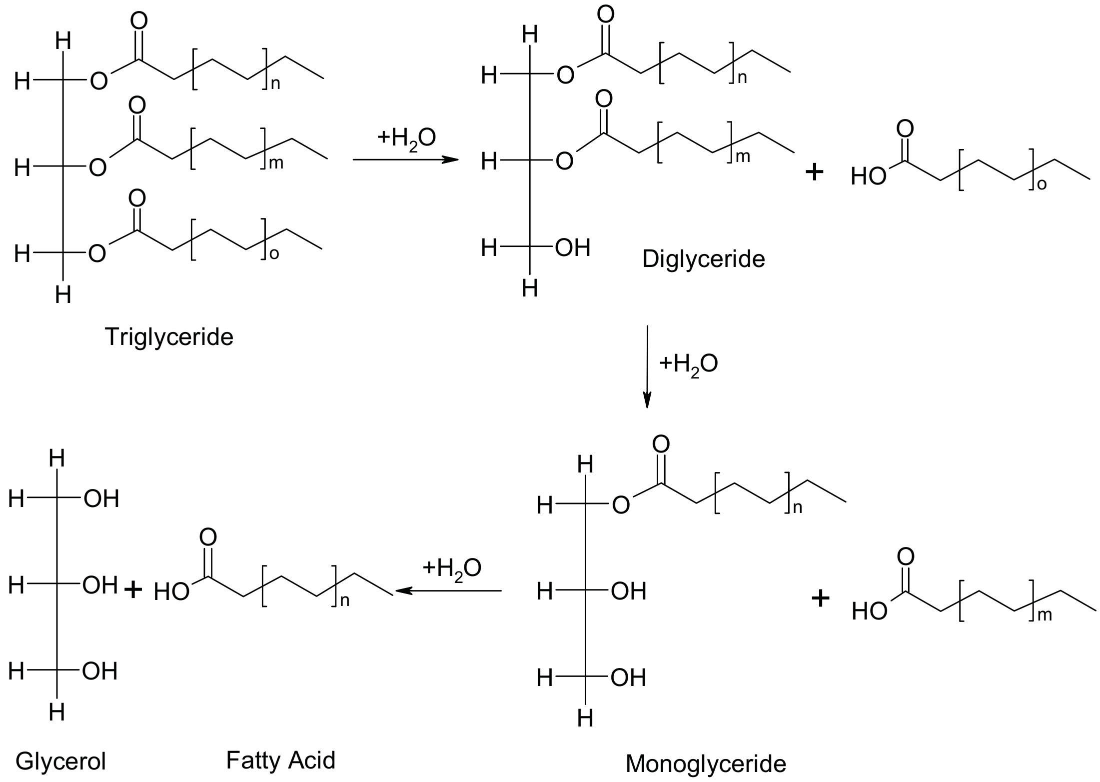


Fig. 1.3.4: Fat hydrolysis: generation of diglycerides, monoglycerides and fatty acids

Lipophilic excipients have been used to control drug release matrix from dosage forms. Due to their low affinity to water they have little tendency to swell or erode, so drug release is mainly diffusion controlled (Faham A., et al. (2000)). Siepmann F., et al. (2006b) elucidated the drug release mechanisms from matrices based on the more hydrophilic, semisynthetic glyceride (Gelucire® 50/02) and found that drug release mechanism was initially diffusion controlled. The preparation technique strongly affected drug release mechanism in later stages. Formulations prepared by melt solidification exhibited purely Fickian diffusion controlled drug release, whereas formulations prepared by extrusion/ spheronization tended to release by erosion of the dosage form. Erosion controlled drug release has also been reported for formulations with high drug loading (Ghaly E.S., et al. (1993)). In these cases dissolution of the water soluble drug resulted in a weakened matrix structure. Erosion may also be attributed to the digestion of the lipids by lipases. Generally, in vivo performance from lipid formulations is known to be affected by digestion of the lipidic formulation components (Porter C.J., et al. (2004)). Therefore, digestion of matrix agents that are also substrates for lipases, such as natural tri- and diglycerides, may change drug release from lipid matrices. This may further result in differences between fasted and fed state.

Lipophilic matrices can be prepared by direct compression of powder blends. Due to their relatively low melting points, lipophilic excipients lend themselves to use as carriers in melt granulation techniques. Zhang Y.E, et al. (2000) described the preparation of lipid matrices from dry blends and melt granulates of glyceryldibehenate. Liu J., et al. (2001) reported CR formulations using glyceroldistearate NF as thermal binder and release retardant. They examined the impact of processing technique on drug release, comparing dosage forms obtained from melt extrusion with high-shear melt granulated formulations. Processing affected performance and appearance of granulates and formulations with regard to particle shape and size distribution, compressibility and drug release. Film coating with lipids has also been investigated, but is not commonly applied in pharmaceuticals. Faham A., et al. (2000) prepared coated tablets with a hot-melt coating technology using glyceroldibehenate as the coating material.

1.4 Techniques for Preparation of CR Dosage Forms

Several techniques are available for preparation of controlled release dosage forms for oral administration. The applicability of certain techniques depends on the desired dosage form design and excipients used. For coated systems, the coating process is the key step in the manufacturing process in terms of setting the release rate. By contrast, matrix systems offer a wider range of preparation techniques. Since drug release is mainly governed by the properties of the matrix-forming excipient, processing has to ensure the formation of the excipient matrix and its reproducibility. Various techniques have been reported to be suitable for preparation of CR matrix dosage forms, including direct compression of bulk powder (DC), dry and wet granulation. Here, as with film-coating, the process itself potentially affects drug release from the CR dosage form (Zhu Y., et al. (2002), Zhang Y.E. (2001)).

Preparation of osmotic devices requires the coating of the dosage form core with a semipermeable film. Further an orifice has to be drilled through the coating to allow drug release from the core.

Different preparation techniques apply to preparation of solid CR dosage forms using ion exchange complexes. Ion exchange complexes may be compressed to matrix dosage forms, but coating of the ion exchange particles has also been reported (Jeong S.H., et al. (2008)).

1.4.1 Preparation of Coated CR Oral Dosage Forms

As described in chapter 1.2, coated systems employ a thin film of excipient(s) to control drug release. The thin, functional film surrounds the dosage form core containing the pharmaceutical active.

Mechanisms of film formation from colloidal polymer solutions differ from film formation from latex dispersions. When using polymer solutions, removal of solvent results in increased polymer concentrations. Polymer chains penetrate each other increasingly as the concentration increases. If the polymer solution is applied as thin layer, dry films are obtained after complete removal of solvent. From latex dispersions small droplets first form a layer of spheres on the surface to be coated. As the water is driven off, packing becomes closer and high capillary forces come into force. Further evaporation of solvent results in coalescence of the polymer spheres. Above an excipient specific temperature – the minimum film forming temperature – a coherent, dense and clear film, free from cracks, is obtained (Bauer K.H., et al. (1997), Stricker H. (1987)).

In coating processes, an aqueous dispersion or organic polymer solution is sprayed as small droplets onto the dosage form cores. The core bed is continuously agitated to ensure homogeneous distribution of polymer over the surface of the cores, and streams of heated air are concomitantly applied to evaporate the aqueous/ organic spraying fluid, resulting in film formation.

Coating processes are commonly divided into two principles. Drum coaters employ a rotating drum to agitate the core bed. Inclination of the rotary axis combined with baffles minimizes the occurrence of akinetic zones within the core bed. Continuous movement of cores is required to evenly distribute sprayed polymer and avoid agglomeration of cores during coating. Evolution of coating equipment has also involved improved penetration of air into the core bed. In order to improve drying of the film coated cores, approaches such as perforation of the drums or insertion of dip pipes have been used. Drum coaters are commonly used for coating of larger solid dosage forms such as tablets, capsules or larger pellets. For CR dosage forms, cellulose derivates (Zema L., et al (2006), Frohoff-Hulsmann A., et al. (1999), Siepmann F., et al. (2006)) or poly(meth)acrylates (Gohel M.C., et al. (2003), Metha K.A. (2001)) are usually applied in film coatings (see chapter 1.3)

The second process, fluidized bed coating, uses air circulation to agitate the bulk bed. Fluidized bed coaters vary in the design of the air stream used for agitation of the bulk. Perforation of the base plate results in a concurrent air stream. The inner concentric circle has more and larger perforations, accelerating the cores upwards within the inner air cylinder. When entering the outer air cylinder, particles fall back down onto the base plate. The Wurster design (e.g. by Glatt GmbH, Binzen, Germany) applies concurrent air flow with a tube controlling the upward movement of particles. In this configuration, the spray coating is applied from the bottom of the base plate. Other designs create a circulating air stream originated from a countercurrent airflow. The air inlet is situated at the top of the equipment and fed through to the base plate via tubing. A lamellar base plate then creates air circulation. Cores are therefore accelerated in a circular direction. Turbojet® (Huettlin GmbH, Steinen, Germany) coaters are constructed according to this design. Each design provides different processing zones within one circulation, such as preheating, spraying or drying zones. The position of the spraying nozzle varies accordingly. Both top- and bottom-spraying can be used. In addition to coating of tablets, fluidized bed coating is commonly used to coat granules

(Rahman N.U., et al. (2005), Beten D.B. (1995)) for use as multiparticulate dosage forms (Lecomte F., et al. (2003)).

1.4.2 Preparation of Osmotic CR Oral Dosage Forms

Preparation of osmotic devices for CR dosage forms requires the preparation of a semipermeable film coating on top of a tablet core. The tablet core comprises the drug and osmotically active excipients. In some case swelling excipients are used to control drug release. The coating is performed by one of the techniques described in chapter 1.4.1. As the coating only allows penetration of water into the core, an orifice has to be drilled into the coating. This usually achieved by a laser device, providing a high precision in size and shape of the orifice.

1.4.3 Preparation of CR Matrix Oral Dosage Forms

Matrices are formed when a carrier excipient phase is densified. Pharmaceutical actives and other excipients can be embedded into the matrix-forming, release controlling excipient.

Matrix formation is usually achieved by compaction of powder blends or granulates. The simplest method to prepare CR matrix dosage forms is direct compression of premixed powder blends consisting of drug and at least one excipient (Bonny J.D., et al. (1991)). Direct compression can be used for blends possessing suitable flow, homogeneity, particle size, compression and compaction properties. Addition of fillers, e.g. lactose or microcrystalline cellulose, and addition of glidants, e.g. magnesium stearate, can be used to improve these properties. Since many drugs have properties that are disadvantageous for direct compression, further processing of primary powder blends, such as granulation, is often required prior to compaction to obtain reproducible product quality. During granulation, powder agglomerates (granules) are formed. Increase and standardization of particle size improves flowability and compressibility of the bulk material and the tendency to segregate into the different ingredients is reduced. In some cases, compaction issues have also been overcome by granulation (Summers M., et al. (2001)).

In pharmaceutical terminology granulation describes the agglomeration of bulk powders (Hunnius C. (1975)). During granulation processes, “primary powder particles are made to adhere to form larger, multiparticle entities called granules” (Summers M., et al. (2001)). In order to form granules, inter-particulate bonds have to be formed. Summers M. (2001) and Bauer K.H. (1997) give a detailed description of the bonds formed between primary particles of bulk material. For pharmaceutical applications, relevant mechanisms can be summarized as (i) attractive, cohesive forces between primary particles, (ii) mechanical interlocking by dense packing, (iii) adhesion/ cohesion of immobile liquid films between primary particles, (iv) capillary forces caused by mobile liquid bridges and (v) solid bridges formed by partial melting, binders, crystallization or sintering.

Different techniques have been used to create bonds between primary particles. They are divided into dry and wet granulation techniques. Wet granulation applies aqueous or organic binder solutions or solvent vapour to form agglomerates. Commonly used techniques for wet granulation are shear/ high shear wet granulation, fluidized bed granulation and extrusion. Spheronization has been applied to obtain spherical beads. It is used as a single process or in combination with other techniques, especially fluidized bed granulation and extrusion. In shear granulation processes, a blended mixture of drug and excipients is agitated by a mixer paddle. A granulating liquid containing binders (often the release controlling agents) is added to the powder blend and a moist mass is obtained. Finally granules are formed from the moist mass by employing a granulation device. In this process the moist mass is, for example, forced through a sieve, resulting in a defined granule size. High shear/ high speed granulation represents a streamlined modification of this process. Addition of a chopper to the mixing blade reduces the number of processing steps enabling blending of formulation ingredients, wet massing and formation of granules to be performed with one piece of equipment. Large agglomerates are removed by screening. Afterwards, granules are either dried in a tray oven or by fluidized bed drying. Shear granulation represents the traditional granulation technique and has been widely applied in preparation of CR matrix dosage forms (Qiu Y., et al. (1997), Nellore R.V., et al. (1998), Huang Y., et al. (2003)).

As a second wet granulation approach fluidized bed granulation has been developed. It is derived from fluidized-bed drying. The working principle is very similar to the fluidized-bed coating process described in chapter 1.4.1. Starting with a powder blend, a particle bed is fluidized by a consistent stream of heated and filtered air. Via a nozzle the particles are wetted with a solution of binders or solvents. Applied moisture makes primary particles agglomerate. Heated air is used to dry the granules. Hence fluidized bed granulation comprises a single process for mixing, wet massing, formation of granules and drying. These advantages have been used for the preparation of CR matrix dosage forms (Radtke G., et al. (2002)). The final particle size depends on the amount of liquid, spray rate, air temperature and air flow, so the granulation process has to be well characterized in order to obtain reproducible results (Summers M., et al. (2001)).

Extrusion has also been used for preparation of CR matrix dosage forms. During extrusion materials are “pushed out”, i.e. they are forced through a die under elevated pressure (Rauwendaal C. (1998)). Firstly a premixed powder blend is fed through a channel, the so-called barrel. Bulk material is agitated and moved by screws or pistons. Besides moving the material, the screws function as mixing devices. The granulation liquid is then added to the powder blend. Similar to other granulation techniques, a moist mass results. The die at the end of the barrel functions as a bottleneck for material throughput, resulting in increased pressure. The moist mass is forced through the die and takes on its shape. Usually rods or ribbons are obtained from extrusion processes. These are then, for example, spheronized, granulated or cut to obtain pellets, beads, granulates or tablets. After drying, extrusion products are ready for further processing such as compaction, encapsulation or coating. The variety of shapes and sizes obtained in processes involving extrusion indicates the versatility of extrusion.

Spherical particles are commonly used for preparation of solid dosage forms (Metha K.A., et al. (2001), Lutchman D., et al. (2005), Debunne A., et al (2002), Zimm K.R., et al. (1996)). Pellets are formed by frictional forces derived from a rotating base plate. Collision of agglomerates with fixed side walls or other agglomerates results in rounding of the granules. Rotor granulation comprises a stand-alone granulation technique with an implicit spheronization process. The quality of the spherical shape depends partly on the processing time. The main advantages of spherical pellets are (i) uniform size and shape resulting in good flow properties and reproducible packing, (ii) high strength, (iii) low friability (iv) reduced dust (Summers M., et al. (2001)) and (v) reduced surface/ volume ratio which facilitates coating.

Dry granulation refers to granulation techniques that are conducted without the use of solvents. Instead, pressure or heat is applied to form bonds between particles. For CR matrix applications, roller compaction and slugging apply pressure to form agglomerates (Hariharan M., et al. (2004), Saravanan M., et al. (2003)), whereas high-shear melt granulation and melt extrusion employ elevated temperatures to form interparticulate bonds (Ochoa L., et al. (2005), Voinovich D., et al. (2000) , DeBrabander C., et al. (2003), Liu J., et al. (2001)).

Roller compaction and slugging are usually two-step processes. First, powder is compacted between two rollers (roller compaction) or with a standard tablet machine (slugging). Desired granulates are obtained by milling of “slugs” or screening of the brittle ribbons.

Melt granulation or melt extrusion represent an alternative to wet and dry granulation. The equipment is in principle similar to that of extruders described above for wet granulation, but instead of addition of granulation liquids, the equipment contains heating facilities. The powder blend is heated above the melting point or film forming temperature of the binder, which must provide thermoplastic properties. Due to formation of liquid bridges, other particles adhere to the (partially) molten binder particles. Upon cooling, the binders re-solidify and solid bridges are formed between particles. Agglomerates obtained from melt granulation processes can be further processed as for these obtained from wet high-shear granulation and extrusion processes.

1.5 Application of (Melt) Extrusion for CR oral dosage forms

Extensive research has been conducted on melt extrusion as a technology for preparation of pharmaceutical products. A wide range of applications has been successfully investigated including improvement of solubility and bioavailability for poorly soluble compounds and drug delivery. The following section gives some historical background and current applications as well as highlighting the pros and cons of melt extrusion technology.

1.5.1 Historic Overview

In the late 1950s and 1960s (melt) extrusion replaced its predecessor, the extruding press that had been used in the celluloid- and rubber industry. In his publication "Kunststoff-Extruder Technik" Schenkel proposed the first diagrams for design and operation of single-screw extruders (Schenkel G. (1959)). In 1963 Schenkel published further theoretical aspects of extrusion. Nowadays, manufacture of plastic products processed by extrusion is standardized, e.g. according to German Industry Standards (Deutsches Institut für Normung (1987)).

The range of plastic materials suitable for extrusion processes covers a vast range of thermoplastics, thermosets and elastomers. Common examples include polystyrene (PS), polymethyl methycrylate (PMMA), polyvinylidene fluoride (PVDF), polyethylene (PE) or nylon (polyamide, PA) (Rauwendaal C. (1998)). Many polymers are suitable for extrusion processing, although in some cases thermal stability and physical properties can be problematic. Appropriate choice of processing conditions can often provide a solution to such material-related processing issues. Extrusion has been used in production of raw materials such as slugging, homogenization or cross-linking of melts. Further it has been used for incorporation of stabilizers into melts. Extrusion further plays a major role in material shaping. For these purposes extrusion lines consisting of raw material "handling devices, drying systems, extruder, post shaping or calibration devices, cooling devices, take-up devices and cutter or saw" (Rauwendaal C. (1998)) are set up. Typical products range from tubes and pipes to films, fibres, etc..

Improvements in extrusion technologies in the pharmaceutical industry have mainly been achieved with engineering of equipment. The advent of single screw extruders in the 1960´s and 70´s represented a major step forward in terms of pharmaceutical processing. Goodhart F.W. (1973) reported the construction and use of a single screw extruder for pharmaceutical purposes which enabled the manufacture of both wet and hot fusion granulates. Later, twin-screw extruders became widely established (Kleinebudde P., et al. (1993), Keleb E.I., et al. (2001)). During the 1990´s melt extrusion became established as a state of the art technology for preparation and development of solid dosage forms. It covers a wide range of applications, including drug delivery and formulation poorly soluble and bioavailable compounds (Breitenbach J. (2000)).

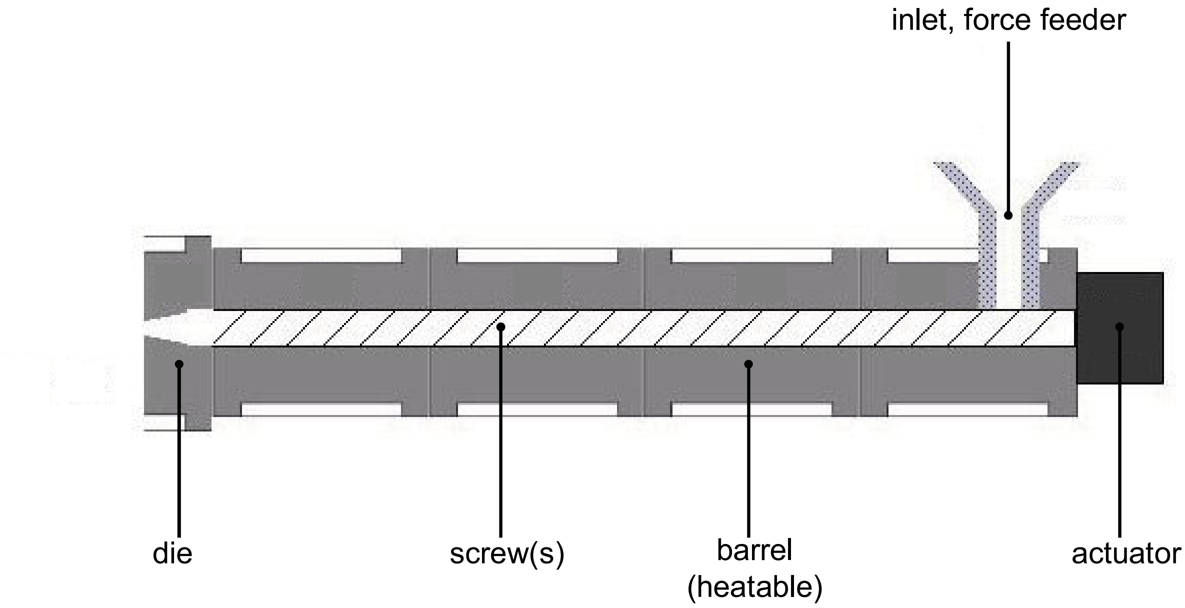


Fig. 1.5.1: Scheme of extruder

The main elements of extruders are screws located within the cavity of the heatable barrel. The die forms the outlet of the barrel. Extruders are generally divided into single and twin-screw devices. For twin screw devices, co- and counter rotating setups may be distinguished. The screw(s) are connected to an actuator via a gear to rotate the screws. The barrel may be divided in different sections with independent process temperatures.

For the melt extrusion process, a powder blend is transferred into the heated barrel of the extruder through the inlet. To control and monitor the feeding rate, gravimetric and force feeder devices may be used. The powder blend is forced through the barrel by the screws. While moving through the barrel, formulation components are heated and blended. Agitation varies according to the screw design. At the end of the barrel, the hot, fluid material is forced through the die. Due to the small size of the outlet, high pressure prevails. The shape of the outlet die determines the shape of the extrudate.

1.5.2 Current Pharmaceutical Applications of Melt Extrusion

Melt extrusion has been widely applied for preparation of solid oral dosage forms. Both immediate release (IR) and controlled release (CR) dosage forms have been reported. Development of IR applications involving melt extrusion processes mostly focusses on preparation of solid dispersions (Ghebremeskel A.N., et al. (2006), Six K., et al. (2003), Forster A., et al. (2001a),), which are typically applied to improve bioavailability (Verreck G., et al (2004), Sethia S., et al. (2003)) of poorly water-soluble, highly permeable compounds such as carbamazepine and sulfamethoxazole. Despite many investigations, solid dispersion technology has not yet resulted in a large number of marketed products (Sethia S., et al. (2003)). For many years, manufacturing difficulties and stability as well as intellectual properties issues have hindered the commercial exploitation of solid dispersion technology (Serajuddin A.T. (1999)).

Excipients that have been used as carriers for solid dispersions include both polymers and small molecules (Leuner C., et al. (2000)). For preparation of solid dispersions, pharmaceutical actives have mainly been melt extruded with excipients such as polyvinylpyrrolidone (PVP), polyvinylpyrrollidone-co-vinyl-acetate (PVP-VA), ethylcellulose (EC), and hydroxypropylmethylcellulose (HPMC) (Verreck G, et al. (2006), Verreck G., et al. (2005), Six K., et al. (2003), Hulsmann S., et al. (2000)). Further polyethylenglycol 6000 (PEG 6000) and poly(meth)acrylates have been used for preparation of solid dispersions by melt extrusion (Hulsmann S., et al. (2000), Six K., et al. (2005)).

As described in chapter 1.1, CR dosage forms pursue a number of goals such as site or time-specific drug delivery, sustained therapeutic plasma levels or reduced drug degradation within the gastrointestinal environment. Melt extrusion represents an alternative processing technology to achieve these goals.

Extending drug release and maintaining therapeutic plasma levels over a longer period of time may permit a once-daily administration, which in turn is associated with improved patient compliance (Young C.R., et al. (2005), De Brabender C., et al. (2003)). CR dosage forms have also been developed for site-specific drug delivery employing melt extrusion technology. Mehuys E. (2005) formulated capsules for enteric drug release by means of melt extrusion, while Fukuda M. (2006) reported the successful development of a gastroretentive dosage form by means of melt extrusion.

So far the number release controlling excipients used with melt extrusion processes is very limited. Amongst the standard excipients for controlled drug release applications only hydroxypropylmethylcellulose, ethylcellulose and poly(meth)acrylates have been used (Young C.R., et al. (2005), De Brabender C., et al. (2003)). For enteric delivery hydroxypropylmethylcellulose acetate succinate (HPMCAS) has been used as melt extruded capsule shell (Mehuys E. (2005)). Further, a few wax matrices have been prepared by melt extrusion. Liu J. (2001) reported glyceride-based matrices comprising glycerylstearate and hydrogenated cottonseed oil. Lipidic matrix pellets consisting of macrogol-glyceryl-stearate (Gelucire® 50/02) were recently described by Siepmann F. (2006). Less common matrix excipients include chitosan, xanthan gum and polyethylenoxides (Fukuda M., et al. (2006a), Zhang F., et al. (1999))

1.5.3 Advantages and Disadvantages of Melt Extrusion for Pharmaceutical Applications

In the pharmaceutical industry, implementation of new technologies requires a positive cost-benefit calculation. Therefore all technologies have to be critically reviewed. The following evaluation reviews the pros and cons of melt extrusion technology for pharmaceutical applications.

Melt extrusion provides the technological capability to deliver a large number of different dosage form designs. The range of possible products includes tablets, capsules, beads and pellets for multiparticulates and films suitable for oral or topical delivery. As described in chapter 1.5.2 these dosage forms can be used for both IR and CR applications. Dosage form design by melt extrusion offers solutions to a number of current challenges in pharmaceutical development. As described in a previous section, solid dispersions and solutions have successfully been used to optimize the biopharmaceutical properties of pharmaceutical actives. Through the amorphisation of drugs, melt extrusion offers an approach to improve solubility and bioavailability of poorly soluble compounds (Breitenbach J. (2002)). The spectrum of application is completed by the drug delivery applications, such as extended release dosage forms for once-daily administration or site-specific drug release. Therefore melt extrusion is probably the most versatile processing technology for pharmaceutical applications.

In addition, melt extrusion seems advantageous for scaling up compared to fluidized bed processes. This may be due to a smaller and number of relevant process parameters.

A further advantage is the short processing time (just a couple of minutes) from the powder to the product. As a result, costs for processing can be reduced: due to higher throughput combined with fewer equipment and staff resources. Further, the avoidance of organic solvents during processes contributes to reduction of processing costs. This saving is mainly related to reduced costs for recovery of solvent vapours and reduction of safety requirements.

On the other hand there has been some reluctance to use melt extrusion in pharmaceutical industry. Reluctance to implement the technology is partly related to the difficult patent situation. In case of melt extrusion a large number of patents cover many interesting commercial applications involving melt extrusion processes. To quote but a few, patent WO02/35991 (2002) claims the production of matrix pellets by a solvent-free hot-melt/ spheronization by a continuous or semi-continuous technique. The main advantage of these melt extruded pellets is seen in their “greater control of drug release” compared to pellets prepared by standard wet granulation techniques. The patent further claims the conversion of IR pellets to CR or ER pellets by hot-melt extrusion/ spheronization processing. Patent WO97/49384 (1997) claims high molecular weight polyethylenoxide based, hot-melt extruded controlled release formulations. The release controlling functionality for high molecular weight polyethylenoxides has been shown. Patents EP0177893 (1986) and WO9625151 (1996) claim sustained release dosage forms based on HPMC and HPC prepared by melt extrusion processes. However, with the expiry of some of the basic patents, the intellectual property situation will become less difficult in coming years.

“Instrumentation is one of the most essential elements of an extruder” (Rauwendaal C. (1998)). This citation already highlights the rather large number of processing parameters influencing product quality of melt extruded products. Barrel and product temperature, melt pressure are the most important parameters to be monitored during melt extrusion processes. They directly impact product quality and process safety. They are further influenced by other parameters such as feeding rate, formulation composition and viscosity, screw design, screw speed, size and shape of dies. With all these parameters in play, melt extrusion is a very complex process. However, other techniques, such as fluidized-bed coating, show comparable complexity in processing parameters (Summers M., et al. (2002)).

Finally, with regard to CR applications, only a very limited number of release controlling excipients have been examined in melt extrusion processes. As already mentioned in the previous section, for research purposes only the properties of EC, HPMC and poly(meth)acrylate melt extrudates have been examined in any depth. Therefore it is important to explore a wider range of established and investigated pharmaceutical excipients in terms of their application to melt extrusion processes. This will broaden the palette of available physical, chemical and technological properties required to exploit the technological capabilities of melt extrusion.

2 Outline and Aims of Thesis

Melt extrusion has been recognized as a useful and flexible technique to tackle various challenges in pharmaceutical development. Its main applications to date are the improvement of solubility for poorly soluble compounds and the development of drug delivery systems. Compared to other manufacturing processes, melt extrusion provides the advantages of a short, continuous and solvent-free process. (Breitenbach J., (2002)).

With increasing numbers of poorly soluble compounds (Leuner C., et al. (2000)), technologies to improve bioavailability by formulation design have become valuable tools in pharmaceutical development. Melt extrusion is commonly applied for preparation of solid dispersions or solid solutions to improve solubility of poorly soluble actives. This approach has widely been used to increase dissolution rate by increasing contact surface of the compound with the dissolution medium. Sometimes increasing compound surface is coupled with solubilizing or wetting effects of applied excipients (Ghebremeskel A.N., et al. (2006)). However, due to stability issues, particularly recrystallization of amorphous compound, and difficulties to reproduce solid state properties of actives, this technology has not taken a foothold in the pharmaceutical market. Hence only a few solid dispersions are currently on the market (Sethia S., et al. (2003)).

On the other hand, melt extrusion is also used as a drug delivery technology. Especially sustained, modified or controlled release dosage forms have been prepared by melt extrusion. Extended release dosage forms derived from melt extrusion are mainly based on a release controlling matrix design (De Brabender C., et al. (2003)).

For both applications only a very limited number of excipients have been investigated for development of formulations. At present, carriers used for melt-extrusion processes are limited essentially to cellulose derivates, especially ethylcellulose (EC) (Young C.R., et al. (2005), Crowley M.M., et al. (2004)), methacrylic acid polymers and co-polymers (e.g. Eudragit®) (Fukuda M., et al. (2006), Zhu Y. (2006)), vinylpyrrolidone and vinylpyrrolidone/vinyl acetate polymers and co-polymers (PVP and PVP/VA), (Forster A., et al. (2001)) and ethylenglycol polymers (PEG) (Hulsmann S., et al. (2000)).

The main goal of this thesis was to identify further suitable carriers for CR oral matrix dosage forms prepared by melt extrusion processes. Several pharmaceutical excipients which have not previously been used for this application were evaluated for their suitability for melt extrusion. In addition to evaluating key processing parameters, dissolution performance, release mechanisms and ease of conversion to standard dosage form formats were assessed. Melt extrusion as a drug delivery technology will benefit from a broadened range of established carriers, as the limited number of carriers for CR applications is one of its main drawbacks. A wider range of possible release mechanisms and a deeper understanding of technological issues will facilitate result-driven development of CR dosage form design for oral application.

The thesis is divided into several chapters, each of them pursuing specific goals.

2.1 Basis for selection and identification of suitable pharmaceutical excipients for melt extrusion

- Feasibility study to examine candidate excipients with regard to general suitability for melt extrusion by thermoanalytical examination; Evaluation of potential drug loading and processing temperatures by processing in a lab scale extruder.
- Melt extrusion processing of selected excipients with a model drug (theophylline); assessment of formulation parameters such as drug loading range, requirement of plasticizer, process temperature
- Evaluation of predictability of melt extrusion parameters from lab scale experiments
- Selection of four carriers for more detailed investigations

2.2 Characterization of melt extruded formulations based on the four selected carriers

- Characterization of melt extruded granulates with regard to flowability and compressibility, particle size and compactibility; effects of processing on drug crystallinity using powder X-ray diffraction (PXRD)
- Compaction of matrix tablets from melt extruded granulates
- Process evaluation based on pharmaceutical quality of matrix tablets, e.g. uniformity of mass and content, friability, tensile strength

2.3 Drug release from matrix tablet formulations based on the four selected carriers

- Characterization of in-vitro dissolution performance of matrix tablets prepared from extrudates, including reproducibility of drug release; evaluation of drug loading as parameter to design drug release
- Analysis of prevailing release mechanisms for each formulation including mathematical modelling, e.g. Higuchi, Hixon-Crowell and Peppas-Sahlin equation fits.
- Robustness of drug release to changes in dissolution media, including variation of pH and ionic strength
- Robustness of drug release to changes in hydrodynamics by variation of dip rates in the USP Type 3 dissolution tester
- Robustness of drug release to presence of food and digestive components such as lecithin, bile salts and proteins
- Global evaluation of excipients as potential matrix carriers for CR oral applications

2.4 In vivo performance of selected matrix tablets

- *In vivo* testing of selected formulations in dogs by evaluation of pharmacokinetics after fasted and fed state administration
- Evaluation of *in vitro–in vivo* correlations for melt extruded matrix tablets

3 Materials and Methods

3.1 Theophylline

Theophylline was chosen as a model active for assessing suitability of various excipients for melt extrusion. The selection was made due to its high melting point and good chemical stability. Also, theophylline represents a class of drugs with a need for CR dosage forms to provide more constant plasma profiles. Finally, the commonly known safety profile of theophylline facilitated handling in the lab. In the following sections a more detailed description of the chemical structure, physicochemical properties and pharmacology of theophylline is given.

3.1.1 Chemical Structure

Fig. 3.1 shows the chemical structure of theophylline. The molecular formula of theophylline is $C_7H_8N_4O_2$ and has a molecular weight of 180.2g/mol. The chemical name is 1,3-dimethyl-3,7-dihydro-1H-purine-2,6dione.

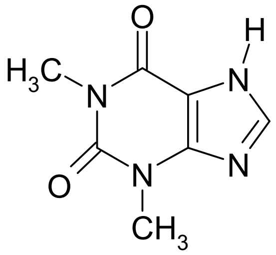


Fig. 3.1 Chemical structure of theophylline

3.1.2 Physicochemical Properties

Melting Point: A melting point ranging between 270°C and 274°C has been reported for anhydrous theophylline.

Ionization: Two pKa values have been reported at 25°C: $pKa_1<0.3$ and $pKa_2 = 8.6$ (ABDATA 2005).

Partition Coefficient: Zhao Y.H., et al (2001) report a log P value for theophylline of –0.002.

Solubility: Theophylline is slightly soluble in cold water, but more soluble in hot water. It also dissolves in solutions of alkali hydroxides, ammonia and in mineral acids. It is sparingly soluble in chloroform, ether and alcohol (Martindale 1999). Its aqueous solubility has been reported to be 8.3mg/ml at 25°C (Merck & Co. (1990)).

Polymorphism and hydrates: Two hydrate forms have been reported and are widely used in pharmaceutical applications. The anhydrous form and the monohydrate appear as crystalline, white needles. Phadnis N.V., et al. (1997) have also reported a metastable polymorph of the anhydrous form, which appears during dehydration of the monohydrate.

3.1.3 Pharmacology and Toxicology

Theophylline has been used in the therapy of asthma, but its use has dwindled due to its narrow therapeutic window and the availability of safer drugs, e.g. inhaled glucocorticoids. Two different actions of mechanism have been reported for theophylline, which both seem to contribute its bronchodilating effect. First, it inhibits the bronchial effects of adenosine and therefore bronchodilation is observed in asthmatic subjects. Secondly an inhibition of phospho-diesterase-enzymes has been reported, which results in bronchodilation by reducing levels of the secondary messengers cyclic-guanosine-monophosphate (cGMP) and cyclic adenosine-monophosphate (cAMP). Both mechanisms of action are considered clinically relevant to bronchodilation (Undem B.J. 2001).

Side effects such as convulsions and even death have been observed at plasma levels over 25µg/ml. This underscores the need for plasma level monitoring during theophylline therapy. Established dosing regimes recommend an initial dose of 12-16mg/kg per day, followed by a subsequent increase in dose up to a maximum of 18 to 22mg/kg per day, with monitoring of plasma levels (Undem B.J. 2001).

According to the Biopharmaceutial Classification System (BCS), Theophylline has been classified as BCS class 1 drug due to its high solubility and high permeability (Lindenberg M, et al. (2004)).

For oral therapy, theophylline is mainly marketed as extended release dosage forms. Available doses range between 100mg (Bronchoretard® junior) and 600mg (Tromphyllin® retard 600). Amongst extended dosage forms encapsulated pellet products (e.g. Aerobin®, Euphylong®) prevail, but matrix tablets (e.g. Contiphyllin®, Solosin® retard) are available. Additionally, a theophylline solution for oral administration (Solosin® Tropfen) and parenteral dosage forms (afpred®, Solosin® Infusionskonzentrat) are also available.

For pellet formulations both coated lactose pellets (Euphylong®) and matrix pellets (Aerobin®) are used. Typically cellulose derivates and polymethacrylate polymers are used for preparation of pellets. Extended release theophylline matrix tablets are based on cellulose carriers. Table 3.1.1 gives some examples of compositions of marketed theophylline dosage forms. For the encapsulated pellet products, the composition of the pellets are given.

Table 3.1.1: Composition of marketed theophylline dosage forms for oral administration

Brand Name	**Manufacturer**	**Composition**
Pellet Composition		
Aerobin® forte 400mg	Farmasan	hypromellose; poly(ethylacrylate-co-methylmethacrylate) (2:1); simeticon-alpha-Hydro-omega-octadecyloxypoly (oxyethylene)-5-sorbic acid (Ph.Eur.); purified water; talc; titanium dioxide, iron(III)-hydroxid-oxide x H_2O; erythrosin; indigocarmin; iron(II/III)-oxide
Euphylong® 125 retardiert	Nycomed Deutschland	lactose-monohydrate, mikrocryst. cellulose, carmellose sodium, celluloseacetate, triethylcitrate, methylcellulose, talc, purified water, titanium(IV)-oxide (E 171), indigocarmin (E132)
ER Tablet Composition		
Contiphyllin	Lindopharm	poly(0-2-hydroxypropyl, 0-methyl)cellulose, shellac, calciumhydrogenphosphate·x $2H_2O$, silicium dioxide, magnesiumstearate (Ph.Eur.)
Solosin® retard mite	Aventis Pharma	hypromellose, macrogol 6000/ 8000, magnesiumstearate, hydrated ricinus oil, silicium dioxide

3.2 Chemicals, Laboratory Supplies and Standard Equipment

3.2.1 Chemicals

Table 3.2.1: Substances used for preparation of dissolution media

Substance	Source	Grade/ Batch
Sodium Chloride	Merck KGaA, Darmstadt, Germany	Analytical Grade/ K 31900304314, K 32004404319
Sodium Chloride	Fisher Scientific UK, Loughborough, Leicestershire, UK	Analytical Grade/ 0560472,
Hydrochloric Acid conc.	Merck KGaA, Darmstadt, Germany	Analytical Grade 37%/ K327324717348, K 32724717
Dichloromethane	Fisher Scientific UK, Loughborough, Leicestershire, UK	
Potassium Dihydrogen Phosphate	Merck KGaA, Darmstadt, Germany	Analytical Grade/ A 398573310
Sodium Hydroxide	Mallinckrodt Baker B.V., Deventer, The Netherlands	Analytical Grade/ 0134840002
Potassium Dihydrogen Phosphate	Fisher Scientific UK, Loughborough, Leicestershire, UK	Analytical Grade/ 0307553, 0414968
Sodium Hydroxide	Fisher Scientific UK, Loughborough, Leicestershire, UK	Analytical Grade/ 0309682, 0568490
Sodium Dihydrogen Phosphate x 2 H2O	Fisher Scientific UK, Loughborough, Leicestershire, UK	Analytical Grade/ 0564049
Acetic Acid glac.	Fisher Scientific UK, Loughborough, Leicestershire, UK	Analytical Grade/ 0563721,
Triton X 100	Fisher Scientific UK, Loughborough, Leicestershire, UK	
Taurocholic Acid Sodium PCA 3013	Prodotti Chimici e Alimentari SPA, Basaluzzo, Italy	Analytical Grade/ 2005010034
Phosphatidylcholin E-PC S	Lipoid GmbH, Ludwigshafen, Germany	

3.2.2 Laboratory Supplies

Table 3.2.2: Materials used for dissolution tests

Material	Source
Syrringe Filter Rezist 30/0.45µm PTFE	Schleicher & Schuell GmbH, Dassel, Germany
Syrringe Filter Acrodisc 25/0.45µm PTFE	Pall Ltd., Portsmouth, Hampshire, UK
Filter VanKel Full FlowTM 10µm	VanKel Inc., Cary, NC, USA
Tubing PTFE	Omnifit Ltd., Cambridge, UK
Gilson Diamond Precision Tips D200	Gilson Inc., Middleton, WI, USA
Gilson Diamond Precision Tips D5000	Gilson Inc., Middleton, WI, USA

3.2.3 Standard Equipment

Table 3.2.3: Dissolution setup #1

Device	Source
Dissolution Tester AT7	Sotax AG, Allschwil, Switzerland
Piston Pump CY7	Sotax AG, Allschwil, Switzerland
UV/ VIS Spectrophotometer Lambda 2	Perkin Elmer GmbH, Ueberlingen, Germany
Dissolution Management System Winsotax V1.1.0	Sotax AG, Allschwil, Switzerland

Table 3.2.4: Dissolution setup #2

Device	Source
Dissolution Tester DT700	Erweka GmbH, Heusenstamm, Germany
UV/ VIS Spectrophotometer U 3000	Hitachi Ltd., Tokyo, Japan
Software UV Solutions, V 1.2	Hitachi Ltd. Tokyo, Japan

Table 3.2.5: Dissolution setup #3

Device	Source
Dissolution Tester VK 7000	VanKel Inc., Cary, NC, USA
Peristaltic Pump PCP 490	Icalis Data Systems, Ltd., Finchampstead, Berkshire, UK
Remote Serial Controller RS 8	Icalis Data Systems, Ltd., Finchampstead, Berkshire, UK
UV/ VIS Spectrophotometer UV-2501-PC	Shimadzu Deutschland GmbH, Duisburg, Germany
Dissolution Software IDIS EE, V 1.25.61	Icalis Data Systems, Ltd., Finchampstead, Berkshire, UK

Table 3.2.6: Standard equipment used for preparation of dissolution media, standard solutions and samples

Device	Source
Balance PB 3002 Delta Range	Mettler Toledo GmbH, Giessen, Germany
Balance AB 204	Mettler Toleodo GmbH, Giessen, Germany
Magnetic Stirrer RCT basic	IKA Werke GmbH & Co. KG, Staufen, Germany
pH-meter 720A	Orion Research Inc., Boston, MA, USA
Balance Ohaus Explorer	Ohaus UK Ltd., Beaumont Leys, Leicester, UK
Sartorius BP 211D	Sartorius Ltd., Epsom, Surrey, UK
Media Preparation System MPS	Sotax AG, Allschwil, Switzerland
Magnetic Stirrer Fisher Scientific	Fisher Scientific UK, Loughborough, Leicestershire, UK
pH-meter Perphect Log R Meter 330	Orion Research inc., Boston, MA, USA
Digital Thermometer DT01C 32°C-42°C (±0.2)	Fisher Scientific UK, Loughborough, Leicestershire, UK
Glass Syrringe 5ml Fortuna Optima	Walter Graf GmbH & Co. KG, Wertheim, Germany
Glass Syrringe 5ml Samco	S. Murray & Co. Ltd., Sheffield, UK
Gilson Pipetman G200 (Lot# S60328L)	Gilson Inc., Middleton, WI, USA
Gilson Pipetman G5000 (Lot #S54636H)	
Balance Sartorius Supermicro	Sartorius AG, Goettingen, Germany

Table 3.2.7: Equipment used for HPLC assay

Device	Source
HPLC System Waters Separations Module 2695	Waters Corp., Milford, MA, USA
UV-VIS Detector Waters 486 Tunable	Waters Corp., Milford, MA, USA
Chromatography Integration Software Waters Millenium® 32	Waters Corp., Milford, MA, USA
Vortex Mixer Fisherbrand Whirlimix®	Nickel Electro Ltd., Weston-Super-Mare, UK
Water Purification System Millipore Milli-Q® Gradient A10	Millipore (UK) Ltd., Watford, UK
Eppendorff Pipette Gilson Pipetman P200/ P5000	Gilson Inc., Middleton, WI, USA

3.3 Methods

3.3.1 Composition of Standard Dissolution Media

All standard dissolution media were freshly prepared according to the compositions listed in the respective sections and consisted of aqueous buffers. All chemicals were accurately weighed and quantitatively transferred into suitable volumetric flasks. pH values were adjusted to the target value (±0.02) using concentrated acid or base, as appropriate. Prior to testing, media were preheated and degassed. For degassing a vacuum was applied to media for at least 20 min at not less than 37°C. Nine hundred millilitres of medium were then carefully poured into each vessel.

Ionic strength was calculated according to Eq. 3.3.1, in which μ is the ionic strength (mol/l), c_j the concentration of the respective ion (mol/l) and z_j the valence of the ion.

$$\mu = \sum_j c_j z_j^2 \tag{3.3.1}$$

3.3.2 Dissolution Test

All tests were performed using a USP II (paddle apparatus) or III (reciprocating cylinder) dissolution systems. Medium temperature was always 37.0°C (±0.5°C). Variations in rotation speeds and dip rates, media and volumes were applied and these are documented in relevant sections. Samples were withdrawn manually or automatically.

In the case of automated sampling, a peristaltic pump withdrew the sample through a filter and transferred it via PTFE tubing into quartz spectrometer cells. After flushing the cells for two minutes prior to reading, the theophylline concentration was measured using UV spectrometry utilizing a wavelength of 272nm. The withdrawn sample was automatically returned into its respective vessel.

When sampling manually, five millilitre samples were withdrawn from each vessel using a glass syringe and replaced by five millilitres of blank medium. The sample was filtered, discarding the first two millilitres of each sample in order to flush used filters. All samples were analysed using the validated HPLC method described in chapter 3.3.3.

Validation of HPLC and UV methods allowed calculation of the theophylline concentrations in the samples according to standard curves of theophylline in the respective medium. All results were plotted as time [min] versus mean cumulative percentage released ($n \geq 3$) [%].

3.3.3 HPLC Assay

For HPLC assays 200µl of sample were transferred into a glass vial. 1.5ml of acetate buffer pH 5.0 were added. The injection volume was set to 100 µl. An 80:20 mixture of demineralised water with methanol was used as mobile phase. A flow rate of 1.2ml/ min was applied and the system pressure was about 2000psi under these operating conditions.

Separation was performed with a LiChrospher 100, RP18 125x4 (5µm) column (Merck KgAa, Darmstadt, Germany). Retention time was 4.6min. Theophylline was detected with a UV-VIS detector at 272nm detection wavelength (Klein S. 2005).

Peaks were integrated using Waters Millenium® 32 integration software. Standards were included in all HPLC runs in order to demonstrate system suitability. The system was considered suitable when the difference in observed content among seven injections of one standard sample was below two per cent. In addition, linearity plots were recorded for the expected range of concentrations. Linearity was assumed when the squared correlation coefficient obtained from a linear regression of the plot was ≥0.999. Fig. 4.5.1 shows a representative peak obtained from an HPLC assay of theophylline.

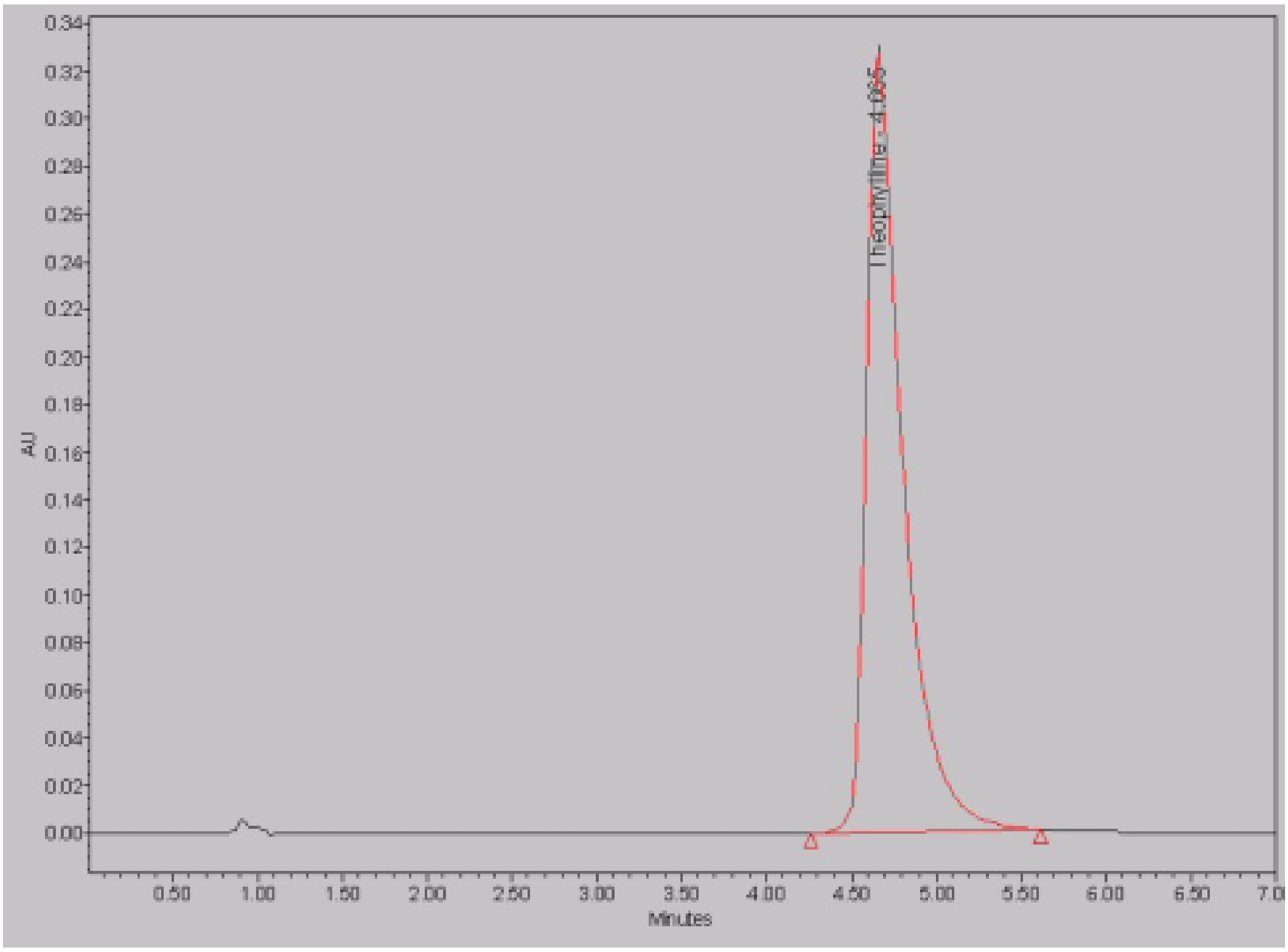


Fig. 3.2: Chromatogram obtained from theophylline HPLC assay

3.3.4 Statistical Comparison of Dissolution Profiles

To test the similarity of two dissolution profiles, e.g. the comparison of newly developed formulations with a reference formulation, the f_2-test (similarity factor) is one of the most commonly applied and recommended methods (FDA 1997a, 1997b, 2000). The ability to base evaluations of similarity of dissolution profiles on one calculated value is regarded as the main advantage of this method (Yuksel N. et al. 2000). In the present study this methodology was applied to examine the impact of various parameters on the dissolution performance of selected formulations.

Similarity factors (f_2) of compared dissolution profiles were calculated according to Eq. 3.3.2, in which n represents the number of samples per test, R_1 and R_2 the single values of released drug [%] at time point t for formulation 1 and 2, log abbreviates the logarithm to the base 10 and Σ the summation of values obtained for all time points.

$$f_2 = 50 \log\left\{\left(1+\frac{1}{n}\sum_{t=1}^{n}(R_1 - R_2)^2\right)^{-0.5} x\,100\right\} \qquad (3.3.2)$$

A value of f_2=100 indicates identical dissolution profiles. The similarity limit for mean difference at all time points was set to 10% by the FDA resulting in $50 \leq f2 \leq 100$ for similar dissolution profiles. Additionally, FDA requires a minimum of 12 samples per time point. In this work, the FDA requirements for performing f_2 tests were not fulfilled due to the insufficient number (n<12) of units tested per dissolution curve. However, all experiments were performed at least in triplicate. According to the FDA, only one time point at which drug release exceeds 85% may be included in the calculation. This criterion was fulfilled in all tests.

The lack of consideration of the shape of dissolution curves and the potentially unbalanced selection of time points used for calculation of f_2 values are regarded as the main weaknesses of f_2-testing. A model-independent method was therefore used in addition to the f_2-test to evaluate the similarity of dissolution profiles. An alternative method recommended for statistical comparison of dissolution profiles is the unpaired t-test. This model-independent method is capable to identify differences in level and shape (Yuksel N. et al. 2000). Unpaired t-tests were performed with SIGMASTAT® V.5.7. Selected time points and the number of tested samples are documented in their respective sections.

4 Carriers for Controlled Release Drug Delivery Systems Processed by Melt-Extrusion

4.1 Pilot Studies

4.1.1 Introduction

When evaluating a new carrier, its properties need to be evaluated with regard to processing and dosage form design. For melt extrusion processing, knowledge of (i) thermal behaviour, (ii) plasticizer requirements, (iii) suitable process temperature range and (iv) potential range of drug loading of a carrier are essential to selection of successful carriers. Additionally, selection of carriers is impacted by formulation goals, for example whether they should retard drug release rate, or conversely improve solubility.

In order to accelerate evaluation of carriers for melt extrusion technology, a scheme to test and evaluate these basic parameters for pharmaceutical excipients was developed. The first step focussed on relevant processing parameters for melt extrusion. Using a lab-scale model extruder, the behaviour of carriers during thermal treatment was examined, including characterization of thermoplastic properties, melting and viscosity of thermally treated systems. Next, the minimum processing temperature was estimated. Differential scanning calorimetry (DSC) was used to support observations made with the development-scale model extruder, as well as to determine a maximum process temperature and allow definition of suitable process temperature ranges for each carrier examined. Following these studies, additional experiments using the lab-scale model extruder were used to estimate potential drug loading ranges for each carrier tested, including identification of the maximum percentage of the carrier suitable for processing by melt extrusion. Based on these values, the need for pharmaceutical fillers, for example mannitol or lactose, to facilitate melt extrusion processing could be calculated. The feasibility of improving thermal processing through the use of plasticizers was also evaluated.

Based on these results, the suitability of pharmaceutical excipients to function as carriers processed by melt extrusion was evaluated and the process temperature range of suitable drug/ excipient loadings and the necessity of plasticizer addition established. A literature search was conducted to obtain an overview of dosage forms that have been previously manufactured using these carriers. Based on results from the experimental screening schema and literature evaluation, several carriers were selected for further investigation.

4.1.2. Materials

Table 4.1.1 lists the pharmaceutical carriers initially tested for their suitability to function as carriers in melt extrusion processes. Table 4.1.2 summarizes the model active, plasticizers and fillers used in the study.

Table 4.1.1: Pharmaceutical carriers screened for suitability for use in melt extrusion processes

Substance	Brand name	Source	Batch
Glyceroldibehenate	Compritol® Ato 888	Gattefossé (Deutschland) GmbH, Weil a. R., Germany	3022094
Hydroxypropylcellulose (HPC)	Klucel® LF Pharm	Hercules Inc. Aqualon Div., Wilmington, USA	1181
Hydroxyethylcellulose (HEC)	Natrosol® 250 HX Pharm	Hercules Inc. Aqualon Div., Wilmington, USA	Z0150
Ethylcellulose N-22 (EC)	EC® N-22	Hercules Inc. Aqualon Div., Wilmington, USA	44481
Poloxamer 188	Lutrol® F 68	BASF AG, Ludwigshafen, Germany	550003
Polyvinylpyrrolidon (PVP)	Kollidon® 30	BASF AG, Ludwigshafen, Germany	91663956O
Copovidone	Kollidon® VA64	BASF AG, Ludwigshafen, Germany	134274
Sucrose-palmitate P1570	Ryoto® Sugar Ester P1570	Mitsubishi-Kagaku Foods Corp., Tokyo, Japan	1Z258101
Sucrose-stearate S 1670	Ryoto® Sugar Ester S1670	Mitsubishi-Kagaku Foods Corp., Tokyo, Japan	29208101
Glycerolpalmitostearate	Precirol® Ato 5	Gattefossé (Deutschland) GmbH, Weil a. R., Germany	28994
Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS)	Aqoat® AS-HF	Shin-Etsu Chemical Ltd., Niigata, Japan	102005
Glyceroltrimyristate	Dynasan® 114	Sasol Germany GmbH, Witten, Germany	112152
Glyceroltristearate	Dynasan® 118	Sasol Germany GmbH, Witten, Germany	106581
Hyrdrogenated Castor Oil Type I NF	Sterotex® NF	Abitec Corp., Janesville, USA	065M3NF

Table 4.1.2: Plasticizers, fillers and actives used in melt extrusion study

Substance	Brand name	Source	Batch
Theophylline anhydrous Ph.Eur.		Roig Farma S.A., Terassa, Spain	0212030
Mannitol	Pearlitol 400DC	Roquette GmbH, Frankfurt, Germany	
Sorbitol DAB		Merck GmbH, Darmstadt, Germany	M795203

4.1.3 Equipment

Equipments used in Pilot studies are summarized in Table 4.1.3. Materials required for performance of excipients are listed in Table 4.1.4.

Table 4.1.3: Equipment used in pilot studies

Device	Source
Balance Mettler PG 503 S Balance Mettler AT21 Comparator	Mettler Toledo (Schweiz) AG, Greifensee, Switzerland
Turbula WAB T2C	W.A. Bachofen AG, Bale, Switzerland
Lab-Scale Model Extruder Haake Rheomix 610P	Thermo Electron GmbH, Karlsruhe, Germany
Actuator Haake Rheocord	Thermo Electron GmbH, Karlsruhe, Germany
Differential Scanning Calorimeter MCA 2910 TA Thermal Advantage, Version 1.1A TA Universal Analysis 2000, Version 3.9A	TA Instruments Inc., Crawley, United Kingdom
Stainless Steel Screen 1000microns	Endecotts Ltd., London, United Kingdom

Table 4.1.4: Additional materials used in experiments

Material	Batch	Material
Sealed Aluminium crucible 900 794.901+900 793.901	TA Instruments Inc., Crawley, United Kingdom	T 10807 T20109

The Haake 610P is a development-scale extruder used to predict process parameters for the larger Haake extruders. It consists of a three-part stainless steel block, each part representing an independent heating device. The block surrounds a chamber, in which two counter-rotating rotors blend or knead the bulk material (see Fig.4.1.1). The bulk material is inserted via a funnel through the inlet of the chamber. A hydraulic device closes the chamber and prevents overflow of material during the process.

A Haake Rheocord actuator drives the rotors of the development-scale model extruder via a gearbox connection. A computer system controls the actuator and lab-scale model extruder. The device enables control of process temperatures and rotation speed and monitoring of the rotor torque.

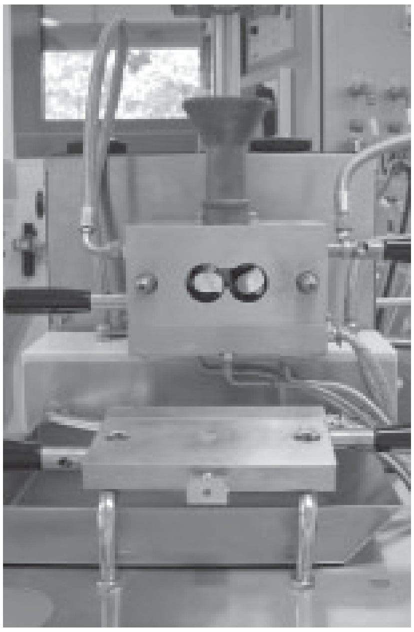


Fig. 4.1.1: Haake Rheomix 610P lab-scale model extruder

4.1.4. Methods

4.1.4.1 Process Temperature Range

It is assumed that at least one of three processes must occur in order to transform bulk powder into homogenous masses or films. The term “minimum process temperature” (MiPT) is used to describe the temperature at which melting, softening or a glass transition is first observed. It was estimated from the visual observations made during lab-scale extrusion experiments. In addition the “maximum process temperature” (MaPT) is defined as the lowest temperature at which degradation has been observed. Differential Scanning calorimetry data were used to determine MaPT.

A suitable process temperature range (*PTR*) was estimated according to (4.1.1) with *PTR* [°C] the calculated suitable process temperature range, *MiPT* [°C] the measured minimum process temperature and *MaPT* [°C] the measured maximum process temperature.

$$PTR = MaPT - MiPT \tag{4.1.1}$$

Thermal analysis of the bulk excipient with DSC was performed in sealed crucibles using accurately weighed samples of 3mg. An empty sealed crucible was used as a reference. The starting temperature was 20°C and a heating rate of 5°C/min was applied.

4.1.4.2 General Suitability for Melt Extrusion

In order to assess the general suitability of the carriers for melt extrusion, very simple formulations of each carrier with a model drug (theophylline) were prepared. By keeping the formulations as simple as possible, differences in observations could be attributed to the characteristics of the individual carrier.

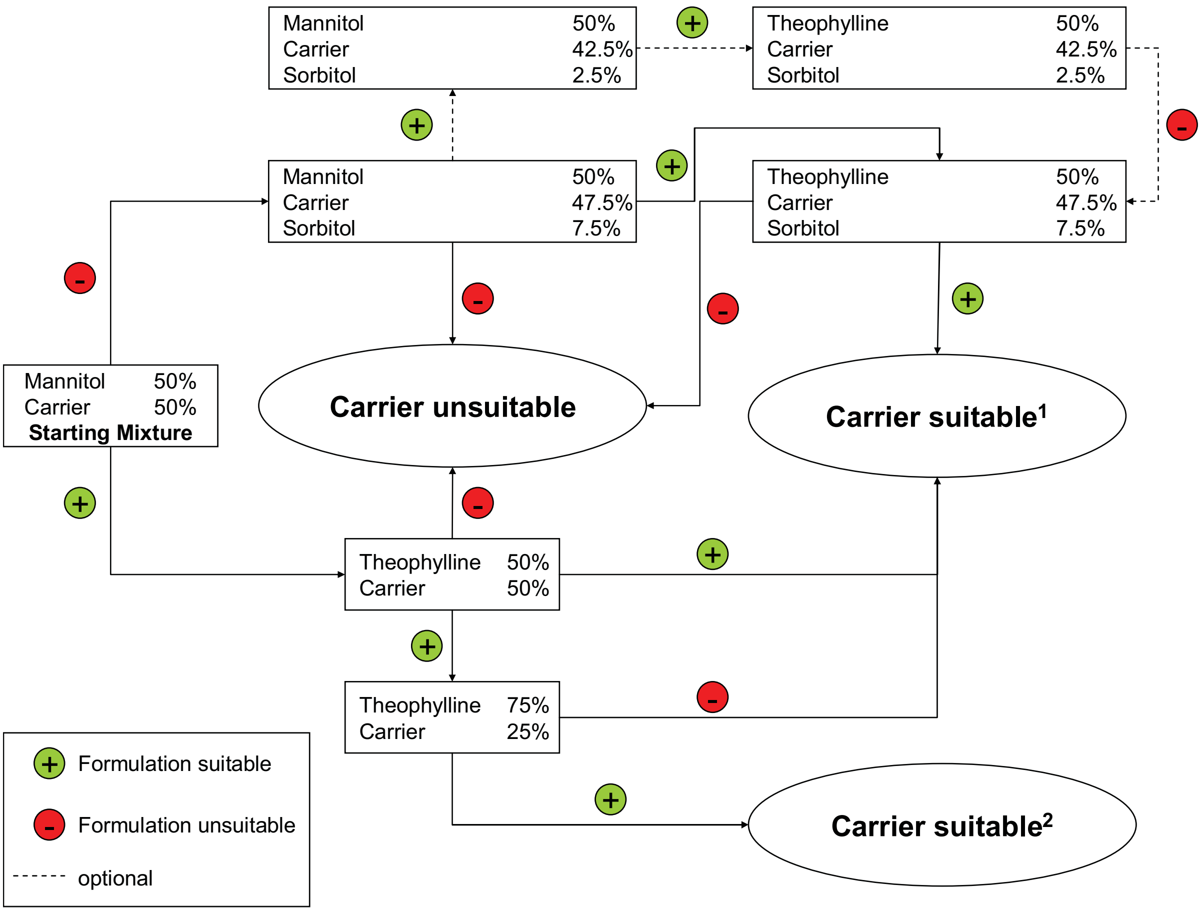
A standard procedure and decision tree (see Fig. 4.1.2) was developed and tested on the formulations. Parameters varied were carrier, drug loading and addition of plasticizer. Active and carrier were weighed accurately using a calibrated balance. Before blending, the ingredients were screened (1000 µm). Next, the ingredients were thoroughly blended for 10 min at 32rpm. If a plasticizer was added, carrier and plasticizer were blended for 10 min before adding the active, and the resulting mixture blended for a further 10 min. Initially 50/50 % [w/w] mannitol/carrier mixtures were processed. If the carrier failed to provide a homogenous mass at a 50/50 % [w/w] mannitol/ carrier ratio, addition of a plasticizer was tried. Sorbitol was chosen as an example of a solid plasticizer (Kibbe A.H. (2000)). The carrier was categorized as “unsuitable for melt extrusion processes” if the carrier still failed to provide a homogenous mass after addition of the plasticizer.
If results were positive, 50/50 % [w/w] theophylline/ carrier mixtures were then tested. Theophylline anhydrous was used as the model active due to its high melting point (270-274ºC) and good thermal stability. It was assumed that theophylline did not contribute to any physical change during processing and hence any changes observed were attributable to the carrier.

Processed materials were visually examined through the inlet of the lab-scale model extruder. The process was continued until a consistent, homogenous mass or dispersion was gained or, alternatively, until a failure was observed e.g. degradation of one of the excipients or blocked rotors.

The feasibility of increasing drug loading was tested with 75/25 % [w/w] theophylline/ carrier mixtures. In a further series, the process temperature was increased sequentially in steps of 5°C, starting from 20ºC. The lowest temperature at which a consistent mass or dispersion was achieved was deemed to be suitable for further melt extrusion experiments.

Rotation speed of the counter-rotating rotors was set at 20 rpm. In case of a visible segregation of the solid drug and the semisolid or liquid excipient, the rotation speed was increased. The maximum value used was 40rpm for glyceroldibehenate (Compritol® Ato 888).

Carriers were considered potentially suitable for melt extrusion if homogenous masses or dispersions were successfully obtained from the formulations tested.



[1] up to 50/50 [%w/w drug/carrier] [2] up to 75% [%w/w drug/carrier]

Fig. 4.1.2: Standard procedure and decision tree for assessment of formulation suitability for melt extrusion

4.1.5. Results

Excipients were compared with respect to their ability to act as carriers in the melt extrusion processes (see 4.2.5.1), process temperature range (see 4.2.5.2) and expected drug release properties (see 4.2.5.3.).

4.1.5.1 Suitability for Melt Extrusion Processes

Table 4.1.5 summarizes drug loading achieved and whether or not a plasticizer was required. HPC and GDB could be processed up to 60 % and 65 % [w/w] drug, respectively. Most of the other carriers tested could sustain up to 50 % [w/w] drug loading. Only EC fell short of this goal, with a maximum drug loading of 40 % [w/w] drug.

Table 4.1.5: Suitability of excipients for melt extrusion processes

Substance	Maximum Drug Load [%w/w]	Plasticizer required
EC	40	Yes (TEC)
Glycerylpalmitostearate	50	No
Glyceryltrimyristate	50	No
Glyceryltristearate	50	No
HPMCAS	50	7.5% Sorbitol
Hydrogenated Vegetable Oil Type I NF	50	No
Poloxamer 188	50	No
PVP	50	Yes (TEC)
Sucrose-palmitate P 1570	50	No
Sucrose-stearate S 1670	50	No
HPC	60	7.5% Sorbitol
Glyceryldibehenate	65	No
HEC	-	-

HEC proved unsuitable for melt extrusion processes as phase separation occurred in all combinations tested, possibly due to the inability of the softened particles to form inter-particle bonds strong enough to form a coherent matrix.

Some materials (HPC, EC, PVP, HPMCAS) required addition of plasticizers to improve the physical properties of the obtained systems. Plasticizers are widely applied for preparation of pharmaceutical dosage forms, especially in film coating processes. Although plasticizers are usually high boiling liquids which lower the processing temperature of polymers, some solid pharmaceutical excipients can also be used to achieve this effect. A drawback with the use of plastcizers is that they can enhance the potential for chemical interactions. Sorbitol proved suitable for processing of HPC and HPMCAS, but was not appropiate for EC formulations, due to its poor miscibility with the molten excipient. In this case another plasticizer, triethylcitrate (TEC), performed adequately.

All other materials tested were suitable for processing in the lab-scale model extruder without addition of plasticizers. Most of these excipients are derived from the chemical class of lipids (Glyceryltrimyristate, Glyceryltristearate, Glyceryldibehenate, Glycerylpalmitostearate, Hydrogenated Vegetable Oil Type I NF), but some polymers also showed suitable thermoplastic properties (Sucrose-palmitate P1570, Sucrose-stearate S 1670, Poloxamer 188).

4.1.5.2 Process Temperature

The general applicability of an excipient as a fusible binder in melt extrusion processes is closely linked to its minimum process temperature (MiPT), the temperature at which the excipient starts to form inter-particle bonds and form homogenous masses. As a prerequisite to the compatibility of an excipient with an active during processing, the excipient must form a homogenous mass below the minimum degradation temperature of the active. Since accelerated degradation of compounds often occurs at temperatures above the melting point of the compound, the minimum process temperature is preferably below the melting point of the compound. As the melting point of most actives ranges between 80°C and 200°C, a minimum process temperature between 50°C and 100°C would offer the greatest versatility with respect to the range of actives that could be incorporated.

All materials tested had minimum process temperatures below the melting point of the model drug, theophylline. Indeed, most carriers showed minimum process temperatures between 45°C and 135°C. Sucrose-fatty acid-esters (Sucrose-Palmitate S1570) showed the lowest minimum process temperatures (45°C). HPMCAS and Ethylcellulose had the highest (estimated) minimum process temperatures of 135°C and 150°C, respectively.

The minimum processing temperature also influences the physical stability of the dosage form. At low minimum process temperature, softening or melting of the dosage form occurs at or near ambient temperatures. According to the ICH guidance Q1A(R2) (ICH 2003), stability tests for new drug products should be performed at several temperature/ humidity conditions, including e.g. 40°C/75%rh. Therefore a MiPT below or near 40°C is regarded as likely to lead to physical instability of dosage forms under ICH storage conditions and therefore be less suitable for matrix tablets. All materials examined provided MiPTs above 40°C, although sucrose-palmitate P 1570 showed a minimum process temperature of only about 45°C. Therefore its use alone as a carrier for solid dosage forms is not recommended, although in combination with other excipients it could still be an option.

Not only the minimum process temperature (MiPT), but also maximum process temperature (MaPT) of carriers is of interest. Determination of the MaPT for each carrier provides a parameter to compare the flexibility of carriers with regard to process temperature. It is especially relevant to the manufacture of solid dispersions by melt extrusion, in which the drug is usually molten during processing. For this process the carrier must be thermally stable at temperatures at and slightly above the melting point of the drug. Hence, carrier MaPT can be compared with the drug melting point to give some indication of drug/ carrier compatibility during melt extrusion.

Table 4.1.6 summarizes the carriers examined in ascending order of their minimum and maximum process temperature.

Table 4.1.6: Excipients and process temperatures

Excipient	**Minimum Process Temperature [°C]**	**Maximum Process Temperature [°C]**
Sucrose-Palmitate P1570	45	>200
Poloxamer 188	50	>200
Glyceryltrimyristate	55	>200
Glycerolpalmitostearate	55	>200
Hydrogenated Vegetable Oil Type I NF	60	>200
Sucrose-Stearate S1670	60	≤190
Glyceryltristearate	70	>200
Glyceroldibehenate	70	>200
HPC	125	≤180
PVP	125	>200
HPMCAS	135	≤180
EC	150	>200
HEC	-	>200

4.1.5.3 Release Properties

Studies in the public domain were examined to clarify the release properties of dosage forms containing the carriers of interest. The cited publications examined formulations in which just one excipient determined drug release. Since drug release can also be affected by choice of dosage form, model drug, share of excipient, surface and crystallinity, etc., direct comparison of the release properties of the various carriers was not feasible. Instead, formulations were classified in three categories: Immediate Release (IR), Modified Release (MR) and Enteric Release (ER).

The release properties of the carriers ranged from immediate to slow, controlled release. Poloxamer188 and PVP have been reported as matrix systems for immediate release dosage forms (Vippagunta S.R., et al. (2002); Vaugelade et al. (2001)). The potential of Poloxamer 188 to function as a surfactant and the hydrophilicity of PVP result in improved solubility and bioavailability of poorly soluble drugs. As the current work was focussed on MR dosage forms, PVP and Poloxamer188 were not considered for further studies.

For all other carriers considered, the open literature provided evidence that drug release could be slowed down by the respective carrier. Using sucrose-fatty acid esters as matrix forming agents AWD Pharma (2001) patented matrix tablets prepared from melt granulates. They achieved modified drug release of drugs such as nifedipine, carbamazepine and calciumvalproate dihydrate. Release rates varied between 80% at 90min and 80% at >1200min, depending on the HLB value of the sucrose-fatty acid-ester. Similarly, Crowley M.M., et al. (2004) described the drug release properties from matrix tablets containing different grades of ethylcellulose (EC). Data indicated a deceleration of drug release with decreasing particle size of EC: 80% of the model drug, guaifenisin, was released within 1h at 80-325mesh, but only after 4h at 30-80mesh. Further, the influence of processing technique on drug release was investigated. Drug release from melt extruded EC matrix tablets released the drug more slowly than matrix tablets prepared by direct compression. For example, melt extruded tablets released 60% of the drug within 11h, while directly compressed formulations released 60% within 1h. Other cellulose derivates, such as HPMC and HEC can also modify release. Vueba M.L., et al. (2004) modified release of ketoprofen from HPMC based matrix tablets, with 60-80% of the drug released within 20h, depending on the HPMC grade used. Roy D.S., et al. (2002) described the release kinetics of HEC based matrix tablets containing chlorpheniramine maleate. About 60% of the chlorpheniramine maleate was released within 7h by an anomalous release mechanism.

Lipophilic carriers, such as GTS, GDB, GPS and hydrogenated vegetable oil, have been reported to modify drug release from matrix tablets. El-Sayed G., et al. (1997) reported drug release from GTS based wax matrices to release salbutamol as slowly as 20% within 480min. Similarly, Obaidat A.A., et al. (2001) modified tramadol HCl release using GBD matrices prepared by direct compression. In this case modification of drug release could be achieved by variation in drug loading. Martini L.G., et al. (2000)) achieved comparable drug release from matrices consisting of hydrogenated vegetable oil.

Due to its acidic function, gastroresistant or enteric drug release is expected from HPMCAS based formulations. Accordingly, Tanno F., et al. (2004) reported fast drug release from HPMCAS-based solid dispersions at pH 6.8.

In summary, the literature evidence suggested that most, but not all, of the carriers in Table 4.1.1 could be applied to slow down the release of actives using a hot-melt extrusion process.

4.1.5.4 General Applicability of Excipients for Melt Extrusion

The carriers under consideration were ranked according to their general applicability for melt extrusion. Evaluation of general suitability was based on the four criteria previously discussed. The suitability of excipients to function as a carrier in melt extrusion processes is naturally the first and most important criterion. Second, the capability of an excipient to control drug release was compared, with ability to slow drug release being a crucial requirement for application to MR formulations. Carriers for IR applications were thus ranked at the bottom, not reflecting their technical suitability for melt extrusion, e.g. Poloxamer 188 and PVP. Third, the MiPT was considered important to minimize thermal degradation of actives, while not jeopardizing performance in stability studies. Finally, a large difference between MiPT and MaPT offers more flexibility in terms of processing temperature, e.g. if the active has a higher melting point. Comparison of these parameters resulted in the ranking displayed in Table 4.1.7.

Table 4.1.7: Ranking of carriers according to their general applicability for melt extrusion processes

Substance	Suitability for Melt-Extrusion [Y/N]	Release Pattern	MiPT [°C]	MaPT [°C]
Glyceryldibehenate	Y	MR	70	>200
Glyceryltristearate	Y	MR	70	>200
Hydrogenated Vegetable Oil Type I NF	Y	MR	60	>200
Sucrose-stearate S 1670	Y	MR	60	≤190
Glyceryltrimyristate	Y	MR	55	>200
Glycerylpalmitostearate	Y	MR	55	>200
HPC	Y	MR	125	≤180
HPMCAS	Y	ER	135	≤180
EC	Y	MR	150	>200
Sucrose-palmitate P 1570	Y	MR	45	>200
Poloxamer 188	Y	IR	50	>200
PVP	Y	IR	125	>200
HEC	N	MR	-	>200

4.1.6 Selection of Carrier Candidates for Further Studies

The present study addresses three major properties of carriers influencing their general applicability for melt extrusion processes: suitability of behaviour upon thermal treatment, suitable process temperature and drug release properties. Thirteen different established or novel pharmaceutical carriers were examined and ranked according to these parameters. Of these, four carriers were selected for further studies.

Lipid carriers were superior with regard to low melting point, potential for high drug loading and high thermal stability. Glycerylpalmitostearate was chosen as an example of a low melting carrier (50-57°C), since it advantageous over other low MiPT lipid carriers in terms of material availability and pricing. In addition, glyceryldibehenate was selected due to its appropriate characteristics for melt extrusion - with a MiPT of 69°C-74°C, expected drug loading up to 65% [w/w] and high thermal stability above 200°C. In contrast to other lipid carriers tested, the long fatty acid chain of GDB hinders digestion by lipases. The decreased affinity to lipase is potentially advantageous for the robustness of dissolution in-vivo.

Sucrose-stearate S 1670 was selected for further examinations as it has a low MiPT (49°C-56°C) coupled with high chemical stability at high temperatures (>200°C) and has not previously been applied as a melt extrusion carrier.

HPC was selected for subsequent investigations as an example of a hydrophilic material. HPC represents the class of hydrophilic cellulose derivates, which are widely used in MR dosage form technology. In contrast to other cellulose derivatives it offered the lowest MiPT coupled with the highest PTR. A potential drawback of HPC is the need to use a plasticizing agent in order to provide suitable processing characteristics.

4.2 Melt-Extrusion Processing

4.2.1 Introduction

The melt extrusion processing properties of the four chosen carriers were then tested on a larger scale. This chapter focuses on the reproducibility and predictability of process parameters, such as process temperatures, rotation speed and screw design for each of the selected carriers. Furthermore, the impact of drug loading on dependent and independent process parameters was examined. Finally the influence of processing on drug crystallinity was addressed. Comparison of the results was used to help discriminate among the excipients in terms of suitability for production of MR matrix dosage forms.

4.2.2 Materials

The four carriers selected from the pilot study (see chapter 4.1.6) were glycerylpalmitostearate (GPS), glyceryldibehenate (GDB), sucrose stearate S1670 (SUS) and hydroxypropylcellulose (HPC). Theophylline was used as a model drug and sorbitol as a plasticizer for HPC formulations. Table 4.2.1 summarizes the carriers, their brands, suppliers and batch numbers used for the study.

Table 4.2.1: Materials for melt extrusion processes

Substance	Brand	Source	Batch
Glyceryldibehenate	Compritol® Ato 888	Gattefossé (Deutschland) GmbH, Weil a. R., Germany	3022094
Hydroxypropylcellulose (HPC)	Klucel® LF Pharm	Hercules Inc. Aqualon Div., Wilmington, USA	1181
Sucrose-stearate S 1670	Ryoto® Sugar Ester S1670	Mitsubishi-Kagaku Foods Corp., Tokyo, Japan	29208101
Glycerylpalmitostearate	Precirol® Ato 5	Gattefossé (Deutschland) GmbH, Weil a. R., Germany	28994
Theophylline anhydrous Ph.Eur.		Roig Farma S.A., Terassa, Spain	0212030
Sorbitol DAB		Merck GmbH, Darmstadt, Germany	M795203

4.2.3 Equipment

Table 4.2.2 lists the equipment used in preparation of powder blends, melt extrusion processes and characterization of powder blends and granulates.

Table 4.2.2: Equipment used for melt extrusion processes

Device	Source
Balance Mettler PM 15k	Mettler Toledo GmbH, Giessen, Germany
Turbula WAB T10B	W.A. Bachofen AG, Bale, Switzerland
Extruder Haake Rheomex PTW 16/25	Thermo Electron GmbH, Karlsruhe, Germany
Actuator Haake Rheocord	Thermo Electron GmbH, Karlsruhe, Germany
Thermostat Haake DC30	Thermo Electron GmbH, Karlsruhe, Germany
Gravimetric Dosage Unit K-CL-20	K-Tron (Switzerland) AG, Niederlenz, Switzerland
Stainless Steel Screen 1000microns	Endecotts Ltd., London, United Kingdom
X-Ray Diffractometer D4	Bruker-AXS Ltd., Madison, Wisconsin, USA

4.2.4 Methods

4.2.4.1 Preparation of Blends

Active and excipient were weighed accurately using a calibrated balance. Ingredients were screened (1000microns) and then blended for 10 min at 32 rpm. If a plasticizer was used, the carrier and plasticizer were first blended for 10 min, then the drug was added and the mixture blended for a further 10 min. In total 1000 g of each blend was manufactured.

4.2.4.2 Formulations

In order to examine the impact of changes in formulation on the performance and process parameters, blends containing 25%, 50% and 75% [w/w] of active were prepared (n=3 per percentage). In preliminary studies, different concentrations of plasticizer (sorbitol) were tested for the HPC formulations with a drug-matrix ratio of 1:1. Sorbitol amounts ranging from 2.5% to 7.5% [w/w] of the formulation were successfully incorporated into HPC extrudates. No difference in appearance was observed. Hence a sorbitol concentration of 2.5% was used for all HPC formulations. Table 4.2.3 summarizes the compositions of all formulations tested.

Table 4.2.3: Composition of formulations tested

Formulation	Theophylline [%]	Glyceryl-dibehenate [%]	Glycerylpalmito-stearate[%]	Sucrose-stearate [%]	HPC [%]	Sorbitol [%]
GDB25	25	75		-		
GDB50	50	50				
GDB75	75	25				
GPS25	25		75			
GPS50	50		50			
GPS75	75		25			
SUS25	25			75		
SUS50	50			50		
SUS75	75			25		
HPC25	25				71.25	3.75
HPC50	50				47.5	2.5
HPC75	75				23.75	1.25

4.2.4.3 Melt Extrusion Process

The powder blend was transferred into the gravimetric delivery system consisting of a balance and force feeder, from which the powder was transferred via the force feeder into the barrel of the extruder. A rotation speed of 20 rpm was found to be suitable for the force feeder. In the beginning the feed rate was set to 10 g/min and then modified if necessary to obtain a reasonable material output. The feed rate and rotation speed of the force feeder were set and monitored externally by an electronic device. In order to avoid melting and blockage of the force feeder near the powder inlet, the force feeder was cooled to 20°C using a thermostat.

For the design of the twin-screw extruder see Fig. 4.2.1. The barrel consisted of four independently heated sections (I-IV) and contained two co-rotating screws. At the outlet of the barrel a 1 mm x 22 mm sheet ribbon die was mounted, which was heated separately (V+VI). The material was extruded onto a slowly moving conveyor belt and allowed to cool and solidify.

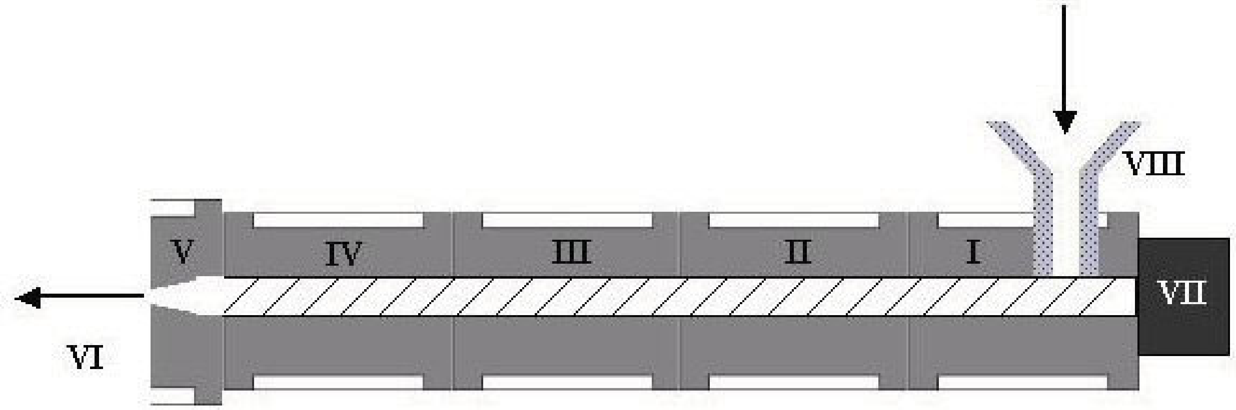


Fig. 4.2.1: Design of twin-screw-extruder; I-V): heating sections (I-IV barrel, V die); VI) 1x22 mm sheet ribbon die; VII) actuator; VIII) cooled inlet

Two screw designs were used, which will be subsequently referred to as screw design No.1 and screw design No.2. The dimensions of both screw designs were 1.6 cm in diameter and 40.0 cm in length. Fig. 4.2.2a shows screw design No.1. It consisted of feeding elements only and was used as the standard screw design. Fig. 4.2.2b shows screw design No.2, which consisted of three feeding and two kneading zones. When screw design No.1 proved unsuitable for a given composition, screw design No.2 was implemented.

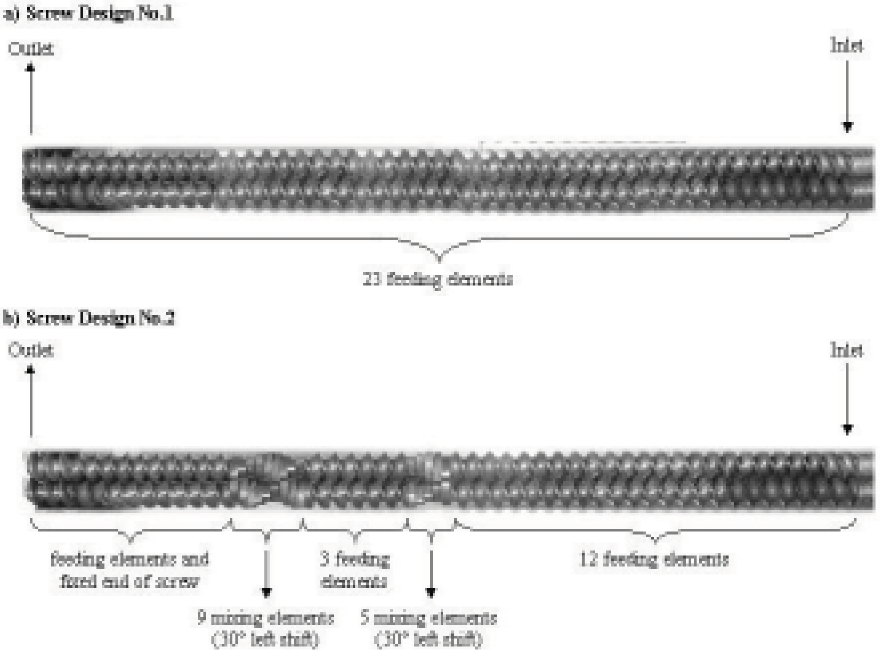


Fig. 4.2.2: a) Screw design No.1 and b) Screw design No.2

Process temperatures were derived from pilot studies and adjusted if necessary, e.g. to avoid blockage of the die. Mean process parameters were recorded when the process was at steady state and no further adjustments in feed rate, rotation speed and temperature were required. Fig. 4.2.3 shows an example of a steady state process. Mean values were calculated from the records made by the control device. The specific mechanical energy (*SME*) was used to compare the mechanical energy input necessary to obtain visually homogenous extrudates (Van Lengerich (1990)). The *SME* for each batch was calculated according to Eq. 4.2.1, where *SME* is the specific mechanical energy [J/g], M is the mean observed torque during steady state [Nm], υ is the rotation speed of the screws [min^{-1}] and f is the feed rate [g/min].

$$SME = \frac{M * rad(\upsilon)}{f} \tag{4.2.1}$$

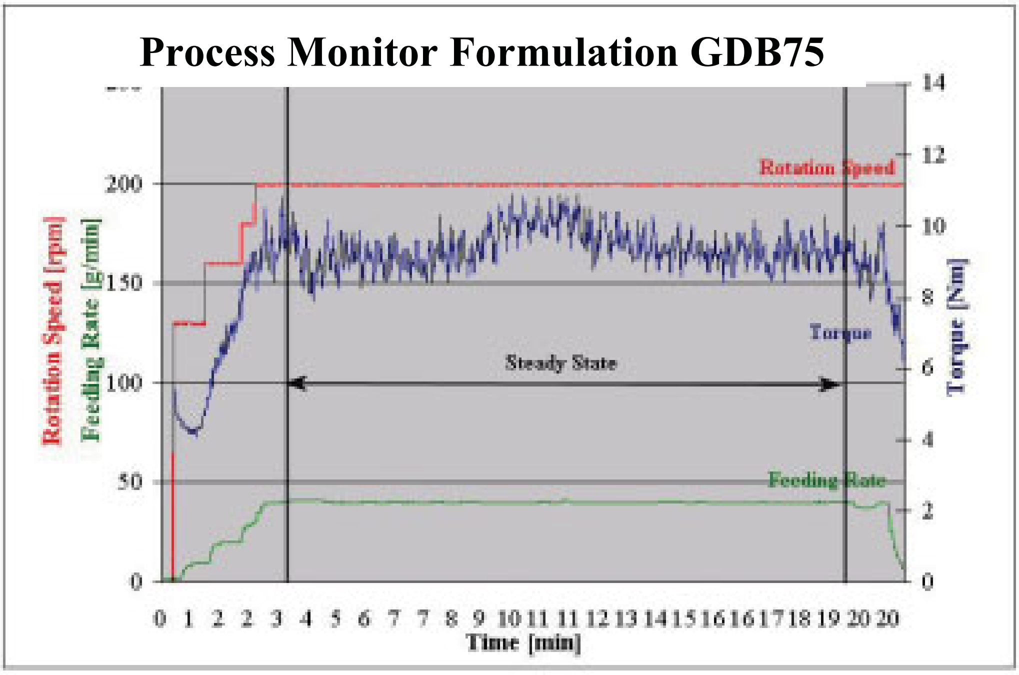


Fig. 4.2.3: Process monitor (formulation GDB75), steady-state section

4.2.4.4 X-Ray Diffraction

The powder X-ray diffraction (PXRD) pattern was determined using a powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. The sample was prepared for analysis by packing the powder into a 12 mm diameter, 0.25 mm deep cavity cut into a silicon wafer specimen mount. The specimen was rotated whilst being irradiated with copper K-alpha$_1$ Xrays (wavelength = 1.5406 Ångstroms) with the X-ray tube operated at 40 kV/ 40 mA. The analyses were performed with the goniometer running in continuous mode set for a 5 second count per 0.02° step over a two theta range of 2° to 40°.

PXRD was used to examine differences in drug crystallinity across the prepared granulates. To assess the impact of melt extrusion/ granulation, diffractograms of the precursor powders were also recorded. Differences between extrudates were used to assess the impact of changes in the mechanism of mixing (screw design) and magnitude of mixing (rotation speed, residence time).

4.2.5 Results and Discussion

4.2.5.1 Formulation Design for Melt-Extrusion Process

For all excipients and drug-carrier ratios (1:3, 1:1 and 3:1) tested, it was possible to perform melt extrusion. Some formulations required adjustment of process parameters such as process temperature (see chapter 4.2.5.2) or screw design and rotation speed (see chapter 4.2.5.3). In all cases, an extrudate of uniform and ribbon appearance, without visible powder residues, could be achieved.

4.2.5.2 Process Temperatures

The process temperatures predicted from the pilot experiments proved suitable for processing most of the formulations into uniform melt-extrudates. Table 4.2.4 summarizes process temperatures from the pilot study and in the 1kg melt extrusion process. For 1kg batches, the set segment process temperatures (n=3) that proved suitable for extruding the formulation are indicated.

Only the glyceryldibehenate formulations GDB25 and GDB50 required a decreased process temperature. This was due to the low viscosity of the melt at low drug loadings (25% [w/w]). An increase in viscosity was necessary to inhibit segregation, which had resulted in blockage. In addition, lower material temperatures accelerated solidification of extrudates, resulting in improved granulation properties. By contrast, formulation SUS75 required an increased process temperature. This was necessary to lower torque during processing and hence prevent blockage of the screws.

Table 4.2.4: Predicted and effective process temperatures for melt extrusion

Formulation	Matrix	Process Temperature Pilot Study [°C]	Process Temperature Melt-Extrusion [°C] I	II	III	IV	V
GDB25	Glyceryldibehenate	80	49	80	65	65	68
GDB50	Glyceryldibehenate		75	70	70	70	70
GDB75	Glyceryldibehenate		80	85	85	85	90
GPS25	Glycerylpalmitostearate	55	39	57	52	52	52
GPS50	Glycerylpalmitostearate		39	57	52	52	52
GPS75	Glycerylpalmitostearate		55	53	53	53	54
SUS25	Sucrose-stearate S1670	60	64	60	60	60	60
SUS50	Sucrose-stearate S1670		50	60	60	60	64
SUS75	Sucrose-stearate S1670		70	75	85	80	85
HPC25	HPC/ Sorbitol	125	128	125	125	125	125
HPC50	HPC/ Sorbitol		128	125	125	125	125
HPC75	HPC/ Sorbitol		128	125	125	125	128

Melt extrusion of the 1kg batches confirmed the feasibility of processing various (binary) mixtures of the four carriers with theophylline to obtain matrix systems. The predicted process temperatures were generally suitable, however, in some cases other parameters relevant to successful processing such as screw setup necessitated minor adjustments in temperature to process the formulations successfully.

Depending on the design of the extruder, die and powder inlet may require special temperature adjustments or additional devices, such as inlet cooling to prevent melting of substance in the inlet or blockage of the die. In order to avoid blockage of the force feeder by molten material close to the inlet of the extruder, the first segment of the extruder was run at a lower process temperature in some cases (GDB25, GDB50, GDB75, GPS25, GPS50). As an alternative approach, the force feeder was cooled with a thermostat (GPS75, SUS25, SUS50, SUS75, HPC25, HPC50, HPC75). The potential effect on drug crystallinity of these variations will be discussed later (see chapter 4.2.5.4).

Process reproducibility (n≥3) was generally acceptable with fixed independent process parameters, although high standard deviations for SME were obtained. Keeping independent process parameters, such as process temperature, feed rate and rotation speed, constant proved to be straightforward, as these parameters were electronically monitored and adjusted. Dependent parameters such as torque and SME had to be measured, with post hoc evaluation of reproducibility. In order to improve reproducibility, constant monitoring and adjustment was required, especially with respect to feed rates. Some dependent parameters proved very reproducible, e.g. formulation GPS50 showed a mean torque of 5.8Nm ±0.12Nm. In other cases, standard deviations were high, e.g. a mean torque of 20 Nm ±6.8 (= 34%!) was observed for formulation GDB25. The importance of variation in SME and torque with respect to the dissolution performance and reproducibility of formulations is discussed in Chapter 5.

4.2.5.3 Process Parameters (Screw Design, Rotation Speed, Feeding Rate, Torque)

Results indicated that screw design No.1 was suitable for processing of 25% and 50% drug loading blends in order to obtain visually homogenous systems. In contrast, 75% drug loading blends required the use of screw design No.2, with the exception of formulation SUS75. Table 4.2.5 summarizes the following process parameters: selected screw design, mean rotation speed of screws, mean feeding rate, mean torque and mean SME (n≥3).

Table 4.2.5: Screw design, mean rotation speed (±sd), mean feeding rate (±sd) and mean torque (±sd) for melt extrusion processes under steady state of process conditions

Formulation	Matrix	Screw Design No.	Rotation Speed [rpm]	Feed Rate [g/min]	Mean Torque [Nm]	SME [J/g]
GDB25	Glyceryldi-behenate	1	48 (±2.8)	38 (±3.7)	20 (±6.8)	160 (±50)
GDB50		1	100 (±0.0093)	40 (±16)	5.2 (±2.3)	78 (±9.4)
GDB75		2	200 (±0.014)	38 (±3.3)	8.6 (±0.72)	288 (±33)
GPS25	Glycerylpalmito-stearate	1	70.0 (±0.0017)	40 (±0.039)	5.6 (±0.75)	61 (±8.3)
GPS50		1	90 (±0.26)	40 (±0.34)	5.8 (±0.12)	81 (±2.2)
GPS75		2	200 (±0.026)	50 (±0.23)	18 (±1.9)	466 (±47)
SUS25	Sucrose-stearate	1	100 (±0.0057)	40 (±0.15)	17 (±1.5)	268 (±23)
SUS50		1	73 (±5.6)	20 (±0.17)	13 (±3.1)	296 (±49)
SUS75		1	60 (±0.18)	30 (±0.94)	36 (±4.1)	451 (±41)
HPC25	HPC/ Sorbitol	1	100 (±0.0072)	40 (±0.85)	9.0 (±1.1)	140 (±20)
HPC50		1	100 (±0.012)	40 (±0.018)	15 (±0.46)	232 (±7.2)
HPC75		2	200 (±0.0014)	30 (±0.27)	72 (±4.6)	3033 (±213)

During melt extrusion the binary theophylline matrix systems consist of a solid inner phase (theophylline particles) and a semisolid or liquid outer phase (molten binder). In order to move material inside the extruder barrel, friction between theophylline particles has to be overcome. This friction rises with increasing theophylline load. The dynamic viscosity of the intermediate matrix system rises with increasing drug loading and more energy input is required to push the material through the extruders. In the case of melt-extrusion both mechanical and thermal energies are applied during processing, but in the present study the process temperatures were minimized to prevent thermal degradation of drug and excipient. Therefore, mechanical energy was the main parameter adjusted to optimise processing of the binary mixtures. The specific mechanical energy (SME) was used as a measure of energy input during melt extrusion. Van Lengerich (1990) showed that the SME is increased by either increasing the rotation speed or decreasing the feed rate, with both being independent process parameters. An increase in torque also increases the energy input, but this process parameter is dependent on the others.

In the current studies, SME rose with increasing drug loading, confirming the requirement of increased energy input with increasing drug ratio. Only formulation GDB50 deviated from this observation. In this case the higher process temperatures increased the thermal energy input, resulting in a reduced viscosity of the system compared to GDB25. Thus, less mechanical energy was required for processing.

Shear stress and SME were increased in three different ways. In some cases, accelerated screw rotation provided an increase in SME. For glycerylpalmitostearate an increase in drug loading from 25% (GPS25) to 50% (GPS50) required a higher rotation speed for successful processing. The higher SME was due to increased rotation speed alone: torque and process temperature remained at comparable levels. In other cases, the viscosity of materials increased with increased drug loading, in turn increasing the resistance to screw rotation and hence the torque required. This led to a greater power consumption. Using sucrose-stearate formulations as an example, SME rose and the rotation speed of screws decreased at higher drug loading, indicating that an increase in power consumption of the engine was necessary to overcome the increased viscosity. For a third group, replacement of feeding elements by kneading, mixing or back feeding sections was used to further increase shear stress, energy input and residence time. In the present study, screw design No.2 employed kneading elements and was therefore suitable for processing high drug loading formulations, e.g. for formulation HPC75. In this case, the increased residence time also improved initial homogenization and stability of the intermediate suspension as well as preventing segregation. Screw design No.1 also proved unsuitable for processing formulations GDB75 and GPS75. Segregation of components was observed and solid particles blocked the die. Enforced screw rotation did not resolve this observation. Instead, a combination of the three approaches was needed for successful processing of HPC75, GDB75 and GPS75. This behaviour is typical of formulations which exhibit shear thinning behaviour. Li. P.X., et al (2003) also hypothesized shear thinning for behaviour for corn starch formulations, since torque decreased at higher rotation speeds.

In contrast to the GDB, GPS and HPC formulations, processing of SUS formulations using accelerated screw rotation or screw design No.2 was unsuitable due to blockage of the screws or exceedingly high torque (>300Nm). These observations suggested shear thickening behaviour of SUS formulations. This hypothesis was supported by the requirement of reduced rotation speed, simple screw design and increased process temperatures (see chapter 4.2.5.4) with increasing drug ratio.

Prediction of process parameters from the pilot study had only taken process temperature into account and neglected other potentially important parameters such as rotation speed and screw design. From the discussion above, it is apparent that the screw design and rotation speed are essential parameters to prediction of suitability for large scale processing. Predictions of these effects can be based on the rheological properties of the carrier as a function of shear and temperature.

These examples underline the complexity of melt extrusion processes, but also indicate their flexibility to adapt to the specific requirements of a given formulation. Theoretically a lack of thermal stability can be compensated for by appropriate choice of carrier systems and enhanced mechanical input enabling a reduction of process temperature. Vice versa an increase in process temperatures can be used to reduce mechanical stress during processing. However, the impact of major changes in SME or process temperature on the structure of the obtained products should be considered. Nakamichi K., et al. (2002) showed supersaturation of solid dispersions of nifedipine in hydroxypropylmethylcellulose phthalate (HPMCP) when applying kneading elements in extrusion processes. This led to changes in appearance, crystallinity of the drug and dissolution performance of the formulation. Yoshinaga M., et al. (2000) observed similar effects when increased residence times and increased shear forces were applied during the process. With an increase of process temperature, the melting point of the compound may be exceeded and cause a structural change of the extrudate, i.e. formation of solid dispersion, amorphous drug or polymorph during cooling. On the other hand excessive mechanical stress may cause a decrease in particle size or change distribution of the compound within the extrudate. Hence, the adjustment of these parameters - though critical to develop a suitable process - is restricted by the effects on the subsequent characteristics and performance of the extrudates.

4.2.5.4 Effects of Process Parameters on Crystallinity of the Drug

With theophylline having a melting point of 270-274°C, the applied process temperatures ranging between 39°C and 128°C are too low to melt the drug and cause formation of amorphous state. Additionally, theophylline has little tendency to polymorphism, as described in chapter 2.1.

The X-ray diffractograms (Fig. 4.2.4-4.2.7) indicate that theophylline remained crystalline in all formulations. For formulations GDB50, GPS50 and HPC50, crystallinity can be interpolated. It is clear that an increase in SME does not transform theophylline into an amorphous state within the range of parameters examined.

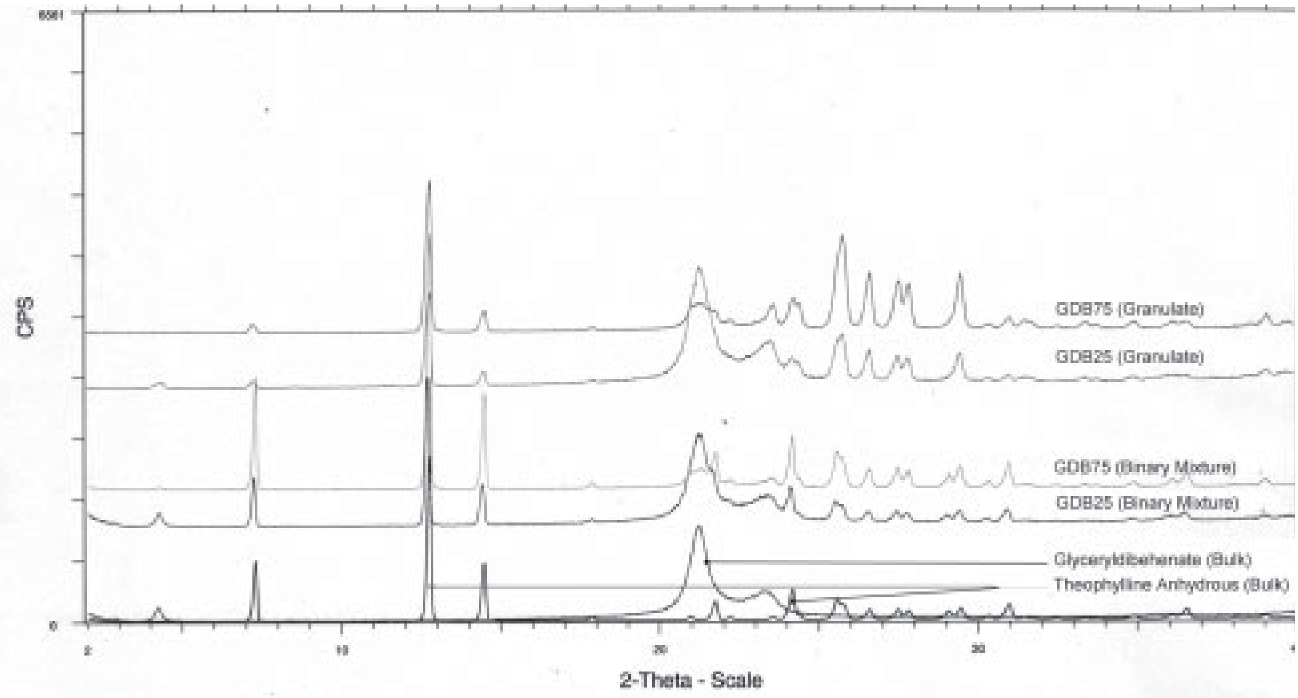


Fig. 4.2.4: Powder-X-Ray diffractograms of anhydrous theophylline, glyceryldibehenate, their unprocessed binary mixtures and the granulates obtained after melt extrusion (Formulations GDB25 and GDB75)

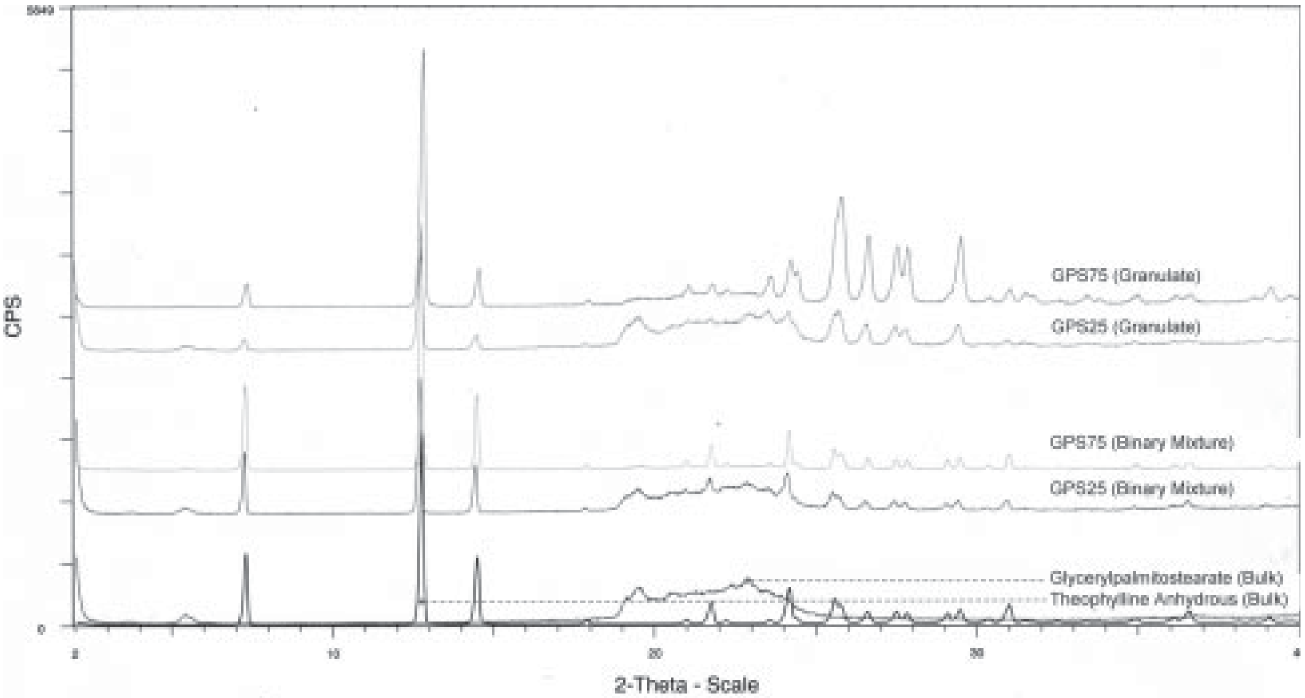


Fig. 4.2.5: Powder-X-Ray diffractograms of anhydrous theophylline, glycerylpalmitostearate, their unprocessed binary mixtures and granulates obtained after melt extrusion (Formulations GPS25 and GPS75)

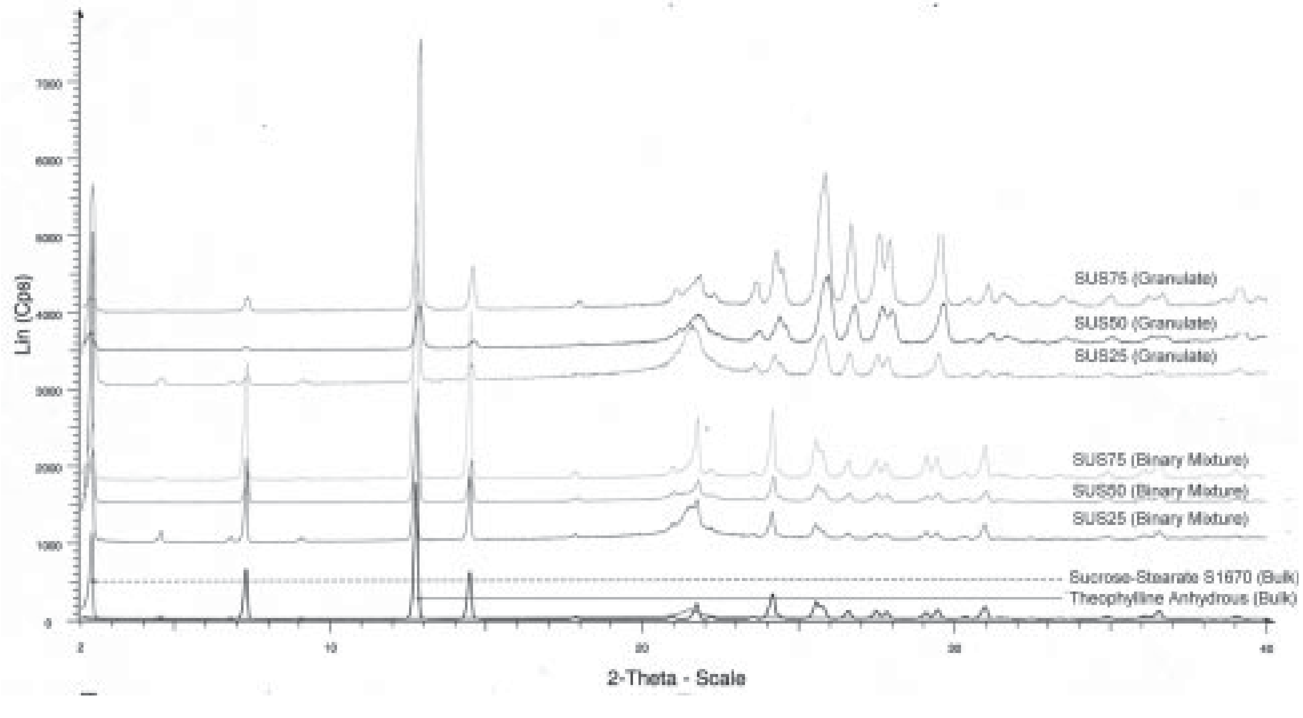


Fig. 4.2.6: Powder-X-Ray diffractograms of anhydrous theophylline, sucrose-stearate S 1670, their unprocessed binary mixtures and the granulates obtained after melt extrusion (Formulations SUS25, SUS50 and SUS75)

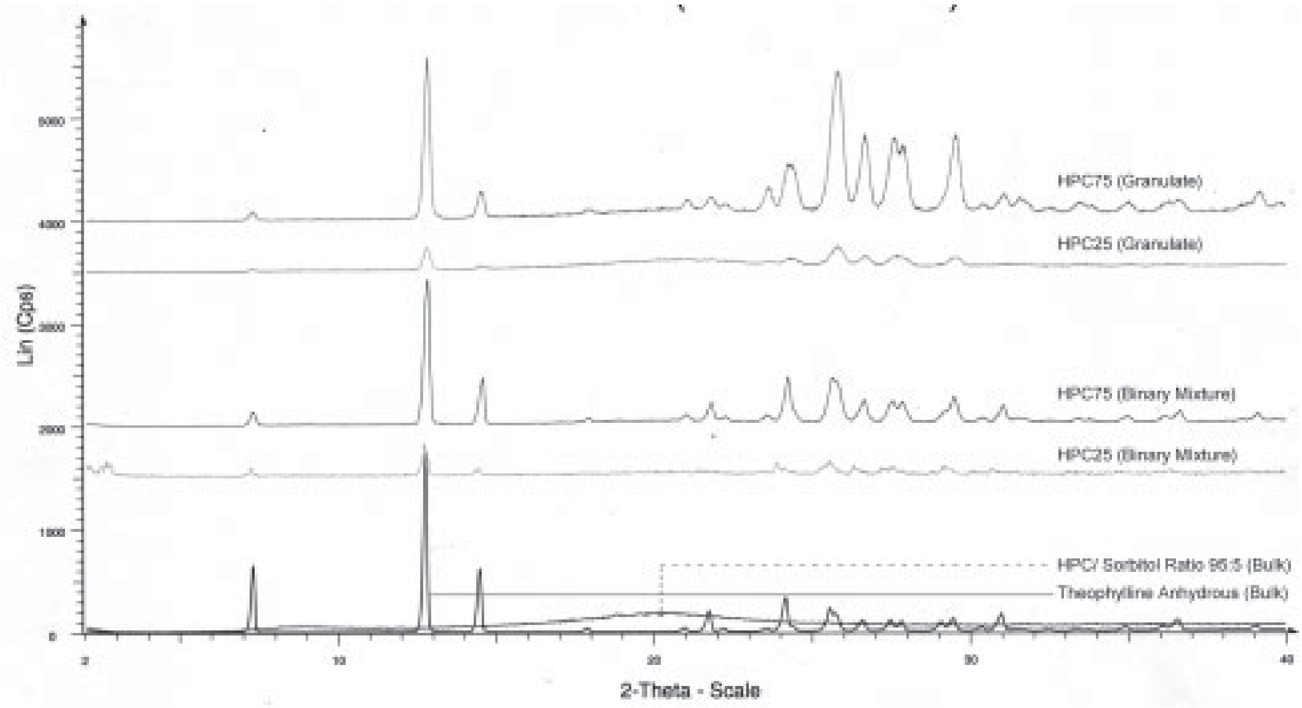


Fig. 4.2.7: Powder-X-Ray diffractograms of anhydrous theophylline, HPC/ sorbitol (95:5), their unprocessed binary mixtures and the granulates obtained after melt extrusion (Formulations HPC25 and HPC75)

4.2.6 Conclusion

All (binary) mixtures of the four selected carriers with theophylline were successfully processed by melt-extrusion in drug loadings ranging from 25% to 75% [w/w]. The four carriers differed in their process temperature range and the flow properties of the intermediate suspension. Both pseudoplastic (GBD, GPS, HPC) and dilatant (SUS) flow properties were observed. Due to low process temperatures, theophylline remained crystalline in all formulations. Increases in specific mechanical energy did not affect crystallinity and therefore an increase in thermal input would be required in order to achieve changes in crystallinity, if desired.

These studies also identified some general relationships between formulation parameters (drug loading, viscosity), independent process parameters (rotation speed, process temperature, feeding rate, etc.) and dependent process parameters (specific mechanical energy (SME), torque, residence time). In general, high drug loading and viscosity of the material results in increased process energy requirements which can be achieved by increasing screw rotation, enhanced power consumption or changes in screw design. Extended residence time was also used to improve homogenization and stability of the intermediate suspension, especially for high drug loading formulations.

Finally, process temperatures for melt extrusion were successfully predicted in most cases from a lab-scale model extruder. However, design of melt extrusion processes also requires consideration of other, independent, process parameters such as screw design, feed rate and rotational speed. Process reproducibility was demonstrated for fixed, formulation-dependent combinations of process parameters. In order to keep dependent process parameters in a narrow range, the feed rate has to be monitored and tightly adjusted. Effects of process parameters on product characteristics and performance are addressed in sections 4.4, 4.5 and 5.1.

4.3 Granulation and Compression Processes

4.3.1 Introduction

After binary powder mixtures have been transformed into ribbons using melt extrusion, they can be further processed to obtain granulates, which can be further compressed into tablets. In this section, the granulates formed from the extruded ribbons are examined with regard to properties that affect compaction processes and the quality of obtained compacts, such as their flow properties, particle size distribution, compressibility and compactibility. Granulates were compared to the powder mixtures to determine whether granulation improves the compression and compaction properties of carrier/theophylline mixtures.

4.3.2 Materials

Table 4.3.1 lists additional materials used for the compaction process.

Table 4.3.1: Materials used for compaction processes

Substance	Brand	Source	Grade/ Batch
Magnesiumstearate Ph. Eur.	Hyqual®, Vegetable Source	Mallinckrodt Baker Inc., Phillipsburg, NJ, USA	Ph. Eur./ C07537
Methanol	Chromasolv®	Sigma Aldrich Company Ltd., Dorset, UK	Gradient Grade

4.3.3 Equipment

Table 4.3.2 gives an overview of equipment used for preparation of granulates and examination of bulk material.

Table 4.3.2: Equipment used for preparation of granulates and evaluation of bulk materials

Device	Source
Balance Mettler Toledo PG-5002-S	Mettler Toledo Ltd., Beaumont Leys Leicester, UK
Balance Sartorius LA 230S	Sartorius AG, Goettingen, Germany
Balance Mettler Toledo AG 245	Mettler Toledo Ltd., Beaumont Leys Leicester, UK
Sieve Machine Frewitt GLA	Frewitt SA, Fribourg, Switzerland
Stainless Steel Screen 75-1000microns	Endecotts Ltd., London, United Kingdom
Sieve Shaker Fritsch Analysette 3 Pro	Fritsch GmbH, Idar-Oberstein, Germany
Granulate Tester Erweka SVM 202	Erweka GmbH, Heusenstamm, Germany
Granulate Tester Erweka SVM 102	Erweka GmbH, Heusenstamm, Germany
Helium Densipyknometer Quantachrome PPY13	Quantachrome Ltd., Hartley Wintney, Hook, UK
Compaction Simulator ESH02	ESH Testing Ltd., Brierley Hill, UK
Round FF Tablet Compression Tool ∅8.0mm	Manesty Ltd., Knowsley, UK
Tablet Hardness Tester Holland C50	I Holland Ltd., Long Eaton, Nottingham, UK
Stop Watch Oregon Scientific C510	Oregon Scientific (UK) Ltd., Maidenhead, UK
Micrometer Mitutoyo ABSsolute 293	Mitutoyo (UK) Ltd., Andover, UK

4.3.3 Methods

4.3.3.1 Granulation

After cooling and solidification, the intermediate melt extruded product was granulated using a Frewitt sieve machine with a 0.65mm*1.00mm sieve insert, run in an oscillating mode at medium speed.

4.3.3.2 Powder Flow

Powder flow was evaluated by measurement of bulk and tapped density and the calculation of the Carr’s index from the obtained values. Bulk and tapped volumes were measured according the Eurpoean Pharmacopeia (Ph.Eur. (2007c)). Tapped densities were calculated according to Eq. 4.3.1 applying V_F. All tests were performed at least in triplicate.

$$\rho_B = \frac{m_B}{V_{0/F}} \tag{4.3.1}$$

Flowability was classified according to Carr R.L. (1965) according to compressibility indices. These were calculated according to Eq. 4.3.2, applying the values measured for bulk (ρ_B) and tapped density (ρ_T).

$$C_i = \frac{\rho_T - \rho_B}{\rho_T} \mathrm{x}\, 100 \tag{4.3.2}$$

4.3.3.3 Particle Size Distribution

Particle size distribution was examined according to the sieve stack method of the European Pharmacopoeia (Ph.Eur. (2007d)). Table 4.3.3 describes the two sets of sieve stacks used to examine powder mixtures and granulates. Briefly, 50 g of bulk were shaken at 1.5 mm amplitude until a constant weight was achieved for each sieve (± 5% max.). Usually 3 min were sufficient to reach constant values. The weight on each sieve was measured and the fraction of total bulk calculated accordingly.

Table 4.3.3: Mesh sizes of sieves used for examination of particle size distribution of blends and granulates

Type of Bulk	Sieve 1 [µm]	Sieve 2 [µm]	Sieve 3 [µm]	Sieve 4 [µm]	Sieve 5 [µm]	Sieve 6 [µm]	Sieve 7 [µm]
Blend	500	355	250	180	125	75	0
Granulate	1000	710	500	355	250	180	0

The median diameter (d_{50}) was determined from the cumulative weight of undersize particles. Mass frequencies (f_m) were calculated according to Eq. 4.3.3, in which Φ_i denotes the sieve range [microns] and d_i the mass percentage [%] in the respective size band.

$$f_M = \frac{d_i}{\Phi_i} \tag{4.3.3}$$

Range of distribution (σ) was calculated according to Eq. 4.3.4, in which d_{10} and d_{90} denote the particle size below which 10% or 90%, respectively, of the bulk mass was found.

$$\sigma = \frac{(d_{90} - d_{10})}{d_{50}} * 100 \tag{4.3.4}$$

4.3.3.4 Compression Properties

For evaluation of the compression properties, yield pressures were determined by a Heckel analysis on sets of data obtained from compaction simulator, which recorded displacement of punches and the forces applied to them. Prior to compaction simulation, true densities of all bulk excipients and drug, blends and granulates were determined using a helium pycnometer. Target weights were calculated according to Eq. 4.3.5, in which *m* is the calculated tablet mass, *r* the radius of the tooling, ρ_T the true density of the bulk material and π the circle constant. Tooling surfaces were wiped with a 5% [m/m] suspension of Mg-stearate in methanol and left to dry. Next, the bulk was accurately weighed (±1mg) and manually filled into the die.

$$m = \rho_T x 2r^2 \pi x 0.3r \tag{4.3.5}$$

Compaction was performed applying a constant speed of the upper punch (30 mm/s) and a compression force of 10 kN (±1 kN). During compaction the displacement of upper and lower punch was continuously recorded and used as measure for bulk density. Eq. 4.3.6, in which d_b is the calculated change in punch displacement after compaction, d_a the punch displacement [mm] at the start of the compaction [mm] and d_0 the minimum punch displacement [mm] during compaction. The change in punch displacement after compaction is attributed to particle rearrangement and thus can be used as an indirect measure for particle rearrangement.

$$d_b = d_a - d_0 \tag{4.3.6}$$

After compaction the weight of the tablet was checked, the thickness of the tablet was measured one minute after compaction was finished, and the tablet hardness was determined. At least four runs were performed per bulk material.

Heckel R.W. (1961) reported a linear relation between applied pressure and the relative density of a bulk according to Eq. 4.3.7, in which *D* is the relative density of the tablet, *P* the applied pressure [MPa] and *K* and *A* are constants. By fitting the raw data to Heckel's equation by linear regression, values for *K* and *A* were obtained, and by calculating the reciprocal of *K* the yield pressure of the bulk was obtained.

$$\ln\frac{1}{(1-D)} = KP + A \tag{4.3.7}$$

In order to interpret yield pressure values correctly, the data were used to calculate the axial elastic recovery r_e (1min), which indicates the extent of elastic deformation of the material. Eq. 4.3.8 was applied to the calculation of r_e, in which d_0 represents the thickness at maximum load and d_1 the thickness 1min after compression ended.

$$r_e = \frac{d_1 - d_0}{d_0} x100 \tag{4.3.8}$$

In order to assess the formation of interparticle bonds the radial tensile strength (RTS) (Parrott E.L. (1990)) was calculated according to Eq. 4.3.9, in which σ_X is the radial tensile strength [MPa], *F* the tablet hardness [N] and *D* the diameter of the tablet [mm].

$$\sigma_X = \frac{2F}{D\,\pi\,d_1} \tag{4.3.9}$$

4.3.4 Results

4.3.4.1 Flow Properties of Powders and Granulates

Table 4.3.4 summarizes compressibility indices for powder blends and granulates. In most cases a significant improvement in flowability was observed when formulations were granulated, e.g. compressibility index of formulation GDB25 decreased from 21 ±1.6% (passable) to 12 ±0.25% (good). No significant improvement was observed for formulation GPS25, for which the granulation process decreased compressibility index from 15 ±1.2% to 13 ±1.8%. However, since flowability of the powder blend was already good, improvement in terms of flowability was not essential. For the HPC formulations (HPC25, HPC50, HPC75), decreasing the percentage of brittle drug while keeping percentage of plasticizer constant led to an increase in elasticity of extrudates with drug load, worsening the granulation properties of the extrudate. For example, the compressibility index of formulation HPC25 increased from 22 ±2.1% to 25 ±1.4%. This granulation cannot be recommended for HPC-based extrudates.

Table 4.3.4: Compressibility indices of theophylline powder blends and granulates

Formulation	**Compressibility Index [%]**	
	Powder Blend	**Granulate**
GDB25	21 (±1.6)	12 (±0.25)
GDB50	19 (±1.7)	13 (±1.5)
GDB75	20 (±0.72)	10 (±0.72)
GPS25	15 (±1.2)	13 (±1.8)
GPS50	16 (±1.4)	12 (±0.85)
GPS75	19 (±2.4)	11 (±0.48)
SUS25	26 (±2.6)	13 (±0.79)
SUS50	20 (±2.4)	12 (±1.7)
SUS75	20 (±1.8)	12 (±2.6)
HPC25	22 (±2.1)	25 (±1.4)
HPC50	22 (±0.23)	20 (±2.0)
HPC75	26 (±1.2)	14 (±3.0)

4.3.4.2 Particle Size Distribution

Table 4.3.5 compares the median particle size (d_{50}) and the range of particle size distribution of powder mixtures and granulates of all formulations. As expected, granulation increased the median particle sizes (d_{50}) and reduced the percentage of fines. The median particle size of granulates ranged between 366µm and 713µm and was higher than for the powder blends (82µm - 221µm). Depending on the carrier used in formulations, the breadth of the particle size distribution was either significantly increased by granulation, e.g. formulations SUS25 and SUS50, or showed no or insignificant changes, e.g. formulations GDB and GPS formulations. A decrease in the breadth of the particle size distribution was observed for HPC formulations.

Fig.4.3.1 – Fig.4.3.4 show representative particle size distributions of the examined powder blends and granulates. Except for HPC formulations, all powder blends showed a positively skewed unimodal particle size distribution. For these a log-normal distribution could be used to describe the particle size distribution of the powder blends. Due to the large particle size of the HPC starting material, HPC/ theophylline powder blends showed a bimodal distribution. All granulates exhibited a (flat) bimodal particle size distribution.

Table 4.3.5: Median particle size d_{50} (±SD) and range of particle size distribution σ (±SD) of powder blends and granulates

Formulation	d_{50} [µm] (±SD)		σ [%] (±SD)	
	Powder Blend	Granulate	Powder Blend	Granulate
GDB25	102 (±4.58)	470 (±43.9)	121 (±10.6)	176 (±10.7)
GDB50	82 (±22.3)	366 (±22.6)	183 (±26.7)	186 (±15.0)
GDB75	93 (±11)	545 (±49.0)	165 (±47.6)	144 (±14.2)
GPS25	103 (±1.00)	431 (±56.7)	202 (±147)	167 (±19.3)
GPS50	99 (±1.5)	450 (±186)	141 (±52.7)	162 (±54.0)
GPS75	98 (±6.0)	527 (±34.2)	155 (±59.9)	153 (±3.79)
SUS25	165 (±3.46)	525 (±122)	95 (±8.1)	149 (±27.4)
SUS50	143 (±16.5)	620 (±81.6)	94 (±4.3)	133 (±17.6)
SUS75	98 (±3.2)	586 (±97.9)	130 (±21.5)	143 (±18.9)
HPC25	221 (±6.08)	713 (±55.7)	177 (±3.00)	144 (±5.03)
HPC50	168 (±7.64)	655 (±27.3)	227 (±4.00)	127 (±3.46)
HPC75	95 (±1.7)	580 (±45.1)	338 (±6.56)	136 (±10.8)

In order to quantitatively evaluate the reproducibility of particle size distributions, median particle size and range of distribution were examined. Overall the results varied with the type of bulk and the carrier used. For most powder blends median particle sizes were reproducible (formulations GDB25, GPS25/50/75, SUS25, SUS75 and HPC75), but other blends showed fluctuations in median particle sizes. Looking at granulates, fluctuations in median particle sizes were observed for most granulates (formulations GDB50, GPS75, HPC25, HPC50 and HPC75). Similar observations were made for the breadth of the particle size distribution. Qualitative comparison of particle size distribution by plotting mass frequency versus particle size showed reasonable reproducibility for all powder blends and some granulates, e.g. formulations GDB75, SUS75 or HPC75. However, for some granulates changes in distribution were observed, such as weakening or complete disappearance of peaks (formulation GPS25) or shifts of peaks (formulation HPC25).

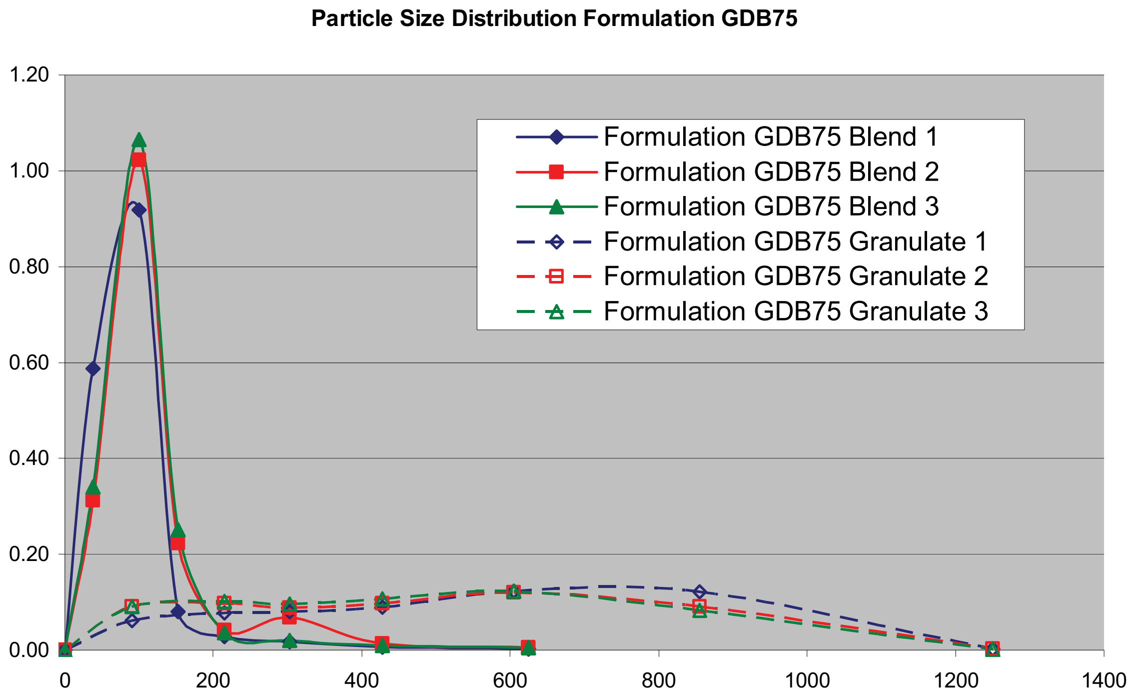


Fig. 4.3.1: Particle size distribution of formulation GDB75: particle size [microns] vs. mass frequency [%/micron]

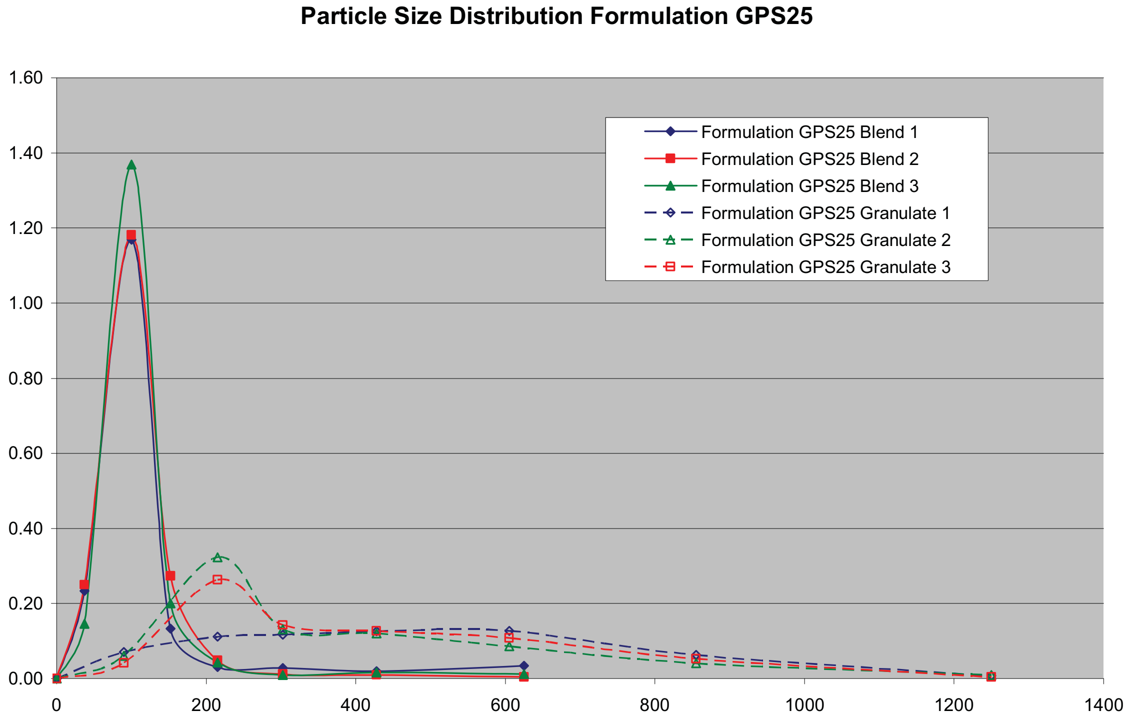


Fig. 4.3.2: Particle size distribution of formulation GPS25: particle size [microns] vs. mass frequency [%/micron]

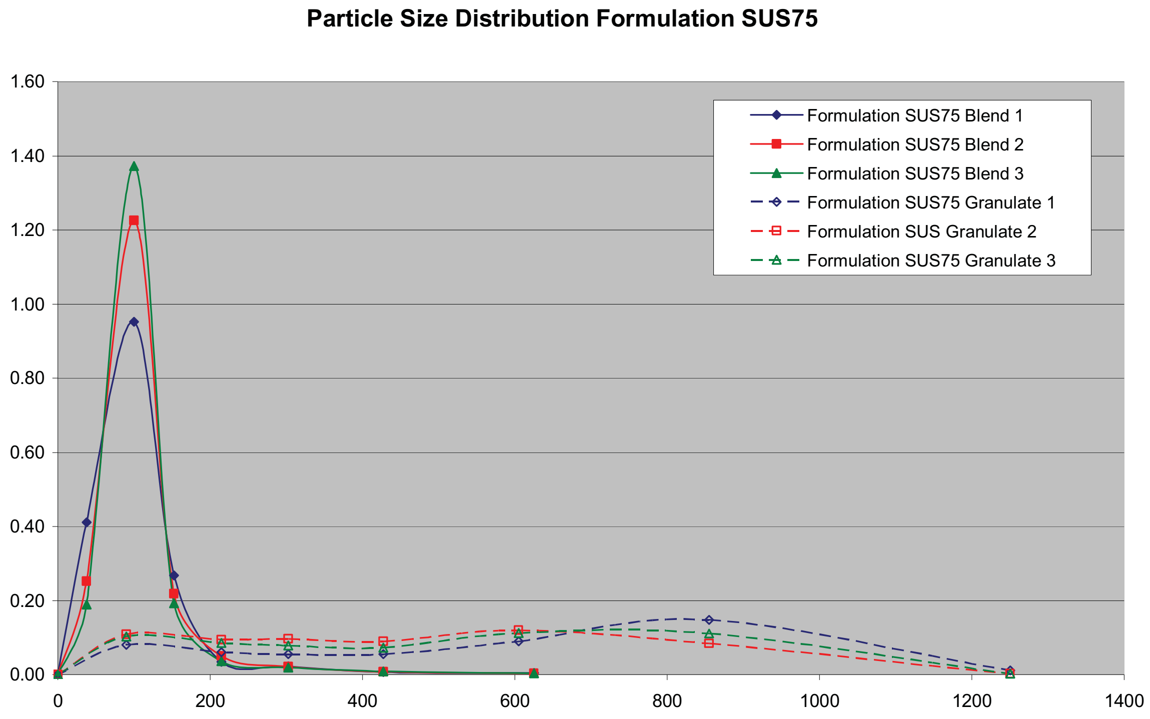


Fig. 4.3.3: Particle size distribution of formulation SUS75: particle size [microns] vs. mass frequency [%/ micron]

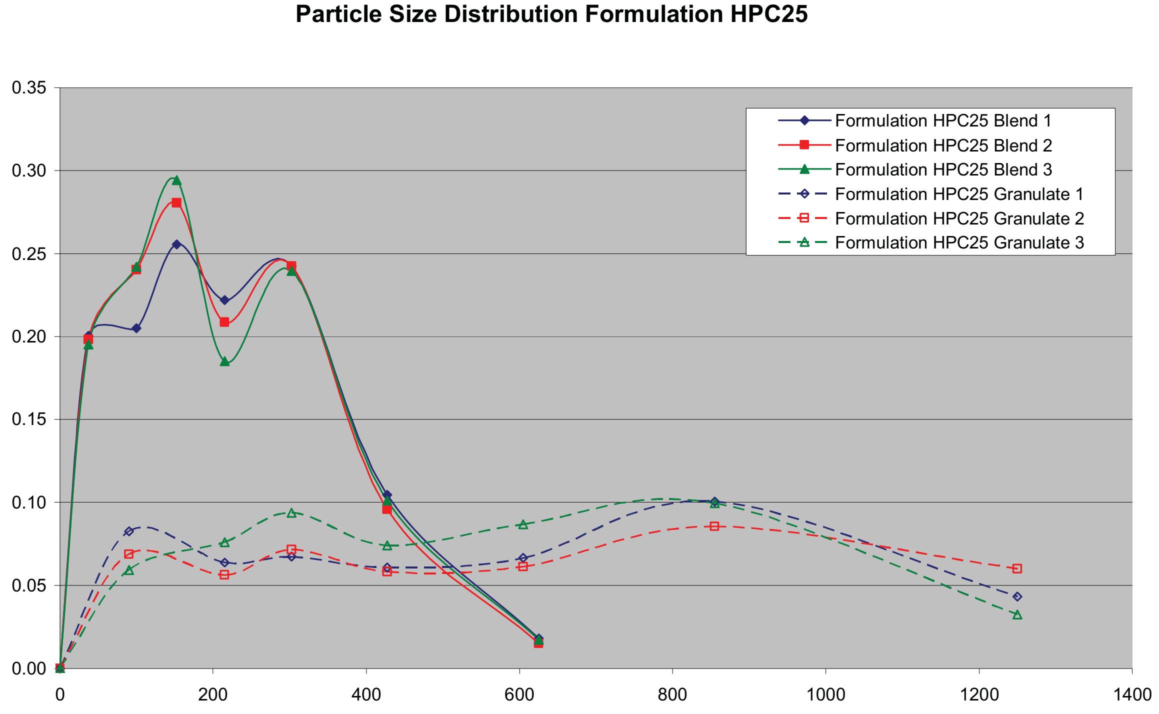


Fig. 4.3.4: Particle size distribution of formulation HPC25: particle size [microns] vs. mass frequency [%/ micron]

4.3.4.3 Compression Properties

Overall, granulates showed denser compacts and less elasticity at the given compression force of 10 ±1 kN.

Table 4.3.6 summarizes the displacement between upper and lower punch as a measure for relative densities compressed bulks. Initial relative densities (d_0) of granulates were comparable to the respective powder blends. Only formulation HPC25 showed decreased initial relative density. As expected, the extent of densification (d_b) was reduced for the granulates. Again HPC25 represented an exception and showed a higher degree of densification during compression.

Table 4.3.6: Relative densities of bulk materials during compaction simulation given as punch displacement

Formulation	Powder Blend			Granulate		
	Mean d_0 [mm] (±SD)	Mean d_a [mm] (±SD)	Mean d_b [mm] (±SD)	Mean d_0 [mm] (±SD)	Mean d_a [mm] (±SD)	Mean d_b [mm] (±SD)
GDB25	**2.397**	**2.615**	**0.218**	**2.398**	**2.560**	**0.163**
GDB50	**2.404**	**2.573**	**0.169**	**2.400**	**2.505**	**0.105**
GDB75	**2.389**	**2.568**	**0.179**	**2.401**	**2.473**	**0.072**
GPS25	**2.411**	**2.533**	**0.122**	**2.377**	**2.440**	**0.063**
GPS75	**2.413**	**2.508**	**0.095**	**2.400**	**2.408**	**0.008**
SUS25	**2.397**	**2.588**	**0.191**	**2.415**	**2.505**	**0.091**
SUS50	**2.400**	**2.625**	**0.225**	**2.404**	**2.423**	**0.019**
SUS75	**2.392**	**2.525**	**0.133**	**2.417**	**2.423**	**0.006**
HPC25	**2.391**	**2.723**	**0.331**	**2.550**	**3.005**	**0.455**
HPC75	**2.391**	**2.635**	**0.245**	**2.396**	**2.593**	**0.197**

d_0 = minimum punch displacement during compaction [mm]; d_a = initial punch displacement [mm]; d_b = change in punch displacement [mm]

Table 4.3.7 summarizes the compression properties of bulk materials with respect to yield pressure and axial elastic recovery. For high drug loading formulations, granulation facilitated plastic deformation, as indicated by a decrease in yield pressure.

Granulation facilitated plastic deformation especially for higher drug loadings, as the most significant reduction in yield pressure was observed for formulations GDB75, GPS75 and SUS50/ SUS75. For example, for formulation GDB75 the yield pressure was reduced from 45.3 ±2.0 MPa for the powder blend to 12.7 ±1.2 MPa for the granulate. Little change in yield pressure of the compacts with granulation was found for the 25% [w/w] drug loading formulations. For example, a slight increase in yield pressure from 6.0 ±0.3 MPa for the powder blend to 6.2 ±0.5 MPa for the granulate was observed for formulation GPS25. As an exception, the yield pressure of HPC formulations was not affected by granulation.

While an increase in yield pressure with drug loading was found for powder blends, only little difference in yield pressure was found for the granulates with increasing drug loading. Only HPC formulations revealed an increase in yield pressures with drug loading also for the granulates.

Table 4.3.7: Compression properties of powder blends and corresponding granulates

Formulation	Yield Pressure [MPa] (±SD)		Axial Elastic Recovery [%] (±SD)	
	Powder Blend	Granulate	Powder Blend	Granulate
GDB25	8.0 (±1.5)	5.5 (±0.7)	9.09 (±0.45)	6.78 (±0.66)
GDB50	10.1 (±0.9)	6.4 (± 0.5)	7.02 (±0.49)	4.36 (±0.39)
GDB75	45.3 (±2.0)	12.7 (±1.2)	7.48 (±0.77)	3.00 (±0.77)
GPS25	6.0 (±0.3)	6.2 (±0.5)	5.06 (±0.37)	2.65 (±0.81)
GPS75	22.4 (±1.9)	7.0 (±0.3)	3.94 (±1.20)	0.323 (±0.44)
SUS25	32.4 (±1.0)	21.8 (±0.8)	7.95 (±0.84)	3.75 (±0.31)
SUS50	40.4 (±1.2)	21.9 (±1.6)	9.37 (±1.43)	0.790 (±0.50)
SUS75	43.8 (±3.0)	21.8 (±0.7)	5.56 (±0.49)	0.238 (±0.56)
HPC25	30.0 (±2.3)	35.5 (±0.7)	13.9 (±0.67)	17.8 (±0.72)
HPC75	60.1 (±1.4)	54.0 (±3.2)	10.2 (±1.42)	8.21 (±0.78)

After granulation, axial elastic recovery decreased for all formulations tested (except HPC 25). In these cases, granulation reduced the elastic properties of the mixtures compared to the powder blends.

Table 4.3.8 lists the radial tensile strength of all powder blends and granulates tested. As a rule of thumb, the target tablet crushing strength [N] is about 10 times the tablet diameter [mm]. Applying this rule of thumb, a desired RTS between 2.5MPa and 3.0MPa should be targeted, depending on the diameter used and the tablet thickness obtained.

Overall tablet hardness was poor; no formulation exceeded a radial tensile strength (RTS) of 2.46 MPa (formulation SUS75). RTS increased with increasing drug loading, indicating the good bonding properties of theophylline. By contrast, all excipients revealed rather poor bonding properties and therefore had a negative impact on tablet hardness. Granulation increased RTS significantly, with the exception of formulation HPC25, which showed a significant decrease in RTS after processing (1.70 ±0.07 MPa for powder blend vs. 1.30 ±0.04 MPa for granulate). For formulation SUS25 processing did not impact the bonding properties of the formulation, as insignificant difference in RTS were observed between the powder blend and the granulate.

Table 4.3.8: Radial tensile strength (RTS) [MPa] of compacts obtained from examined powder blends and granulates

Formulation	RTS [MPa] (±SD)	
	Powder Blend	Granulate
GDB25	0.18 (±0.00)	0.52 (±0.014)
GDB50	0.45 (±0.029)	0.93(±0.029)
GDB75	1.05 (±0.0283)	1.51(±0.0263)
GPS25	0.54 (±0.054)	0.85 (±0.043)
GPS75	1.06 (±0.0483)	1.39 (±0.0435)
SUS25	0.79 (±0.067)	0.73 (±0.087)
SUS50	1.14 (±0.0403)	1.47 (±0.0976)
SUS75	1.92 (±0.102)	2.46 (±0.221)
HPC25	1.70 (±0.0705)	1.30 (±0.0424)
HPC75	1.87 (±0.0506)	2.38 (±0.111)

4.3.5 Discussion

Powder flow is an important factor in the manufacture of tablets, where it is essential to have continuous and controlled movement of the bulk material. This is related to the fact that tablet compression involves volumetric dosing of the bulk into the compression unit.

Increasing particle size represents a commonly applied approach to improve the flow properties of a bulk material. The decrease in particle surface reduces cohesion, resulting in improved flowability. Different granulation techniques, such as wet granulation and granulation of melt extruded materials, agglomerate powders into larger particles. The four carriers were suitable for granulation and an increase in median particles size (d_{50}) was found after granulation compared to the initial powder blends.

Densification of bulk materials during processing complicates the matter, as flow rates are also dependent on bulk densities. Decreased potential for bulk densification during processing facilitates the reproducible manufacture of solid dosage forms with respect to weight.

Carr R.L. (1965) developed a general methodology to assess and compare the flow properties of bulk materials, which takes both particle size and bulk density into consideration. A decrease in the Carr index values of a bulk material after extrusion/granulation indicates improved flowability of the granulates. This was the case for most formulations. For GDB, GPS and SUS formulations, flowability of granulates was superior compared to initial powder blends. Overall, granulates provided good flow properties and drug loading had only little effect on flowability of granulates. Increase in median particle size is considered the main driver for the improvement in flow properties. Similarly, for HPC75 an increase in median particle size resulted in good flow properties.

However, increase in particle size did not result in improved flow properties for HPC 50 and HPC 25. In fact, a deterioration in Carr index was observed for HPC25 after granulation. In addition to particle size, the shape of particles can also affect flowability (Carr R.L. (1965)), so this parameter should also be considered when discussing the lack of improved flowability of HPC formulations. Indeed, the highly elastic behaviour of HPC ribbons during granulation resulted in needle shaped particles with poor flowability. Rough particle surfaces or spicular particles hamper slippage of particles and promote cohesion of particles. To obtain suitably shaped particles for HPC formulations a change in granulation process such as using different equipment or decreasing the elasticity of the extrudates would be necessary. In particular, a reduced percentage of plasticizer or addition of fillers would result in brittleness.

For formulations other than HPC, granulation provided not only increased mean particle sizes, but also adequate particle shapes.

The present work shows that the oscillating granulator is useful for granulation of most melt extrudates. However, the reproducibility in particle size distribution has to be viewed critically, as some major interbatch deviations were observed. Although the granulations produced in this series all had higher median particle sizes than the corresponding powders, for some the particle size distribution became broader. This was most pronounced at low drug loadings. The breadth of particle sizes generated is of concern, as segregation is favoured by a combination of large and small particles in bulks. (Venables H.J., et al. (2001)). Hence it is desirable to obtain granulates with narrow particle size distributions.

The compressibility of bulks is a further, crucial issue for the production of tablets. Parrott E.L. (1990) lists four main parameters impacting the formation of a compact: (i) repackaging, (ii) fragmentation, (iii) elastic deformation and (iv) plastic deformation. At first particles are densified during the first stages of a compression process by repackaging, i.e. particle rearrangement and slippage, leading to less void spaces within the compact. When no further repackaging is possible, particles start to deform. As expected, granulation reduced the degree of particle rearrangement during compression. Only for HPC25, an increase in particle rearrangement was observed compared to the initial powder blend. This was attributed to the needle-like particle shape. This is in accordance with powder flow results and underlines the importance of particle shape and surface. York P. (1978) explains an increased ability of particles to slip and rearrange during compression when spherical and smooth particles are present. The formulation HPC25 had a less suitable particle shape for flow and the high elasticity further impeded compression.

Depending on the particle properties, three types of deformation can be distinguished. Elastic particles change shape under pressure, but go back to their original shape after pressure is released. By contrast, during plastic deformation the particle shape is modified by pressure. After the pressure is released, particles maintain their new shape. Some particles can fragment upon pressure, allowing further repackaging of particles. Depending on the properties of the material to be compressed, either fragmentation of particles prevails or deformation is observed after densification has reached its final state and compression forces are further increased. Fragmentation and plastic deformation result in further densification of compacts and lead to increased tablet hardness, as these are irreversible processes. By contrast, elastic deformation, as a reversible process, results in axial recovery and weak compacts or a tendency to cap.

In the present study the Heckel analysis was applied to understand the compression characteristics of the formulations. Yield pressures and changes in density with applied pressure were recorded as a measure to assess the densification properties of materials. Duberg M., et al. (1982) and Humbert-Droz P., et al. (1983) facilitated Heckel plots to identify the prevailing mechanisms of densification. Low yield pressures and densification (given as d_b) were attributed to prevailing plastic deformation during the compression process. In turn, high yield pressure and densification indicated prevailing fragmentation. For granulates, generally lower yield pressures were observed compared to powder blends, indicating facilitated plastic deformation. Further, the extent of densification during compression was reduced for granulates as indicated by d_b values. The lipid carriers (GDB, GPS) showed the lowest yield pressures indicating the least force required to trigger plastic deformation. HPC showed the highest yield pressures, indicating that plastic deformation only occurred at higher compaction forces. Except for HPC25, melt extrusion/granulation reduced yield pressure and thus facilitated plastic deformation and reduced fragmentation of particles during compression. Increases in plastic deformation became particularly pronounced with increasing drug load. On the other hand, materials seemed to undergo fragmentation during densification, indicated by high d_b values. In addition to increasing plastic deformation, extrusion/granulation reduced fragmentation of granules. By contrast, formulation HPC25 showed increased fragmentation for the granulate as increases in yield pressure and densification (d_b) were observed.

However, Duberg M., et al. (1986) suggested that low yield pressures can also be due to elastic deformation, so plastic and elastic deformation must be differentiated by other means. They proposed the examination of the decompression process as an indicator of plastic or elastic behaviour. Elsewhere the measurement of elastic recovery has been applied to assess the elasticity of a material under compression (Garekani H.A., et al. (2001)). In the present study, melt extrusion/granulation reduced the elastic properties of the compressed materials, except for HPC25. GPS and SUS formulations were slightly less elastic than GDB formulations. Further, extrusion/granulation decreased the elastic properties of the materials. Only HPC25 showed an increase in elasticity and the highest degree of elastic deformation throughout. The reduction in elastic deformation seemed not be related to drug loading.

As a conclusion, melt extrusion/granulation improved the compression properties by increasing plastic deformation and concomitantly reducing fragmentation and elasticity. This resulted in an increase in tablet hardness. GDB and GPS formulations provided best compression properties due to highest extent of plastic deformation. SUS formulations provided least fragmentation during compression. By contrast, for HPC25, processing resulted in a deterioration of compression properties due to a decrease in plasticity and an increase in elasticity.

Although tablet hardness was at the lower end of the scale, elastic deformation and fragmentation of particles seemed to occur during compression. Addition of a binder would increase the plastic properties of materials and result in harder tablets.

Turning to the question of balancing process efforts and material properties, some major differences between the four carriers were observed. Three of the four carriers (glyceryldibehenate, glycerylpalmitostearate and sucrose-fatty acid-ester S 1670) clearly required granulation in order to improve flowability and compressibility. Sucrose-fatty acid-ester formulations benefit especially from a granulation step with respect to their flowability and fragmentation and elasticity. For glyceryldibehenate and glycerylpalmitostearate, the major advantage of granulation was the reduced tendency to granule fragmentation and elastic deformation.

4.4 Tablet Characterization

4.4.1 Introduction

The previous section focussed on various processing characteristics of carriers used for production of CR dosage forms by melt extrusion. This section addresses aspects of tablet quality such as the physical robustness and reproducibility of weight and content, and creates a basis for interpretation of the dissolution results presented in the following sections.

4.4.2 Materials

Table 4.4.1 lists additional materials used for the manufacture and characterization of tablets.

Table 4.4.1: Materials used for manufacture and characterization of tablets

Substance	Brand	Source	Grade/ Batch
Magnesiumstearate	Hyqual®, Vegetable Source	Mallinckrodt Baker Inc., Phillipsburg, NJ, USA	Ph. Eur./ C07537
Methanol	Chromasolv®	Sigma Aldrich Company Ltd., Dorset, UK	Gradient Grade/ several batches
Demineralized Water	Milli-Q®	Millipore (UK) Ltd., Watford, UK	Gradient Grade/ -
Acetic Acid glacial	Fisherbrand/ A/0400/PB15	Fisher Scientific Ltd., Loughborough, UK	Analytical Grade/ 0563721
Sodium Chloride	Fisherbrand/ S/ 3160/ 60	Fisher Scientific Ltd., Loughborough, UK	Analytical Grade/ 0560472
Sodium Hydroxide	Fisherbrand/ S/ 4920/ 53	Fisher Scientific Ltd., Loughborough, UK	Analytical Grade/ 0552788
0.45μm PTFE membrane filter	Acrodisc® CR 25mm	Pall Life Sciences, Portsmouth, UK	-/ A10418862
Pipette Tips	Gilson Diamond Precision Tips D200/ D5000	Gilson Inc., Middleton, WI, USA	-/ IFAA/10739, ISA4/ 34196

4.4.3 Equipment

Table 4.4.2 summarizes additional equipment used for tablet manufacture. Table 4.4.3 lists the equipment used for the determination of tablet hardness and friability, Table 4.4.4 the equipment used to characterize uniformity of mass and content.

Table 4.4.2: Equipment used for tablet manufacture

Device	Source
Balance Mettler Toledo PG-503-S	Mettler Toledo GmbH, Giessen, Germany
Turbula WAB T2C	W.A. Bachofen AG, Bale, Switzerland
SRC Tablet Compression Tool ∅9.0mm/ 10.0mm	Notter GmbH, Oelbronn-Duernn, Germany
Single-Station Tablet Press Korsch EK0-DMS	Korsch AG, Berlin, Germany
Measurement Amplifier Spider 8-Maxi	HBM GmbH, Darmstadt, Germany
Compaction Software Beam-Spider 8, Version 3.8 a2	AMS GmbH, Floeha, Germany
Tablet Hardness Tester Erweka TBH 200D	Erweka GmbH, Heusenstamm, Germany
Stainless Steel Screen 1000microns	Endecotts Ltd., London, United Kingdom

Table 4.4.3: Equipment used for hardness and friability testing

Device	Source
Balance Sartorius BP-211-D	Sartorius AG, Goettingen, Germany
Stainless Steel Screen 1000microns	Endecotts Ltd., London, United Kingdom
Tablet Hardness Tester Holland C50	I Holland Ltd., Long Eaton, Nottingham, UK
Friability Tester Erweka TA 200	Erweka GmbH, Heusenstamm, Germany

Table 4.4.4: Equipment used for determination of uniformity of content and mass

Device	Source
Balance Mettler Toledo PG-5002-S	Mettler Toledo Ltd., Beaumont Leys Leicester, UK
Water Purification System Millipore Milli-Q® Gradient A10	Millipore (UK) Ltd., Watford, UK
Magnetic Stirrer Hotplate	Stuart Scientific Ltd., Redhill, UK
5ml Glass Syrringe with Luer Lock	Sam Murray & Co. Ltd., Sheffield, UK
Infrared Thermometer	

4.4.4 Methods

4.4.4.1 Tablet Manufacture

Prior to compaction, one per cent [w/w] Mg-stearate was added to granulates and blending was performed for two minutes at 32 rpm using a Turbula blender. Tablets containing 100 mg of theophylline were compressed using 9.0 mm or 10.0 mm standard round concave compression tooling. An instrumented single station tablet press (Korsch EK0) was used for compression. At least three batches per formulation were compressed. Usually a fitted hopper filled the die automatically. During compression processes, tablet weight and hardness were continuously monitored and adjusted if necessary.

In order to arrive at reproducible tablet hardness, compression force–tablet hardness profiles were established prior to preparation of tablets for further experiments. Tablets were compressed at increasing compression forces. At each compression force ten tablets were sampled for hardness testing. The experiment was conducted in triplicate. Data were pooled based on applied compression force and tablet hardness was plotted versus mean compression force. Preferred ranges of compression forces were derived from the plots under consideration of maximum tablet hardness.

4.4.4.2 Tablet Hardness

Ten randomly selected tablets per batch were tested for hardness and mean tablet hardness (n=10) was calculated. Test setup and analysis corresponded to the European Pharmacopoeia (Ph. Eur. 2005). Tablets were freed from dust and trimmed on 1000 µm stainless steel sieve with compressed air. Each formulation was tested in triplicate and mean values were compared applying Tukey´s “honestly significant difference” (HSD) procedure (p=0.05), which is a pairwise comparison of means assuming Student´s distribution. A value t_S was calculated according to Eq. 4.4.1, in which M_i and M_j are the compared mean values, MSE is the mean square error and M_h the harmonic mean value. A critical value for t_S was obtained from the number of compared means and their distribution. A confidence level of 95% was set (p=0.05).

$$t_S = \frac{M_i - M_j}{\sqrt{\frac{MSE}{M_h}}} \qquad (4.4.1)$$

4.4.4.3 Tablet Friability

Friability was tested according to the European Pharmacopoeia (Ph. Eur. 2003a). Twenty tablets were thoroughly freed from dust and then accurately weighed. After transfer into the friability tester, the tablets underwent one hundred revolutions under compendial conditions. Afterwards the tablets were again freed from dusted with compressed air and reweighed. Friability was calculated from the difference of initial and final weight and expressed in per cent. According to the European Pharmacopoeia (Ph. Eur. 2003a), friability below one per cent [w/w] is regarded as acceptable. Additionally, if tablets capped during testing, the tablets were considered to have failed. All formulations were examined in triplicate.

4.4.4.4 Uniformity of Mass

Uniformity of mass of single-dose preparations was tested according to the European Pharmacopoeia. Specifications were applied according to the European Pharmacopeia (Ph.Eur. 2003b). All formulations were tested in triplicate.

4.4.4.5 Uniformity of Content

Content uniformity of single-dose preparations was tested according to the European Pharmacopoeia. The batch passed the content uniformity test if the European Pharmacopeia specifications were fulfilled (Ph. Eur. 2003c).

In order to quantitatively extract drug from dosage units, tablets were accurately weighed and then transferred into a 50 ml volumetric flask. Approximately 40 ml of water were added and the flask was heated to about 80°C under continuous stirring. After the tablets had fully dissolved, the theophylline solution was cooled to room temperature. At room temperature water was added to 50.0 ml. A sample of approximately 5 ml was withdrawn with a glass syringe and filtered through a 0.45 µm PTFE membrane filter. The content of the filtered sample was determined by HPLC assay. Prior to testing the method was validated for all excipients using simple drug/carrier powder mixes. Validation experiments confirmed that the determined values ranged within ±3.5% of the true content over the range 75 mg to 125 mg theophylline. All formulations were tested in triplicate.

4.4.5 Results

4.4.5.1 Manufacturing Process

Generally, a target compression force range was defined for each formulation, for which reproducibility of mean tablet hardness was assumed to fall within a certain bracket. In order to find these ranges, the relation between compression force and tablet hardness was examined.

Initially, tablet hardness increased with enhanced compression forces, but above a certain compression force threshold tablet hardness did not increase further. An example is provided in Fig.4.4.1, which shows a tablet hardness plateau reached at about 3-5 kN compression force.
In case of formulation GDB25 tablet hardness was not significantly increased when compression forces exceeded 5.5 kN. In order to prevent damage from the compression tooling, compression forces were selected within the first two thirds of the tablet hardness plateau. The target compression force was fixed at 9.0 kN, at which the compression force-tablet hardness relation showed least standard deviation. Accordingly the confidence interval (p=0.05) of mean tablet hardness ranged between 33 N and 36 N. Deviations of up to three kN were assumed not cause significant changes in tablet hardness, as mean values and standard deviations showed comparable levels.

In some cases very high compression forces resulted in weaker tablets, indicating over-compression of the bulk. In these cases, such as Fig. 4.4.2, respective compression force–tablet hardness plots showed a decline after the tablet hardness plateau. For these an optimum tablet required appropriate selection of compression forces. Formulation SUS50 showed a decline and much wider distribution of mean tablet hardness, which was adverse to the aim of manufacturing reproducible tablets. This was observed for compression forces higher than 15 kN. In this case a target compression force of 11.2 kN was fixed with maximum deviations of two kN. The respective confidence interval (p=0.05) estimated the mean tablet hardness to range within 41 N to 48 N.

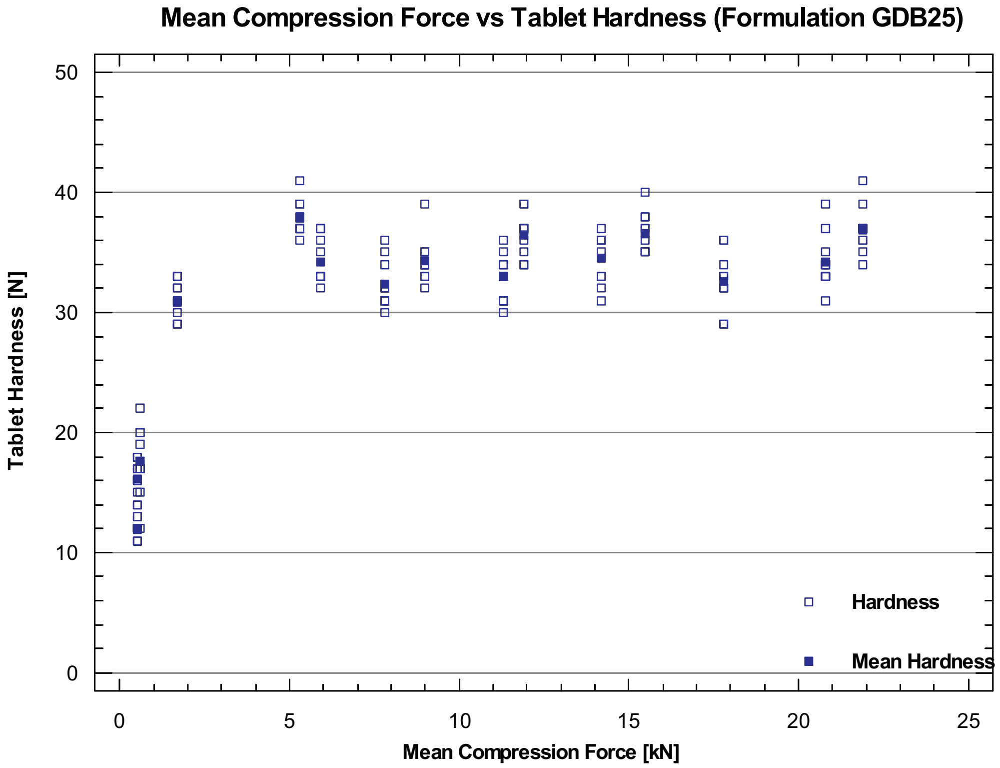


Fig. 4.4.1: Mean compression force vs. tablet hardness (formulation GDB25)

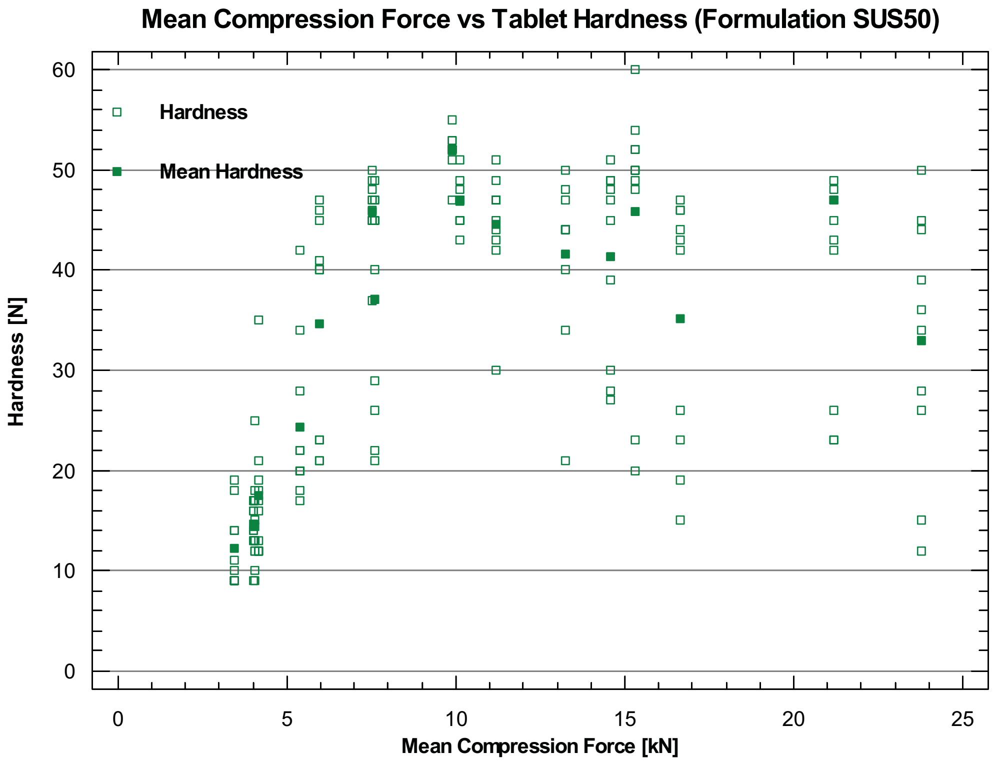


Fig. 4.4.2: Mean compression force vs. tablet hardness (formulation SUS50)

Compression force setting became even more important when tablet capping was observed (see Fig.4.4.3). For formulation GPS25 compression had to be monitored closely in order to avoid capping. In this case, capping was observed at compression forces of ≥5 kN. Within a relatively narrow window of compression forces, tablets of acceptable and reproducible hardness were produced (1.0 kN to 3 kN). Compression forces below 1 kN produced weaker tablets.

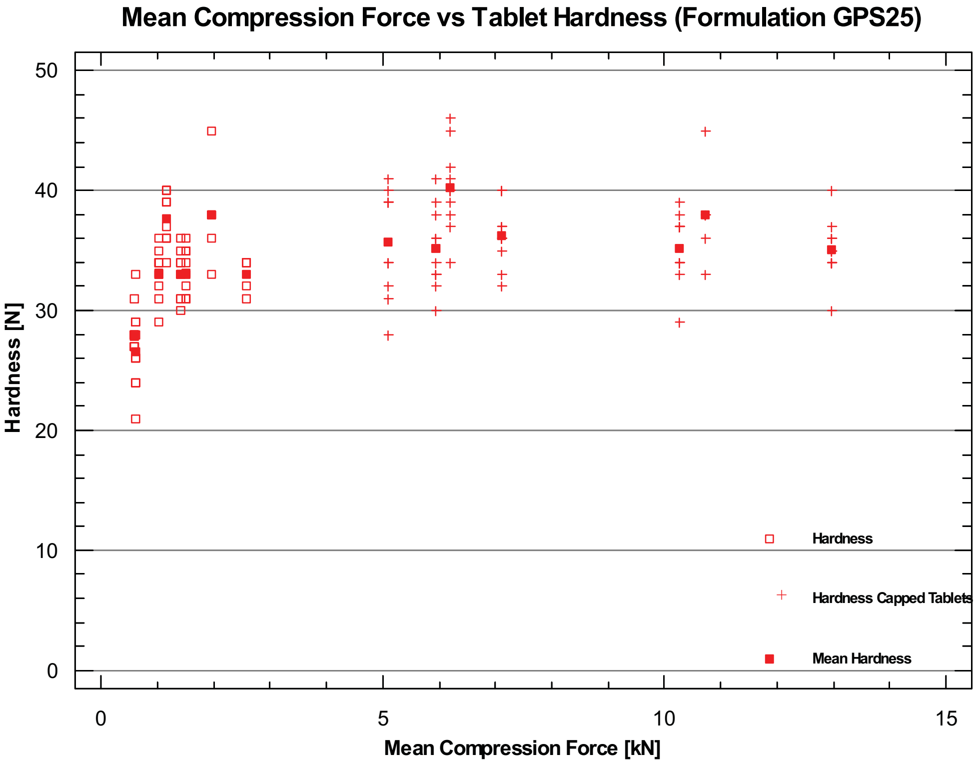


Fig. 4.4.3: Mean compression force vs. tablet hardness (formulation GPS25)

Comparable considerations led to target compression forces and acceptable specification ranges for the manufacture of matrix tablets for all formulations.

It has to be noted that differences in tablet hardness not only resulted from changes in formulations, but also variation of tablet diameter and thickness. Tablet weights of 134.68 mg, 202.02 mg and 404.04 mg required different tablet sizes. Twenty-five percent drug loading formulations (GDB25, GPS25, SUS25 and HPC25) were compressed to 10.0 mm tablets. Fifty percent and 75% drug loading formulations were compressed to 9.0 mm, with 75% drug loading tablets (formulations GDB75, GPS75, SUS75 and HPC75) thinner than 50% drug loading tablets (formulations GDB50, GPS50, SUS50 and HPC50). Therefore compression forces and obtained hardness values cannot be directly compared among drug loadings. Table 4.4.5 summarizes the obtained results for target compression forces and expected mean tablet hardness.

Table 4.4.5: Compression force ranges for manufacture of CR matrix tablets

Formulation	Target Compression Force (Range) [kN]	Tablet Hardness [N]		Confidence Interval Mean Tablet Hardness [N] (95%)	
		Minimum	Maximum	Lower Limit	Upper Limit
GDB25	9.0 (±3)	32	39	33	36
GDB50	7.7 (±2)	30	34	32	34
GDB75	9.7 (±2)	21	36	25	30
GPS25	1.2 (±0.2)	34	40	36	39
GPS50	7.5 (±3)	36	40	38	40
GPS75	5.1 (±2)	21	42	22	30
SUS25	9.5 (±2)	18	23	19	21
SUS50	11.2 (±2)	30	51	41	48
SUS75	14.3 (±2)	20	31	22	27
HPC25	13.8 (±3)	66	83	71	77
HPC50	13.3 (±2)	57	69	62	66
HPC75	18.0 (±3)	30	37	32	36

4.4.5.2 Tablet Hardness

Compression forces for manufacture of CR matrix tablets were fixed for all formulations in order to produce tablets of comparable hardness. Reproducibility of these parameters was checked by compression of three batches of tablets for each formulation, applying the same compression forces. Fig.4.4.4 shows results yielded for mean tablet hardness and highlights the distribution of individual values.

In order to evaluate the reproducibility of mean tablet hardness, the Tukey HSD procedure (p=0.05) was applied to detect significant deviations in mean tablet hardness. From a statistical point of view, significant differences between mean tablet hardness values were observed for formulations GDB25, GSB50, SUS50 and HPC75, whereas for all other formulations no significant changes in mean tablet hardness were revealed. Since t_S exceeded its critical value (t_S>5.1) a significant difference in mean tablet hardness between batch SUS50a and SUS50c occurred. For formulations GDB25 and HPC75, insignificant differences were observed between GDB25a and GDB25c (t_S<2.0) as well as HPC75b and HPC75c (t_S<2.9). A worst case was found for formulation GDB50, where all pair comparisons displayed significant differences among mean values (t_S>1.3). Additionally, observed mean values did not fall into the confidence interval (p=0.05) obtained from the compression force – tablet hardness datasets. Only formulations GDB75, GPS75 and SUS75 complied with all predicted values. However, it should be noted that two thirds of the formulations exhibited reproducible tablet hardness under controlled compression conditions.

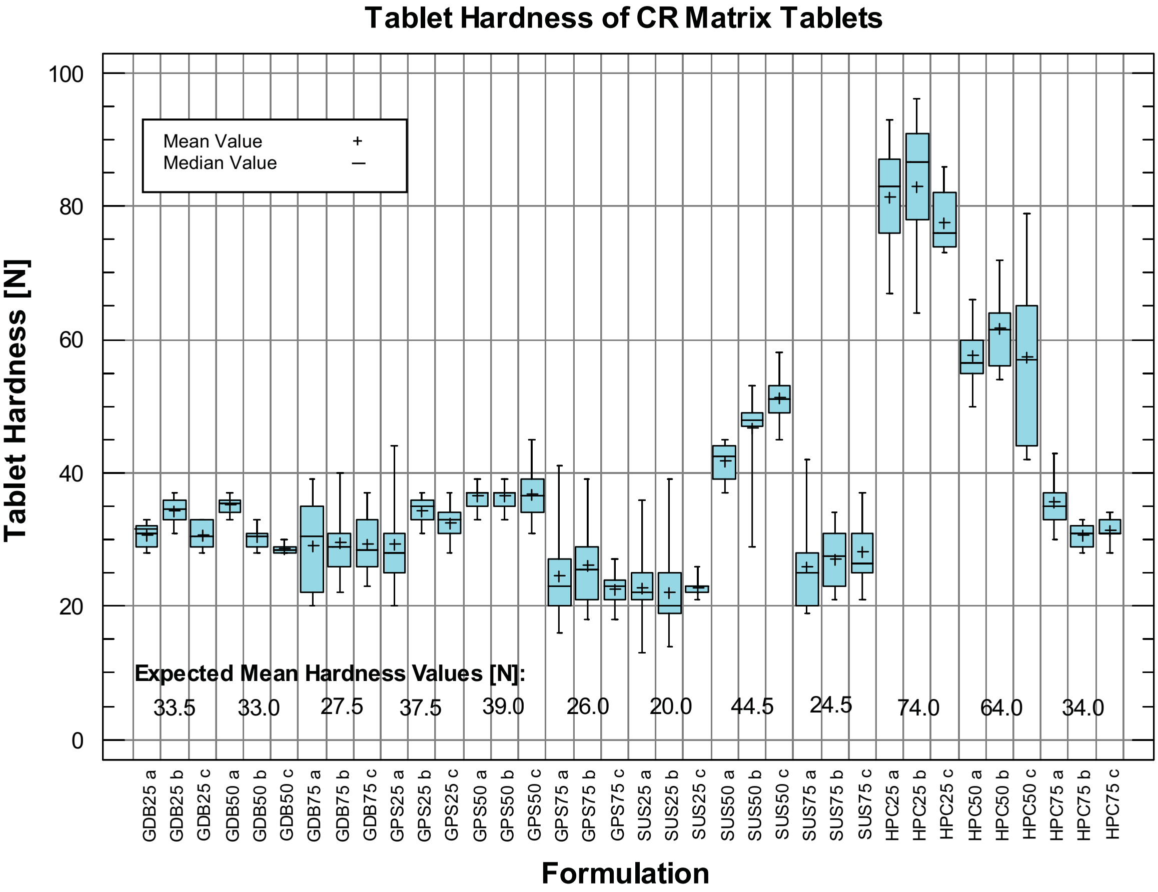


Fig. 4.4.4: Tablet hardness of CR matrix tablets

4.4.5.3 Friability

Table 4.4.6 summarizes the results obtained from friability testing. Except for GPS25 and SUS25, all formulations revealed acceptable friability (less than 1% [w/w]). Formulations GPS25 and SUS25 failed the test because formulation GPS25 contained units that capped during friability testing and formulation SUS25 exceeded the limit of one per cent friability.

Table 4.4.6: Friability of tablets compressed from melt-extruded granulates

Formulation	**Mean Weight Loss [g] (±SD)**	**Mean Friability [%] (±SD)**	**Pass/ Fail**
GDB25	0.00638 (±0.000720)	0.079 (±0.0085)	Pass
GDB50	0.00160 (±0.000785)	0.039 (±0.019)	Pass
GDB75	0.00396 (±0.00116)	0.148 (±0.0424)	Pass
GPS25	0.02216 (±0.004893)	0.276 (±0.0588)	**Fail/ Capping**
GPS50	0.00433 (±0.000873)	0.107 9±0.0217)	Pass
GPS75	0.00521 (±0.000802)	0.199 (±0.0327)	Pass
SUS25	0.10003 (±0.014081)	1.239 (±0.1789)	**Fail**
SUS50	0.01375 (±0.001048)	0.338 (±0.0262)	Pass
SUS75	0.00549 (±0.000346)	0.206 (±0.0141)	Pass
HPC25	0.00268 (±0.000344)	0.034 (±0.0049)	Pass
HPC50	0.01140 (±0.005653)	0.276 (±0.135)	Pass
HPC75	0.00379 (±0.00312)	0.084 (±0.010)	Pass

4.4.5.4 Tablet Weight and Uniformity of Mass of CR Matrix Tablets

A target tablet weight of 404.04mg was computed for tablets compressed from a 25% [w/w] drug loading granulate (formulations GDB25, GPS25, SUS25 and HPC25). Addition of magnesium stearate reduced the drug loading to effective 24.75%, leading to the targeted tablet weight. All mean values were found within a ±2.5% range of the target tablet weight. With the exception of formulation HPC25, all individual weights ranged within a ±5% [w/w] range of the target value. Formulation HPC25 contained tablets outside the five per cent range (minimum 378.46mg). Fig. 4.4.5 shows the tablet weight distributions found for 25% drug loading formulations.

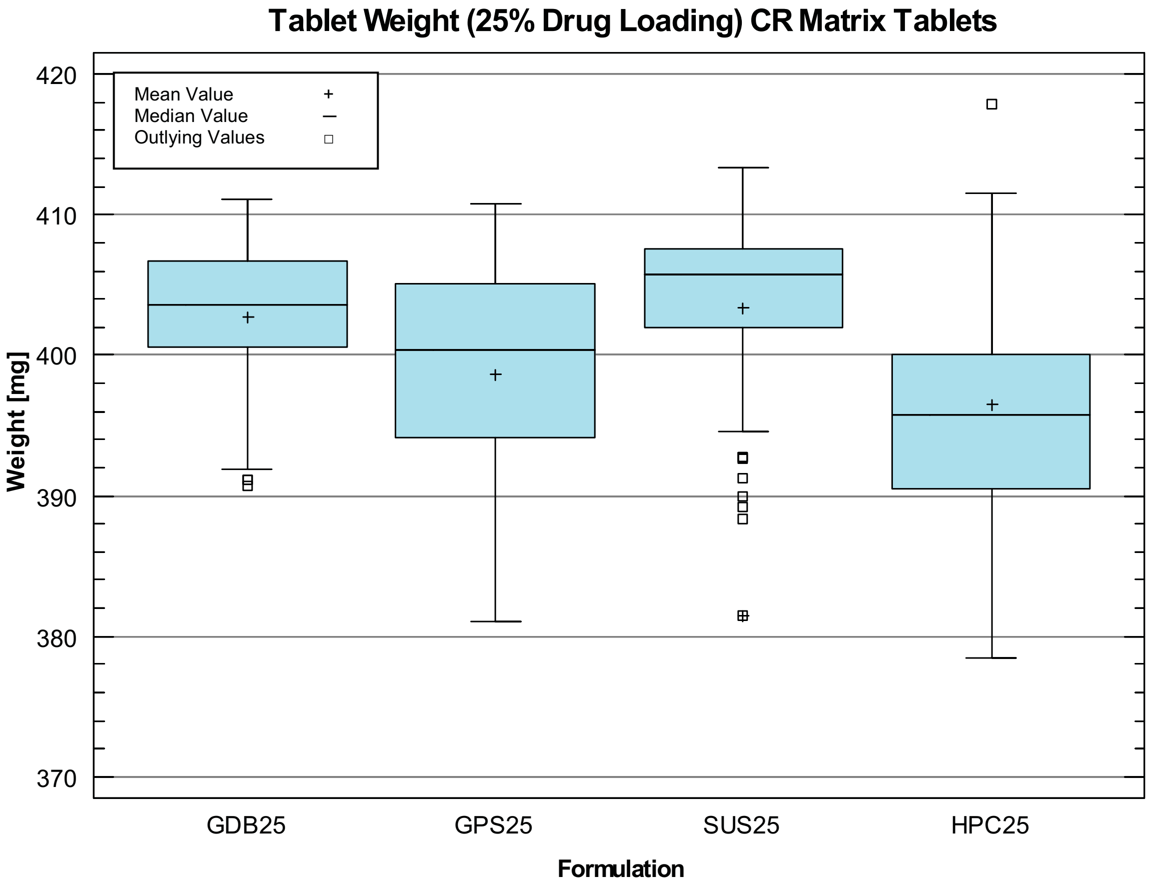


Fig. 4.4.5: Tablet weight (25% drug loading) of CR matrix tablets

The target tablet weight was also computed for tablets compressed from 50% drug loading granulate (formulations GDB50, GPS50, SUS50 and HPC50). Due to addition of magnesium stearate the drug loading was reduced to 49.5% resulting in target tablet weight of 202.02 mg in order to obtain 100.0 mg drug content. In contrast to 25% drug loading formulations, individual values did not fit within a 5% [w/w] of the targeted value. For formulations GDB50, GPS50 and SUS50 all individual values fell within a ±7.5 per cent range. Only formulation HPC50 contained tablets deviating more than 7.5% from the targeted value (maximum 221.59 mg). However, all mean tablet weights were within ±2% [w/w] window of the target value. A confidence interval (p=0.05) confirmed the mean values to be within the 2.5% [w/w] range of the desired tablet weight. Fig.4.4.6 summarizes the data for 50% drug loading formulations.

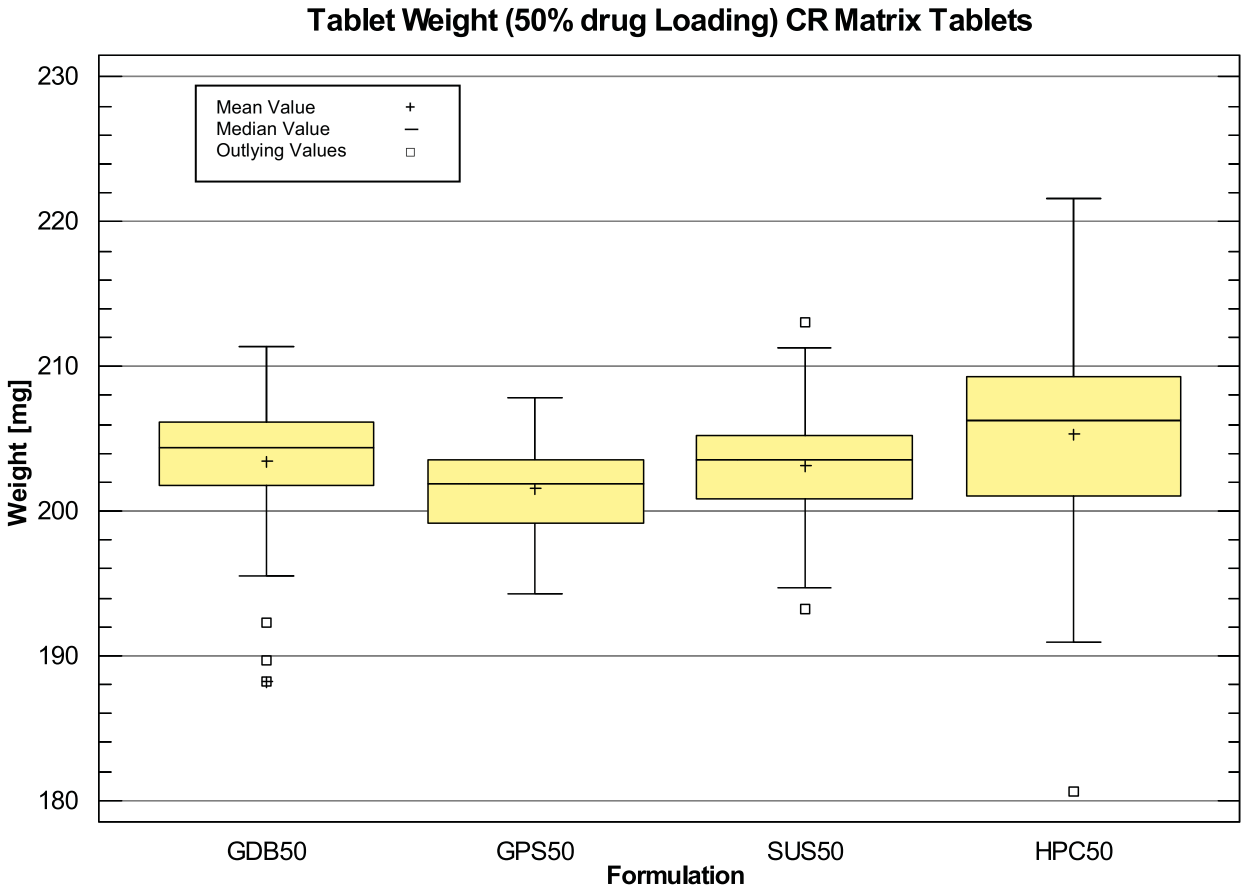


Fig. 4.4.6: Tablet weight (50% drug loading) of CR matrix tablets

The target tablet weight for 75% drug loading formulations was also computed. Addition of magnesium stearate lowered the effective drug loading to 74.25% resulting in a desired tablet weight of 134.68 mg for tablets compressed from 75% drug loading granulates (formulations GDB75, GPS75, SUS75 and HPC75). All individual tablet weights were within ±7.5% [w/w] of the target value. All mean values fitted into a ±2.5% [w/w] window of the target value. Estimation of real means by confidence interval ($p=0.05$) yielded in a three per cent window above and below the target tablet weight. Fig.4.4.7 shows the results obtained for formulations GDB75, GPS75, SUS75 and HPC75.

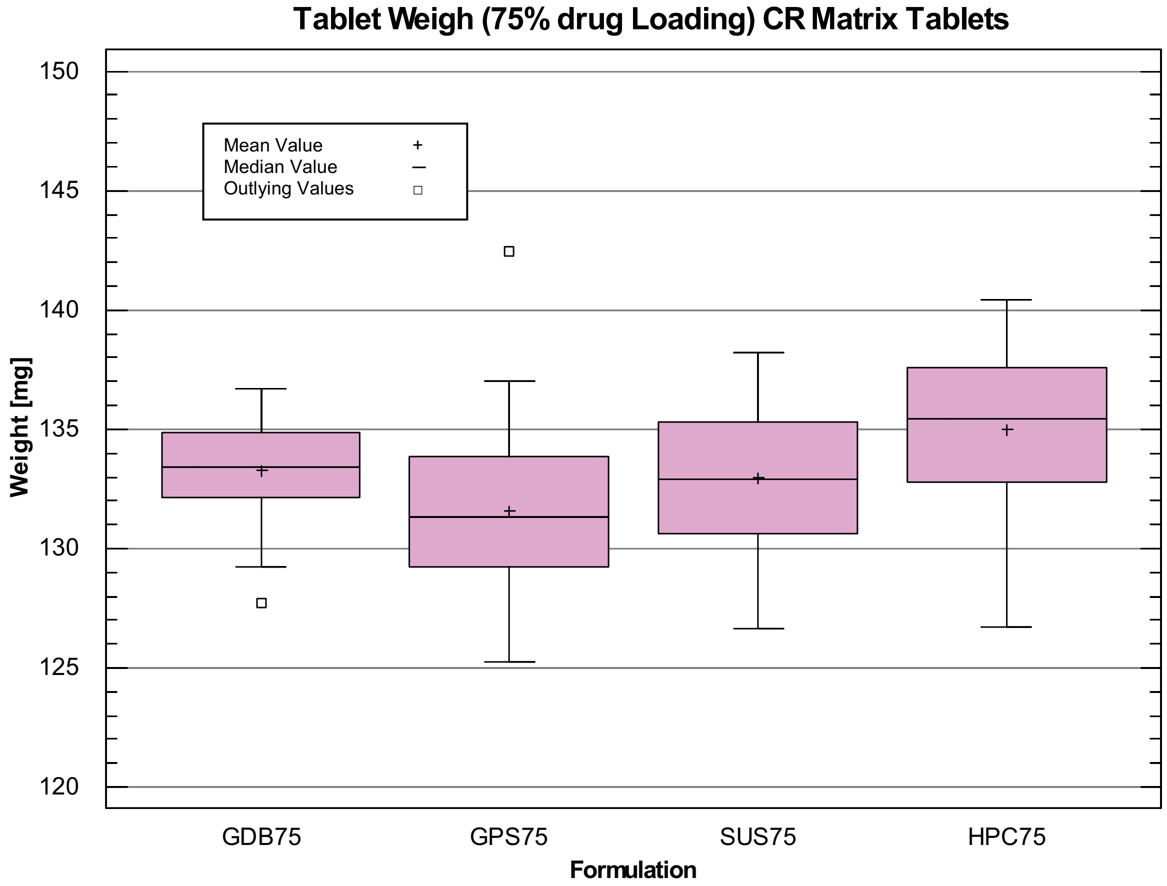


Fig. 4.4.7: Tablet weight (75% drug loading) of CR matrix tablets

Table 4.4.7 summarises results obtained for uniformity of mass of tablets. Generally, formulations corresponded to pharmacopeial test criteria regarding uniformity of mass. In addition, most examined batches did not contain faulty tablets with respect to weight. Outliers were only found in formulations GPS75, SUS25, and HPC25; in each case a single tablet exceeded minimum or maximum weight limits. For HPC50 batches, two single units exceeded minimum and maximum weight limits. However, both the number and weight of faulty units fell within the range corresponding to pharmacopeial requirements.

Table 4.4.7: Uniformity of mass of tablets compressed from melt extruded granulates (bold face type indicates outliers)

Formulation	Mean Weight [mg] (±SD)	Maximum Weight [mg] Range	Maximum Weight [mg] Found	Minimum Weight [mg] Range	Minimum Weight [mg] Found	Pass/ Fail
GDB25	402.74 (±1.8640)	422.88	411.09	382.61	390.66	Pass
GDB50	203.11 (±2.1799)	218.34	209.40	187.87	188.18	Pass
GDB75	133.31 (±1.1260)	143.31	136.73	123.31	127.73	Pass
GPS25	398.70 (±5.8466)	418.64	410.74	378.77	380.99	Pass
GPS50	203.20 (±2.4040)	218.44	208.97	187.96	194.26	Pass
GPS75	131.61 (±2.6729)	141.48	**142.46**	121.74	125.27	Pass
SUS25	403.36 (±1.6178)	423.53	413.39	383.19	**381.45**	Pass
SUS50	203.17 (±1.7336)	218.41	213.06	187.93	193.24	Pass
SUS75	132.96 (±0.77454)	142.93	138.19	122.99	126.65	Pass
HPC25	396.45 (±5.1185)	416.27	**417.89**	376.63	378.46	Pass
HPC50	205.28 (±1.0078)	220.68	**221.59**	189.88	**180.58**	Pass
HPC75	134.98 (±0.39850)	145.10	138.99	124.86	126.71	Pass

4.4.5.5 Drug Content and Uniformity of Content of CR Matrix Tablets

Fig. 4.4.8 summarizes the drug content of CR matrix tablets relative to the target value of 100.0 mg theophylline. Overall the mean theophylline content of examined tablets ranged within ±4% [w/w] of the target value of 100.0 mg. With the exceptions of formulation GDB50, HPC25 and HPC50 all individual values were found within a range of 100.0 mg ±10% [w/w], most single values were within 100 mg ±5%. The confidence intervals (p=0.05), estimates of mean drug contents ranged from 94.7mg to 105.2mg.

Table 4.4.8 summarizes results obtained from content uniformity measurements.
In addition all examined batches corresponded to pharmacopoeial requirements regarding uniformity of content. None of the tested tablets exceeded compendial limits. Accordingly, theoretically computed drug loadings matched effective ones closely.

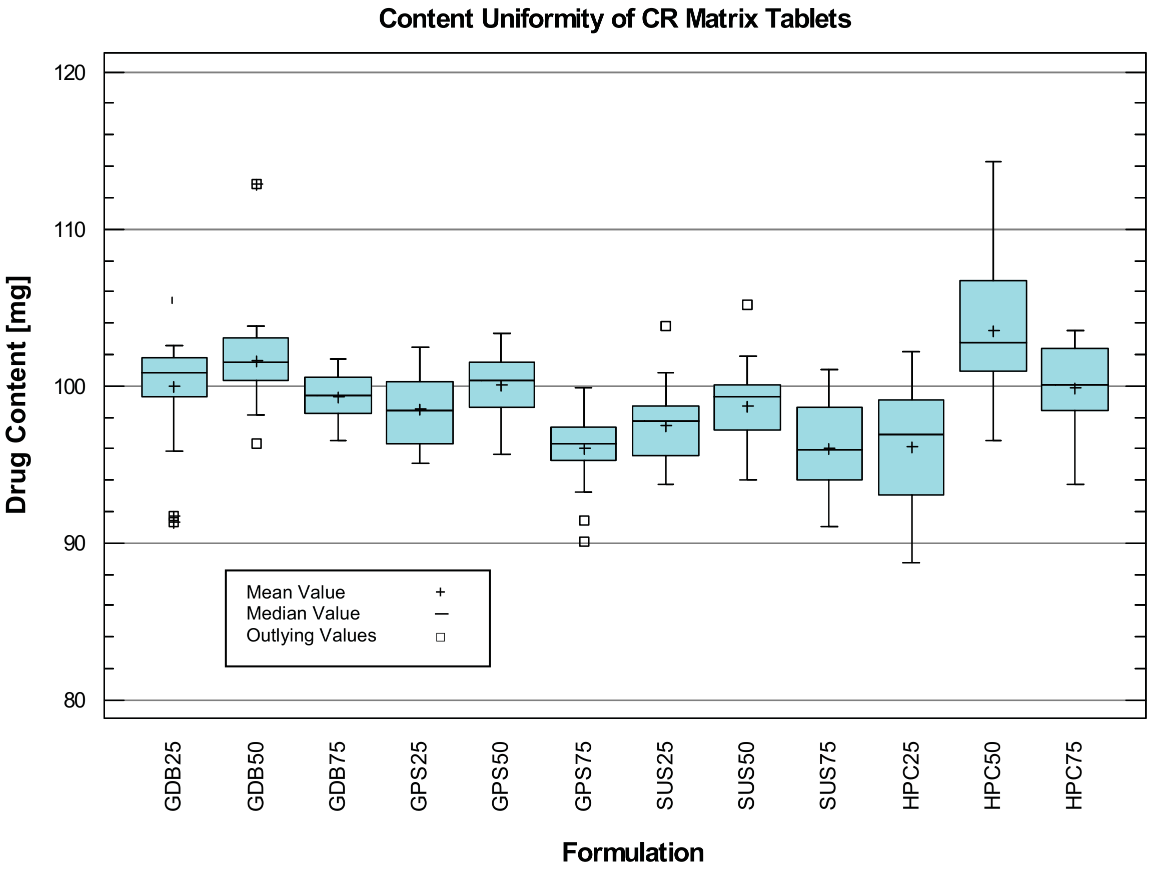


Fig. 4.4.8: Content uniformity of CR matrix tablets

Table 4.4.8: Uniformity of content of tablets compressed from melt extruded granulates

Formulation	Mean Content [mg] (±SD)	Maximum Content [mg] Range	Maximum Content [mg] Found	Minimum Content [mg] Range	Minimum Content [mg] Found	Pass/ Fail
GDB25	99.94 (±1.458)	114.93	102.56	84.95	91.37	Pass
GDB50	101.60 (±0.57570)	116.84	112.89	86.36	96.33	Pass
GDB75	99.27 (±0.2857)	114.16	101.70	84.38	96.56	Pass
GPS25	98.52 (±1.732)	113.30	102.44	83.74	95.08	Pass
GPS50	100.13 (±0.81525)	115.15	103.39	85.11	95.62	Pass
GPS75	96.01 (±0.9307)	110.41	99.84	81.61	90.04	Pass
SUS25	97.51 (±0.7586)	112.13	103.81	82.88	93.71	Pass
SUS50	98.70 (±0.7617)	113.50	105.17	83.89	94.04	Pass
SUS75	96.05 (±1.028)	110.45	101.00	81.64	91.06	Pass
HPC25	96.09 (±2.271)	110.50	102.19	81.68	88.74	Pass
HPC50	103.56 (±2.412)	119.09	114.33	88.03	96.53	Pass
HPC75	99.86 (±1.779)	114.84	103.56	84.88	93.70	Pass

4.4.6 Discussion

The present chapter deals with the pharmacopoeial requirements of single unit dosage forms, which also builds the foundation for interpretation of the dissolution test results. When performing a dissolution test, some background information such as the accuracy of drug content is essential for correct interpretation of obtained data. Other, physical parameters , e.g. the effective surface of a tablet, may additionally affect the reproducibility of dissolution rates.

As already discussed previously (see chapter 4.3), bulk material is densified during compression and particles potentially undergo fragmentation and deformation depending on applied compression forces. Compression defines the structure and effective surface of a tablet, tablet hardness and friability. For this reason it is essential to control and monitor the impact of compression forces on the quality of the obtained tablets, using standard parameters, such as hardness and friability. Changes in compression force can also result in changes in the dissolution rate of tablets. Valleri M., et al. (2004) described decreasing dissolution rate with increasing tablet hardness for fast dissolving glyburide tablets. Kabanda L., et al. (1994) showed that decreased tablet hardness increased the initial burst effect of hydrophilic propylthiouracil matrix tablets. It is thus essential to understand effects of changes in compression processes on tablet quality in order to exclude random effects on dissolution.

The present study has successfully shown that by defining target compression forces, reproducible tablet quality regarding friability and tablet hardness can be achieved. On the other hand, statistically significant inter-batch differences regarding tablet hardness were observed, so some inter-batch difference in dissolution rate might be expected. Yet the absolute difference among mean values was always below 11%, which might result in borderline significant differences in dissolution in some cases.

Since all batches complied with pharmacopeial requirements, it can be assumed that the measures applied to control and monitor compression processes and tablet quality were appropriate for obtaining batch-to-batch reproducibility. Therefore, the tablets were consistent with industry-wide norms.

Low tablet hardness and friability failures were caused by unsuitable formulation design. Due to high degrees of elastic deformation during compression (see chapter 4.3) most bulks were assumed to be less than ideal for compression. Hence it is not a surprise that tablet hardness and friability were less than ideal in some cases, e.g. formulation GPS25 (glycerylpalmitostearate, 25% drug loading) showed a very narrow bracket of suitable compression forces and failed friability testing due to capping. Similarly formulation SUS25 failed friability testing due to a loss in weight exceeding 1% [w/w]. On the other hand, all other formulations passed friability testing despite showing rather low mean tablet hardness. This result indicates a generally good feasibility of preparing matrix tablets from (binary) mixtures of theophylline with a carrier material.

Regarding uniformity of mass, all formulations show satisfactory values, with flow properties suitable for consistent die fill from a hopper. The exception was formulation HPC25, for which the die had to be filled manually due to insufficient flow of the bulk. HPC formulations (HPC25/50/75) show the widest distribution of tablet weights, again underlining the poor flowability of the material. Results are in concordance with observations made for flowability of bulk materials (see chapter 4.3).

Finally, tests confirmed the uniformity of content of tablets, as drug content ranged within pharmacopeial specifications of the target value of 100.0 mg theophylline. Only a few outlying values were found, but these values were related to high tablet weight. For safety reasons, especially for drugs with narrow therapeutic windows, such as theophylline, a narrow distribution of drug content is often desirable.

Retrospectively, glyceryldibehenate showed the best “global” results as, in contrast to glycerylpalmitostearate, sucrose-fatty acid-ester S 1670 and hydroxypropylcellulose, tablets with acceptable quality were obtained for all tested drug loadings.

4.4.7 Conclusion

Reproducibility of tablet quality was demonstrated for most formulations of the four carriers. Glyceryldibehenate proved most suitable for manufacture of matrix tablets applying a simple formulation design. Glycerylpalmitostearate and sucrose-fatty acid- ester S1670 delivered comparable tablet quality, but show less flexibility regarding drug loading. Hydroxypropylcellulose formulations produce the hardest tablets, but poor flowability of the granulate detracted from the quality of the prepared tablets.

5 *In Vitro* Dissolution of Controlled Release Dosage Forms processed by Melt-Extrusion

In order to develop CR matrix systems, a model active, theophylline, was processed with various carriers by melt extrusion and the resulting granulates were compressed to matrix tablets. So far, various aspects of formulation and processing of these materials and formulations have been described. This chapter is devoted to the in-vitro release characteristics of the CR matrix systems.

In the first section, the mechanisms of drug release are elucidated. Then, the effects of further parameters with potential effects on dissolution, such as time and conditions of storage, pH and ionic strength of dissolution media are examined. Thus, a comprehensive picture of the release properties of the formulations and carriers used to modify the drug release from matrix tablets will be constructed. Based on these and previous results, the robustness of the CR matrix systems is addressed, including sensitivity towards hydrodynamics or presence of food and enzymes.

5.1 *In vitro* dissolution

5.1.1 Introduction

The dissolution performance is a crucial measure of the ability of a carrier to produce a controlled drug release. To understand the mechanisms of the various CR formulations generated, a theoretical analysis of their drug release profiles was undertaken.

Over the last few decades several techniques have been established for elucidating release mechanisms from different kinds and geometries of dosage forms. Diffusion controlled release (or Case I) is typified by drug diffusion through a polymer matrix along a concentration gradient (Higuchi T. (1961), Paul D.R., et al (1976)). Case II describes drug release from swellable controlled release systems by a coupling of Fickian diffusion and polymer relaxation processes (Ritger P.L. et al (1987, 1987b)). It is governed by the formation and movement of a sharp boundary between rubbery and glassy phase formed by solvent penetration into the polymer (Enscore D. et al (1977), Kosmidis K. et al. (2002)). Generally, drug release from porous systems can be divided into release controlled by diffusion and release controlled by Case II transport.

Intermediate cases, with profiles lying between Fickian and Case II release, have been referred to as anomalous release behaviour Ritger P.L., et al. (1987)).

Ritger P.L., et al. (1987, 1987b) have applied semi-empirical models to describe Case II drug release. Their publication pointed at the high non-linearity of drug release caused by simultaneous presence of diffusion and relaxational mechanisms. Therefore, they suggested numerical solutions to model drug release from swellable system belonging to the moving boundary problem category. The semi-empirical solutions reflect for example the geometry of the dosage form and particle size distribution of the drug.

It is often asserted that hydrophilic colloid systems release by Case II kinetics. In these systems the pharmaceutical active is dispersed or dissolved in a hydrophilic excipient network. Upon contact with the penetrant the polymer swells and forms a hydrogel. The swollen (hydrogel) phase can be distinguished from the unswollen (rubber) phase. Drug release depends on the rate at which the the rubber/ gel interface proceeds. Gels with low viscosity tend to erode under physical stress such as gastric motility and interface movement is governed largely by erosion of the gel layer. For most hydrocolloid matrices, a combination of Fickian diffusion and Case II controlled drug release has been described (Gurny R., et al. (1982), Ritger P.L., et al. (1986), Collins R. (1998)).

Model-dependent analysis of drug release represents a powerful tool to elucidate the release mechanism of a drug/ carrier system. Various models are available to describe the prevailing release mechanism of a tested system.

For example, the Higuchi model is used to fit a diffusion controlled (Case I) drug release ($r^2 \rightarrow 1$). Eq. 5.1.1 shows the model established by Higuchi T. (1963), describing fractional drug release as the ratio of drug release at time t (M_t) and release after an infinite timespan (M_∞). According to Higuchi, fractional drug release depends on the square root of time and the kinetic constant k_X.

$$\frac{M_t}{M_\infty} = k_X \sqrt{t} \qquad (5.1.1)$$

Another approach is the Power-Law (Korsmeyer R.W. et al. (1983)), which uses the term n to describe the main mechanism of drug release. The Power-Law model suggests diffusion controlled release for $n = 0.5$; under these conditions the equation converts to Higuchi's model. A value of $n = 1$ demonstrates Case II dominated release. For $0.5 < n < 1$ an anomalous (non-Fickian) diffusion mechanism (Langer R.S. et al. (1981)) was proposed. Eq. 5.1.2 describes the Power-Law model.

$$\frac{M_t}{M_\infty} = k'_X t^n \tag{5.1.2}$$

Using the Peppas-Sahlin model, described in Eq. 5.1.3 (Peppas N.A. et al. (1989)), the terms *m*, k_D and k_R describe the main mechanism of drug release. k_{DX} and k_{RX} describe diffusion (Case I) and relaxation (Case II) constants of system X, while *n* is the release exponent, which is dependent on the release mechanism and the geometry of the tested dosage form (Ritger P.L. et al. (1987)). Furthermore, the model provides an estimate of the relative contributions of Fickian diffusion and Case II (erosion, relaxation) transport to drug release. Fractional drug release is calculated as the sum of diffusion controlled drug release and drug release by Case II mechanisms, with both terms including specific kinetic constants (k_D, k_R). Therefore the ratio of both constants roughly indicates the relative contributions of diffusion mechanisms (k_D) and Case II mechanisms (moving boundary, erosion) (k_R) to the overall drug release.

$$\frac{M_t}{M_\infty} = k_{DX} t^m + k_{RX} t^{2m} \tag{5.1.3}$$

Finally, the Weibull model (Langenbucher F. (1972)) can be used to describe the shapes of release profiles. When $b < 1$, the model indicates parabolic dissolution curvature with accelerated initial drug release leading into a phase of slower and constant dissolution rate. On the other hand, $b = 1$ indicates that an exponential release profile exists and $b > 1$ corresponds to a sigmoidal release profile.

$$\frac{M_t}{M_\infty} = 1 - EXP\left[\frac{-\left(t - T_{lag}\right)^b}{a}\right] \tag{5.1.4}$$

$$M_t = M_\infty * \left[1 - EXP\left(\frac{t^b}{T_D}\right)\right] \tag{5.1.5}$$

In addition to the release mechanisms, the effective dissolution surface has been recognized as a key parameter to release rate. Several factors are known to determine release rate by affecting the surface available for dissolution, namely the wetting behaviour of the drug, the porosity of the dosage form and the particle size of the drug (Hoerter D. et. al. (2001)). These parameters can be modified to tweak the dissolution rate of actives (von Orelli J. et al. (2004), Zhang Y.E. et al.

(2001), Mehta K.A. et al. (2000)). Considering CR matrix tablets, the dimensions of the tablet and the surface of its pores define the total surface available for dissolution. However, poor wettability of excipients reduces the tendency of solvents to penetrate the pores and hence potentially reduces the effective surface. Friedrich H. et al. (2005) identified enhanced dissolution rate of nifedipine due to improved wettability when this was optimized by selection of hydrophilic carriers. Similarly Schreiner T. et al. (2005) reported an increased dissolution rate of ketoprofen by employing hydrophilic agents such as lactose or cellulose to improve wettability of the pure active. The present study applies measurement of contact angles of the CR tablets with water as an estimate for wettability (Hoerter D. et al. (2001), Friedrich H. et al. (2005)).

5.1.2 Methods

5.1.2.1 Dissolution Tests

All dissolution tests were performed at least in triplicate using USP II paddle apparatus (also see chapter 3.3) applying a rotation speed of 50 rpm and 900ml of pH 6.8 phosphate buffer (see Table 5.1.1) per vessel.

Table 5.1.1: Dissolution media used for examination of dissolution performance and release mechanism

Phosphate Buffer USP 26 pH 6.80	
KH_2PO_4	6.8g
NaOH pellets	0.90g
Water (Purified)	qs ad 1000ml
pH	6.80
Ionic Strength	0.30mol/l

5.1.2.2 Theoretical Examination of Release Mechanism

To assess release mechanisms, different models were applied in this section. Release data were fitted to the Higuchi model (Eq. 5.1.1), Power-Law model, (Eq. 5.1.2), the Peppas-Sahlin model (Eq. 5.1.3) to evaluate the presence of diffusion controlled, Case II release mechanisms and combinations thereof. In order to assess the shape of the release profiles obtained, data were fitted to the Weibull model (Eq. 5.1.4 and Eq.5.1.5).

In the above equations, fractional drug release as the ratio of drug release at time *t*, (M_t), and release approaching infinity, (M_∞), are calculated as a function of time, *t*, by employing kinetic constants (k_X, k_X') specific for a drug/excipient system X. The diffusion coefficient *m* applied in the Peppas model was determined to be 0.43 according to the method given by Ritger P.L., et al. (1987) and the aspect ratio of the tablets ranged between 1 and 3. Only the first 60% of drug release were fitted to each model.

According to Costa P. et al (2001) the original Weibull function can be modified by replacing parameter *a*, the scale parameter, by the more comprehensive term T_D, which is defined by $a = (T_D)^b$ and represents the dissolution time interval required for release of 63.2% of the total drug released M_∞. In the present case no lag-time, T_{lag}, was expected for drug release and hence the term was set to $T_{lag} = 0$, resulting in the Weibull function shown in Eq. 5.1.5.

Release data were fitted using the least square residual method and the quality of fit was assessed by calculation of correlation coefficient (r^2). All values were calculated using Microsoft Excel 2000 V9.0.7616 with Solver® Add-In.

5.1.2.3 Reproducibility of Dissolution Performance

In order to assess the reproducibility of drug release, three batches per formulation were compressed according to recommendations given in chapter 4.5. Drug release was then tested using USP II paddle apparatus and 900ml of Phosphate Buffer USP 26 pH 6.8. A stirring speed of 50 rpm was applied and six units were tested per batch.

Statistical comparison of dissolution profiles was performed to compare drug release profiles. To test the similarity of two dissolution profiles, e.g. the comparison of newly developed formulations with a reference formulation, the f_2-test (similarity factor) is one of the most commonly applied and recommended methods (FDA 1997a, 1997b, 2000). The ability to base evaluations of similarity of dissolution profiles on one calculated value is regarded as the main advantage of this method (Yuksel N. et al. 2000). However, the advantageous simplicity of this method is partly offset by some relevant statistical issues (Costa P. et al. 2001, Liu J.P. et al 1997), with the invariant consideration of shape of dissolution curves and the potentially unbalanced selection of time points used for calculation of f_2 values regarded as the main weaknesses of f_2-testing. Alternative methods recommended for statistical comparison of dissolution profiles are repeated measures one-way analysis of variance (RMANOVA) and the unpaired t-test. These model-independent methods rely on raw data, do not require curve fitting procedures and are capable of identifying differences in level and shape (Yuksel N. et al. 2000).

5.1.3 Results and Discussion

5.1.3.1 Dissolution Performance

The dissolution performance was one of the main criteria to assess suitability of the various carriers for making controlled release devices using melt extrusion. Figs. 5.1.1 - 5.1.3 show some representative dissolution profiles of formulations with drug/carrier ratios of 25% (GDB25, GPS25, SUS25 and HPC25), 50% (GDB50, GPS50, SUS50 and HPC50) and 75% (GDB75, GPS75, SUS75 and HPC75), respectively. All formulations released theophylline in a controlled manner and therefore indicated general suitability of the carriers for CR matrix applications.

> HPC formulations revealed the fastest drug release at a given theophylline drug loading. Considering the example of a 25% drug/carrier ratio, drug release from formulation HPC25 reached 85% at 12h while formulation SUS25 only reached 40% drug release within the same interval. The lipophilic carriers (GDB, GPS) produced the slowest release among carriers tested and had released only 15% and 10%, respectively, at 12h. These results suggested that the choice of carrier had a great impact on the rate of drug release.

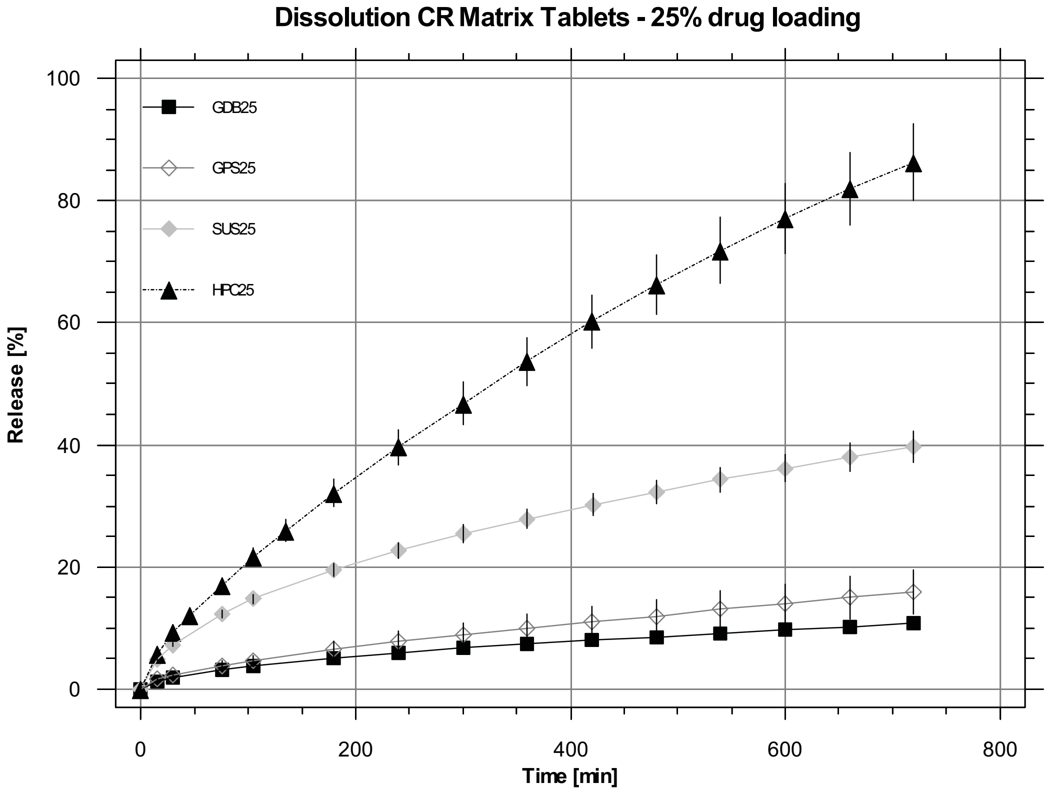


Fig. 5.1.1 Dissolution CR matrix tablets, phosphate buffer USP 26 pH 6.8 (n≥3) – 25% drug loading

Varying the drug/ carrier ratio gives further flexibility in manipulating the release rate to achieve the desired release characteristics. For HPC, increasing the drug/carrier ratio increased the drug release rate. At 75% [w/w] drug loading 85% of the total theophylline content were released within 180min, whereas at 25% [w/w] drug loading only 30% [w/w] of theophylline was released within the same time-frame. By contrast, SUS formulations showed little variation of drug release rate with changes in drug loading. Between 25% [w/w] and 75% [w/w] drug loading, theophylline release within 720min rose from 40% to 50%. Thus, release from SUS extrudates can be considered robust to minor fluctuations in drug loading from batch to batch.

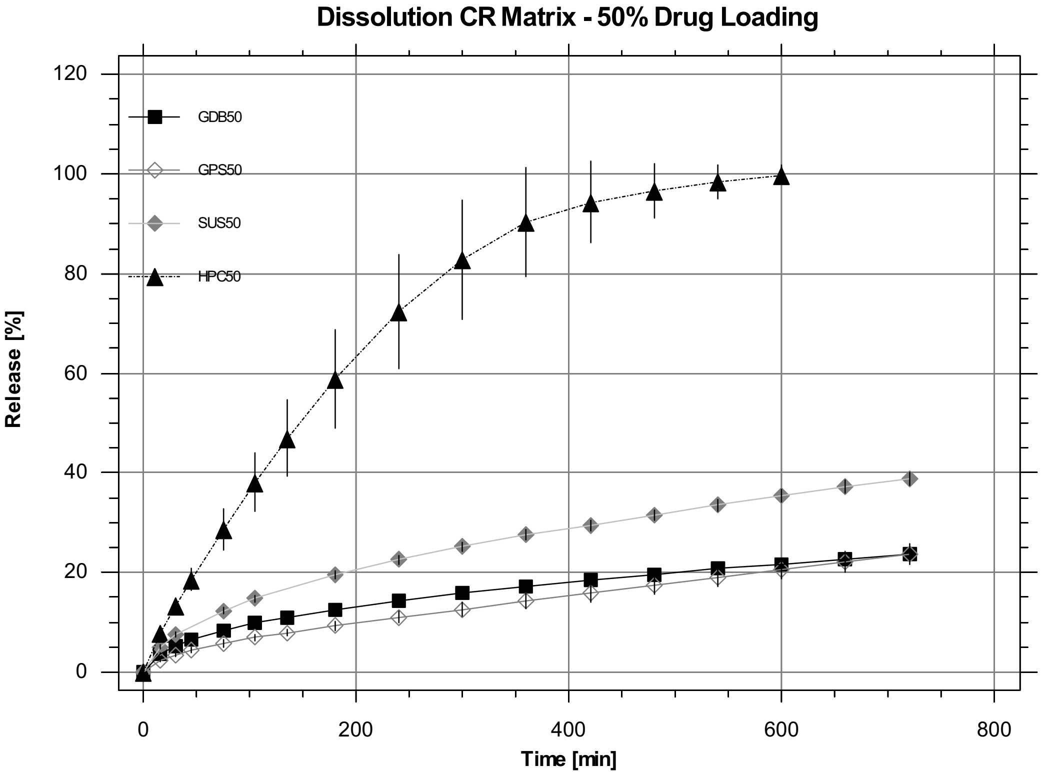


Fig. 5.1.2 Dissolution CR matrix tablets, phosphate buffer USP 26 pH 6.8 (n=5) – 50% drug loading

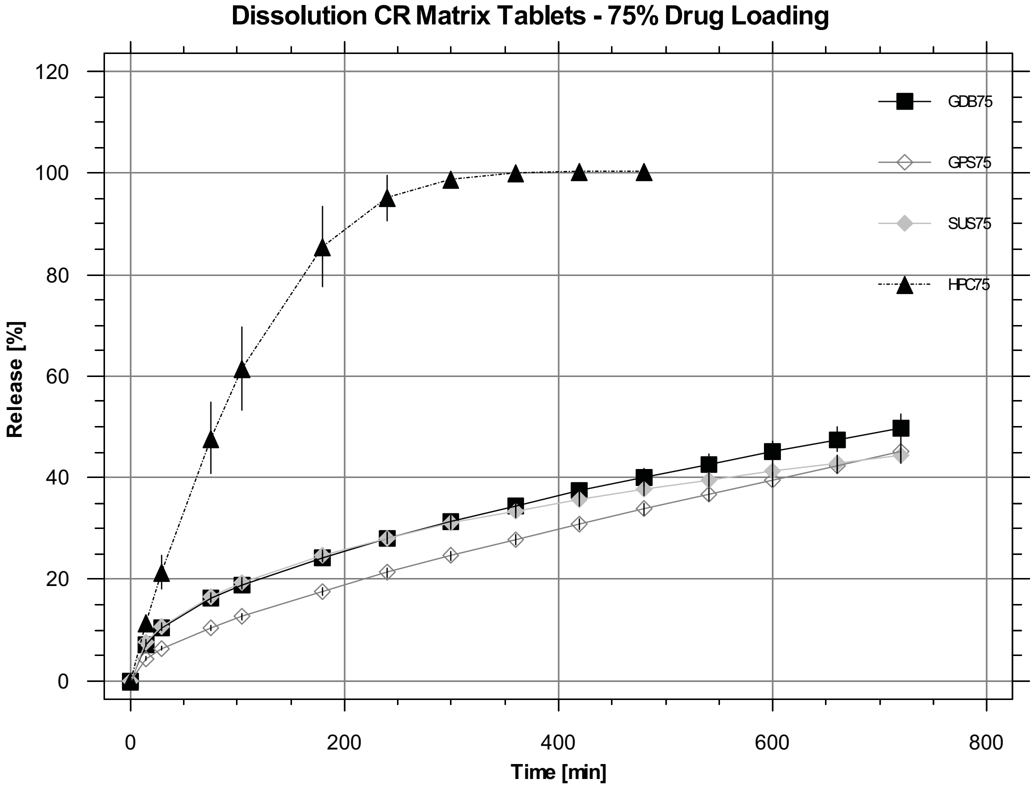


Fig. 5.1.3 Dissolution CR matrix tablets, phosphate buffer USP 26 pH 6.8 (n=5) – 75% drug loading

The lipophilic carriers GDB and GPS showed their potential to provide a slow, controlled drug release even at high drug loading. Even at 75% [w/w] drug loading, these carriers still released only 40-50% [w/w] theophylline within twelve hours.

5.1.3.2 Impact of Drug/ Carrier Ratio on Dissolution

In this section the influence of the drug/carrier ratio on the dissolution rate of the individual systems is examined in more detail.

For glyceryldibehenate formulations, release rate was dependent on the drug/carrier ratio. Increasing the proportion of theophylline resulted in faster drug release, for instance formulation GDB25 released 12% within 12h whereas formulation GDB75 had released 54% within the same interval (see Fig. 5.1.4).

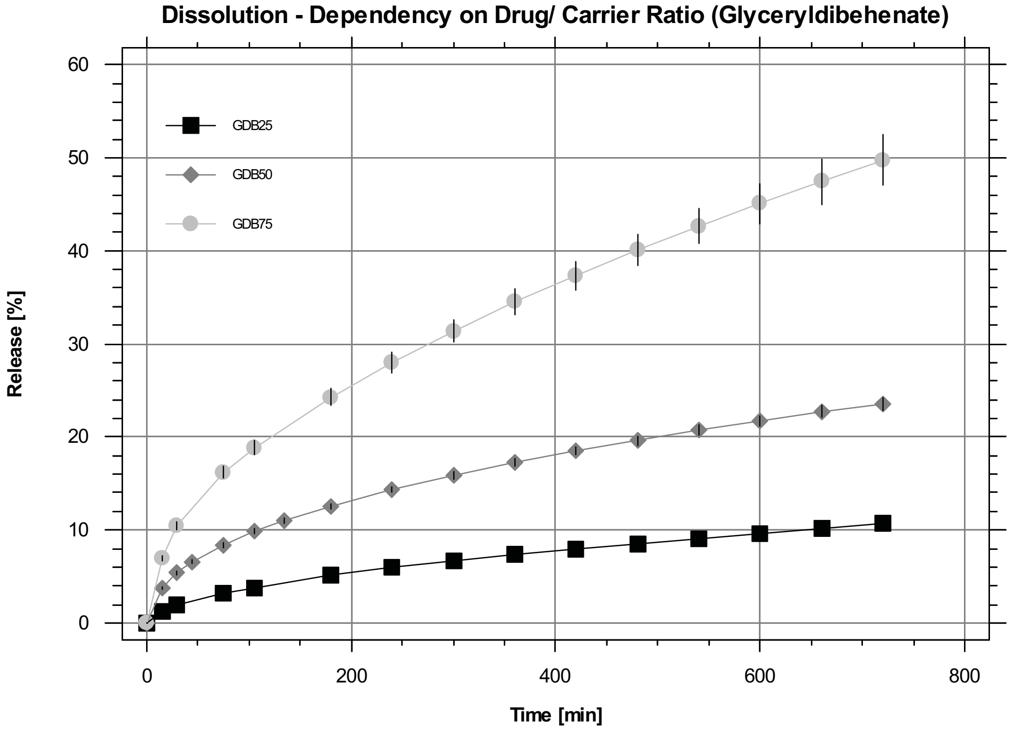


Fig. 5.1.4 Dissolution – dependency of drug/ carrier ratio: glyceryldibehenate formulations GDB25, GDB50 and GDB75, phosphate buffer USP 26 pH6.8 (n=6)

Likewise, glycerylpalmitostearate formulations GPS25, GPS50 and GPS75 exhibited a dependency of release rate on drug loading (see Fig. 5.1.5). As observed for glyceryldibehenate, mean drug release from glycerylpalmitostearate formulations increased with an increase in drug loading. Within 12h, GPS25 released 15%, GPS50 24% and GPS75 37% of the theophylline contained.

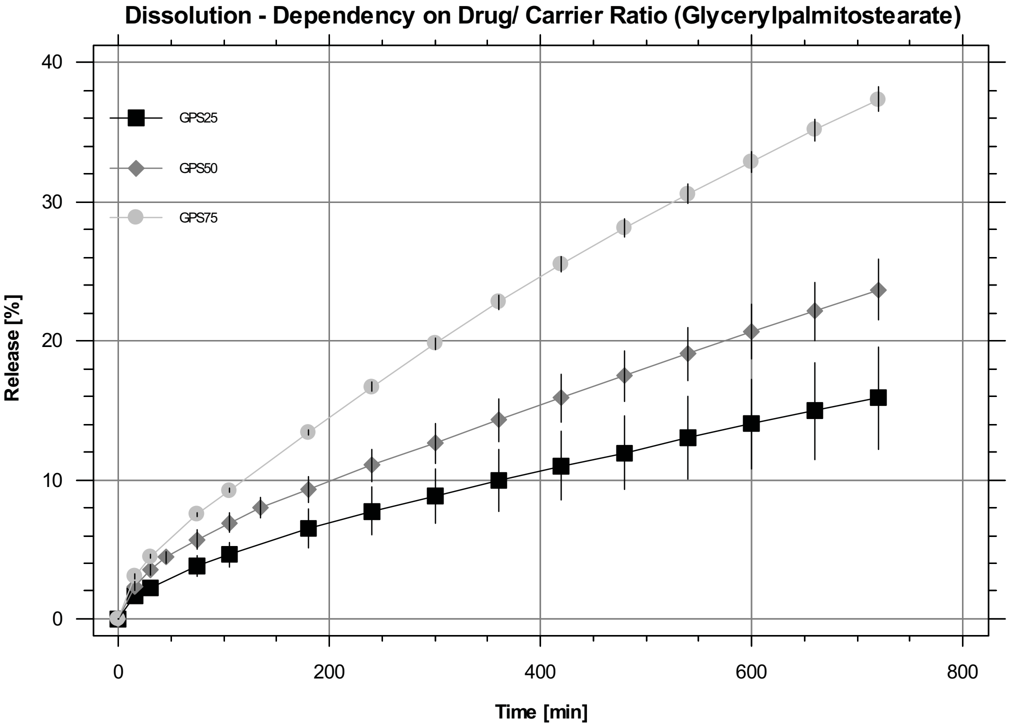


Fig. 5.1.5 Dissolution – dependency of drug/carrier ratio: glyceryldibehenate formulations GPS25, GPS50 and GPS75, phosphate buffer USP 26 pH6.8 (n=6)

In contrast to glyceryldibehenate and glycerylpalmitostearate formulations, no dependency of drug loading on dissolution rate was observed for sucrose-fatty acid ester formulations (Fig. 5.1.6). Hence comparable amounts of drug were released at 12h (40% vs. 38% vs. 42%) from formulations SUS25, SUS50 and SUS75. Fig. 5.1.6 shows representative dissolution profiles of sucrose-stearate S 1670 formulations.

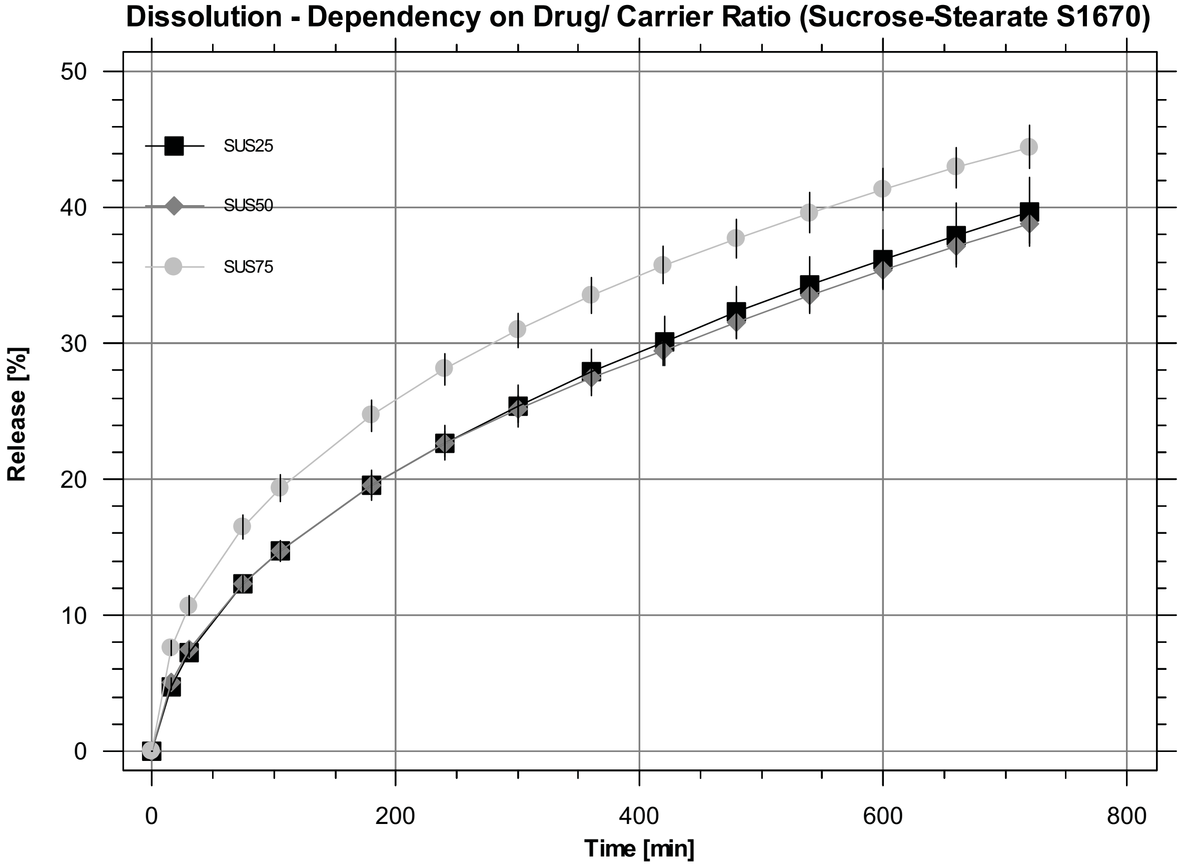


Fig. 5.1.6 Dissolution – dependency of drug/carrier ratio: sucrose-stearate formulations SUS25, SUS50 and SUS75, phosphate buffer USP 26 pH6.8 (n=6)

Finally HPC formulations displayed controlled release of theophylline from the compressed matrix tablets. Drug release reached 80% after 11h, 5h or 3h respectively depending on drug loading and hence dissolution was faster than for all other formulations tested. Fig. 5.1.7 shows that changes in drug loading had more impact on drug release from HPC formulations than for the three other carriers examined.

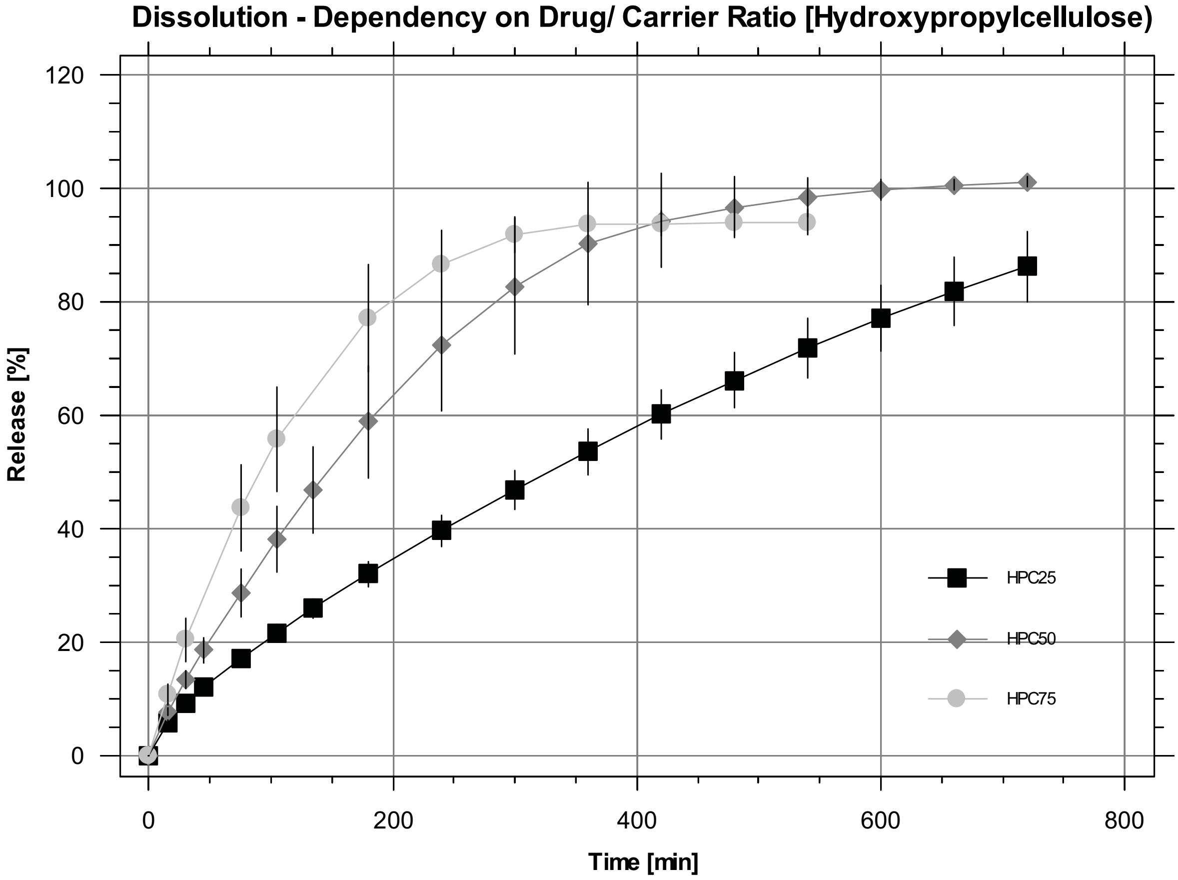


Fig. 5.1.7 Dissolution – dependency of drug/carrier ratio: hydroxypropylcellulose formulations HPC25, HPC50 and HPC75, phosphate buffer USP 26 pH6.8 (n=6)

5.1.3.3 Contact Angles of Bulk Materials

Initial dissolution studies demonstrated a wide range of drug dissolution rates from the different CR matrix tablets. Investigating the physicochemical properties, in particular the wettability, of the excipients used and the dosage forms prepared may help to understand the differences in drug release. Table 5.1.2 summarizes the contact angles with water for the bulk excipients, as well as tablets prepared at 25% [w/w] and 75% [w/w] drug loading tablets for each of the carriers.

In the present study theophylline was used as a model active with high water-solubility. Determination of its contact angle with water further indicated superior wetting behaviour (ω=37.2°) compared to the carriers used for embedding the drug. Therefore, it can be reasoned that embedding the drug in less wettable carriers contributed slowing down the kinetics of drug dissolution in the formulations.

As indicated in table 5.1.2, best wettability was observed for sucrose-stearate (ω=44.0°) followed by HPC (ω=58.0°). As expected, the two lipophilic carriers GDB (ω=98.5°) and GPS (ω=93.4°) showed comparably poor wettability. This can be attributed to their small polar surface area, which is also expressed in a high logP and low aqueous solubility. Based on their physicochemical properties, glyceryldibehenate and glycerylpalmitostearate should provide the least wettable dosage forms.

A good qualitative ranking was obtained when comparing contact angles of the matrix tablets (see Table 5.1.2) with their corresponding bulk carrier materials (SUS<HPC<GPS<GDB). For the two lipid carriers, contact angles of tablets were similar to those of the bulk carrier material. By contrast, a decrease in contact angle was found for SUS and HPC formulations compared to the bulk excipients.

One hypothesis for the behaviour of HPC and SUS formulations is that compaction of the material removed air from the material. Since air is a hindrance to wetting, its removal could result in a decreased contact angle. Another hypothesis is that theophylline crystals were emulsified in the carrier during melt extrusion. Depending on the phase behaviour of the emulsion, hydrophilic components may be concentrated on the surfaces of the extrudates, resulting in increased surface hydrophilicity. This mechanism was widely applied to improve wettability of poorly wettable compounds or formulations (Felton L.A., et al. (2000), Buckton G., et al. (1991), Efentakis M., et al. (1991)).

Table 5.1.2: Contact angle of bulk materials and CR matrix tablets with 25% [w/w] and 75% [w/w] drug loading

Material/ Formulation	Mean Contact Angle [°] (±SD)
Glyceryldibehenate (GDB)	98.5 (±1.9)
Glycerylpalmitostearate (GPS)	93.9 (±1.7)
Sucrose-Stearate (SUS)	44.0 (±9.9)
Hydroxylpropylcellulose (HPC)	58.0 (±4.1)
Theophylline Anhydrous	37.2 (±6.4)
GDB25	97.1 (±3.3)
GDB75	102.4 (±8.7)
GPS25	94.6 (±6.8)
GPS75	94.4 (±2.2)
SUS25	16.9 (±5.2)
SUS75	15.7 (±7.6)
HPC25	34.7 (±7.4)
HPC75	39.0 (±2.1)

A comparison of contact angles partly explains differences in drug release rates between the formulations. As expected, formulations composed from lipophilic carriers (GDB, GPS) were less wettable than SUS and HPC formulations and showed slower drug release. However, the wettability of bulk materials and matrix tablets does not explain the slower drug release from GPS tablets compared to GDB tablets, nor the rank order of release rates from HPC and SUS tablets.

Interestingly, changes in drug loading had little impact on wettability, e.g. contact angles of ω=97.1° and ω=102.4°were found for GDB25 and GDB75, respectively. Thus the differences in drug release between GDB25 and GDB75 tablets were not explained by changes in wettability. Similar observations were made for GPS and HPC formulations. Hence, other parameters need to be identified to explain the differences in drug release from the carriers examined.

5.1.3.4 Release Mechanism

Table 5.1.3 summarizes the values obtained for the relevant variables applicable to the models tested. Values are given for all formulations examined.

Table 5.1.3: Theoretical Examination of Drug Release Mechanism

Formulation	Higuchi Model		Power-Law Model			Peppas-Sahlin Model			Weibull Model			
	k	r^2	k'	n	r^2	k_D	k_R	r^2	T_d	b	R_{max}	r^2
GDB25	0.0039	0.999	0.0031	0.54	1.00	0.0041	0.00013	0.999	37000	0.56	100	1.00
GDB50	0.0081	0.999	0.0095	0.47	0.999	0.011	0.00012	0.999	12000	0.51	99.8	0.999
GDB75	0.018	1.00	0.018	0.50	1.00	0.022	0.00044	1.00	1500	0.59	100	0.998
GPS25	0.0054	0.991	0.0026	0.62	0.999	0.0040	0.00032	1.00	11000	0.65	100	1.00
GPS50	0.0062	0.990	0.0029	0.63	0.999	0.0045	0.00038	1.00	8300	0.66	100	0.999
GPS75	0.012	0.979	0.0035	0.71	0.999	0.0055	0.00099	1.00	1900	0.80	100	0.998
SUS25	0.015	1.00	0.013	0.53	1.00	0.016	0.00044	0.998	2300	0.60	100	1.00
SUS50	0.014	1.00	0.014	0.51	1.00	0.017	0.00036	0.999	2500	0.58	100	0.999
SUS75	0.017	0.996	0.024	0.45	0.999	0.025	0.000073	0.999	2000	0.52	99.6	0.998
HPC25	0.025	0.976	0.0075	0.72	1.00	0.010	0.0025	1.00	510	0.89	100	1.00
HPC50	0.038	0.952	0.0082	0.82	1.00	0.0036	0.0064	1.00	210	1.0	100	0.999
HPC75	0.058	0.943	0.013	0.84	1.00	0.0026	0.011	1.00	110	1.0	100	0.998

The results can be used to compare drug release regarding two characteristics: (i) ranking the drug release rate and (ii) identifying the main mechanism of drug release.

At 50% drug loading, the Higuchi model provided increasing values of the release constant k_X in the order $k_{GDB50}<k_{GPS50}<k_{SUS50}<k_{HPC50}$. This corresponded well to the ranking of drug release rates found in dissolution experiments (see Fig.5.1.2). Analysis with the Higuchi model also confirmed the increased drug release with increased drug loading from GPS formulations ($k_{GPS25}<k_{GPS50}<k_{GPS75}$, see Fig.5.1.5) or the low impact of drug loading on drug release from SUS formulations ($k_{SUS25}\approx k_{SUS50}\approx k_{SUS75}$, see Fig.5.1.6). Analysis with the other three models was also performed, using the respective release constants (k',k_D,k_R, T_D). Within one carrier system, all models rank the drug dissolution rates similarly to the Higuchi model. However, some deviations from dissolution experiments occurred when comparing release constants of different carrier systems.

The theoretical models were also used to identify the main mechanism of drug release. For example, all models suggested diffusional (Fickian) controlled drug release from glyceryldibehenate formulations GDB25, GDB50 and GDB75, with the Power-Law model revealing $n \approx 0.50$ and the Peppas-Sahlin model showing that $k_D >> k_R$. Generally high levels of fit ($r^2 > 0.998$) were found for Weibull, Peppas-Sahlin and Power-Law model indicating their appropriateness for fitting the data. Drug release from the glyceryldibehenate was mainly controlled by diffusion. Excellent fits to the Higuchi model ($r^2 \geq 0.999$) were found, as well as $n \leq 0.54$ for the Power-Law model. According to the Peppas-Sahlin model, there was a much higher proportion of diffusion controlled drug release. Further, the models confirmed a strong dependency of drug release rate of the drug/carrier ratio.

All models consistently suggested a diffusion controlled drug release from sucrose-stearate S 1670 formulations, with excellent fits to the Higuchi model ($r^2 > 0.996$). Both the Power-Law model ($n \leq 0.53$), and the Peppas-Sahlin model ($k_D >> k_R$) confirmed this observation. Parameter analyses confirmed the low impact of the drug/carrier on the drug release rate from SUS formulations.

For both SUS and GDB formulations, tablets maintained their shape during dissolution tests confirming the predominance of diffusion as the driving mechanism for drug release

By contrast, model analysis showed that Case II controlled drug release was exhibited for all three HPC formulations (HPC25, HPC50, HPC75). This was supported by the low correlation of the Higuchi model ($r^2 < 0.976$). The Peppas-Sahlin model indicated that the proportion of release by Case II mechanisms increased with increasing drug/carrier ratio, which was supported by observations during dissolution tests: HPC formulations visibly eroded during dissolution tests. Hence drug release from HPC formulations with a high theophylline load was particularly dominated by a Case II mechanism. The related swelling (relaxation) and erosion of the dosage form at the dissolving surface is increased, providing the biggest surface available for media contact among formulations.

Glycerylpalmitostearate formulations (GPS25, GPS50, GPS75) released theophylline by an anomalous mechanism ($0.5 < n < 1$) combining diffusion with Case II mechanisms. At lower drug/carrier ratios (GPS25 and GPS50) the diffusion mechanism prevailed, as shown by improved fit to the Higuchi model ($r^2 > 0.990$), whereas at 75% drug loading, enhanced erosion and relaxation during drug release occurred. GPS75 tablets showed highest extent of erosion during dissolution amongst GPS formulations. The Peppas´ model indicated the presence of a combination of diffusion and Case II release controlled mechanism.

Carrier selection determines the main physicochemical properties of the tablet. For example the lipophilicity and aqueous solubility of the carrier material will strongly affect the wetting behaviour. For example, by selection of glyceryldibehenate as the carrier, comprising a high logP, low polar surface area and low aqueous solubility, a less wettable dosage form was obtained than with the sucrose-stearate based systems. In accordance, release from the GDB formulations was lower than from the SUS systems.

However, differences in wettability don´t explain differences in the release mechanisms. For example, SUS formulations released drug by diffusion, whereas for HPC based formulations Case II mechanisms prevailed. This was experimentally confirmed by the disintegration of HPC based tablets. While diffusion controlled SUS based dosage forms maintained their shape, structure and effective surface area, Case II controlled HPC devices showed swelling and erosion upon contact with the dissolution medium. The erosion and subsequent pore formation resulted in an increase in effective surface area and faster drug release. In this case, SUS formulations showed slower drug release despite better wettability properties. Apparently, the increase in surface area for HPC formulations has to be considered the more dominant parameter with respect to drug release rate. The work of Ferrero et al. had previously shown that the effective surface area of the dosage form exposed to dissolution medium can determine the amount of drug released (Ferrero C. et al. (2003), Colombo P., et al. (1999)).

An increase in the proportion of Case II mechanisms also resulted in accelerated drug release for glycerylpalmitostearate (GPS) formulations. GPS75 showed fastest drug release with a predominance of erosion controlled drug release. Another influence on release rate for the GPS formulations was the drug/carrier ratio. Effective contact (surface) area of the model drug with dissolution increased with drug load since theophylline is more hydrophilic than GPS. Similar results were obtained for GDB formulations, with $k'_{GDB25} < k'_{GDB50} < k'_{GDB75}$ according to the Power-Law.

For sucrose-stearate formulations, no increase in release rate with increasing drug/ carrier ratio was found. As formulations also showed comparable wettability and release mechanisms, it may be concluded that the SUS properties dominated release at all drug loadings.

Compaction simulation (see chapter 4.4) was used to investigate tablet porosity and to judge its impact on drug release and to explain differences in drug release rates across different carriers. In our study, it was shown that the HPC formulations had smaller relative densities than SUS formulations when compressed at equal compression forces (10kN ±1kN). Additionally HPC formulations surpassed SUS formulations in terms of elastic recovery, also suggesting higher porosity. Due to higher porosity of tablets an increase in the initially exposed surface area is suggested resulting in accelerated drug release. Thus, differences in tablet porosity may impact drug release for comparably wettable formulations, as tablet porosity defines the starting point for intrusion of the dissolution medium into the dosage form. However, these effects may have partly been masked by the need to adjust compression forces for each formulation (see chapter 4.5). For example, target compression forces for SUS formulations were lower than for the respective HPC formulations (SUS25 was compressed at 9.5 kN, whereas formulation HPC25 at 13.8 kN). In conclusion the possibility of differences in porosity between SUS and HPC formulations cannot be neglected, but further examination of tablet porosity at similar compression force would be required to make more quantitative comparisons. On the other hand reproducibility of dissolution performances for three out of four carriers indicates that observed variation of compression forces, tablet hardness and tablet porosity can be considered of subordinate importance for these melt-extruded formulations. This was probably due to the high density of granulates obtained during melting process. Similar conclusions were reached in previous works by Young C.R. et al. (2005) and Kidokoro M. et al. (2001) and highlight the robustness of melt extruded formulations in terms of processing.

5.1.3.5 Reproducibility of Dissolution

Due to the number of variables during manufacture such as process parameter deviations during melt extrusion and granulation or compression processes (see chapter 4), reproducibility of the dissolution profile was a concern. Statistical comparison of release profiles by f_2-test indicated similarity of drug release in all cases. However, statistically significant differences in drug release were found for GDB and GPS formulations by repeated measures ANOVA and t-test comparison of single time points (720min).

Starting with glyceryldibehenate formulations (GDB), comparison of dissolution profiles suggested similarity between batches. All f_2 values obtained from inter-batch comparison of dissolution profiles exceeded the critical limit ($f_2 \geq 50$, see Table 5.1.4). According to f_2-tests, the formulation with the highest drug loading (formulation GDB75) exhibited the lowest level of similarity between batches. However, all GDB formulations showed statistically significant differences in drug release at 720min when comparing drug release from three different batches of respective formulations by repeated measures ANOVA (720min) and the t-test (720min, see Table 5.1.4). In all cases one of the batches tested showed a significant difference from the two others, whereas two batches were found not significantly different. Based on these results, the drug release still seemed reasonably reproducible, but process parameters, e.g. compaction force, dwell time and processing temperature might affect drug release to some extent. Amongst the four carriers tested, only GDB showed significant inter-batch variability in drug release for all three formulations. Therefore GDB formulations were considered least robust towards process parameters.

Table 5.1.4: Statistical comparison of dissolution profiles from glyceryldibehenate (GDB) formulations by t-test (720min) and f_2-test ($n \geq 4$)

Formulation	Compared Batches No. A	No. B	Mean Difference Mean A-Mean B	95% Confidence Interval Lower bound	Upper Bound	f_2
GDB25	1	2	-0.8*	-1.291	-0.366	94
	1	3	-0.03	-0.753	0.684	99
	2	3	0.8*	0.340	1.247	96
GDB50	1	2	0.6	-0.116	1.396	72
	1	3	3.7*	2.732	4.686	88
	2	3	3.1*	2.226	3.912	82
GDB75	1	2	-2.2	-5.068	0.609	76
	1	3	-4.2*	-6.982	-1.349	66
	2	3	-1.9*	-3.572	-0.300	84

*** statistically significant difference between groups ($p<0.05$)**

Table 5.1.5 summarizes the statistical analysis of the reproducibility study for different GPS formulations. The inter-batch reproducibility of drug release was confirmed for glycerylpalmitostearate formulations (GPS) with drug/carrier ratios ranging between 25% and 75% by similarity tests. Here too 75% [w/w] drug loading formulation (GPS75) displayed the lowest level of similarity (f_2=65) and a statistically significant difference in level of drug release was confirmed by repeated measures ANOVA and t-test. The higher variability in be drug release may be attributed to the mainly erosion controlled drug release from GPS75 (see 5.1.3.4). By contrast, GPS25 and GPS50 revealed mainly diffusion controlled release. Both showed nicely reproducible drug release. Therefore, reproducibility of drug release from GPS formulations may be affected by changes in the dominating release mechanism.

Table 5.1.5: Statistical comparison of dissolution profiles from glycerylpalmitostearate (GPS) formulations by t-test (720min) and f_2-test ($n \geq 5$)

Formulation	Compared Batches		Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	Mean A-Mean B	Lower bound	Upper Bound	
	1	2	-5.0	-11.654	1.734	82
GPS25	1	3	-2.2	-5.802	1.564	93
	2	3	2.8	-3.145	8.827	90
	1	2	-0.6	-2.672	1.525	73
GPS50	1	3	-0.2	-2.117	1.813	73
	2	3	0.4	-0.341	1.185	99
	1	2	-7.8*	-9.787	-5.817	65
GPS75	1	3	-6.345*	-7.429	-5.261	71
	2	3	1.5	-0.295	3.207	90

*** statistically significant difference between groups ($p<0.05$)**

Table 5.1.6 summarizes the statistical comparison of drug release for sucrose-stearate formulations. F_2-testing revealed batch-to-batch similarity of drug release for all three drug loadings. In this case, the 25% drug loading formulation (SUS25) showed the lowest level of similarity according to the obtained f_2 values ($f_2=73$). Profile similarity was confirmed by repeated measures ANOVA, with which there were no indications of significant differences in the level of drug release. Only comparison by t-test indicated some significant differences of drug release at 720min for SUS25 and SUS50. This may be attributed to differences in processing. In addition, the number of samples should be increased to confirm the significance of these differences. Overall, the reproducibility of drug release was still well within an acceptable range according to regulatory recommendations (FDA 1997a, 1997b, 2000).

Table 5.1.6: Statistical comparison of dissolution profiles from sucrose-stearate formulations by t-test (720min) and f_2-test ($n \geq 3$)

Formulation	Compared Batches		Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	Mean A-Mean B	Lower bound	Upper Bound	
	1	2	3.0*	0.525	5.452	76
SUS25	1	3	3.5	-0.193	7.096	73
	2	3	0.5	-0.871	1.797	97
	1	2	1.9*	0.422	3.337	87
SUS50	1	3	0.1	-1.840	2.051	97
	2	3	-1.8*	-3.452	-0.0953	90
	1	2	2.1	-0.550	4.746	88
SUS 75	1	3	0.9	-3.221	5.114	92
	2	3	-1.2	-5.064	2.760	96

*** statistically significant difference between groups ($p<0.05$)**

Table 5.1.7 shows the statistical comparison of drug release from different hydroxypropylcellulose (HPC) formulations. Dissolution profiles among batches were similar ($f_2 \geq 50$) for all HPC formulations HPC25, HPC50 and HPC75, the lowest similarity was obtained at a 75% drug loading (HPC75). Neither RMANOVA nor t-test indicated significant differences in level of drug release at 30min (not shown) and 180min. This may be attributed to the high variability of single values and the resulting large confidence interval. As for the GPS75 formulation, the mechanism of drug release, mostly erosion, was considered responsible for the observed variability.

Table 5.1.7: Statistical comparison of dissolution profiles from hydroxypropylcellulose (HPC) formulations by t-test (180min) and f_2-test ($n \geq 5$)

Formulation	Compared Batches		Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	Mean A-Mean B	Lower bound	Upper Bound	
HPC25	1	2	0.5	-7.858	8.893	93
	1	3	-1.2	-6.100	3.683	82
	2	3	-1.7	-4.663	1.211	92
HPC50	1	2	-0.2	-12.237	11.753	99
	1	3	1.8	-9.964	13.581	88
	2	3	2.1	-9.091	13.192	87
HPC75	1	2	-8.3	-20.141	-3.573	63
	1	3	-5.7	-18.616	7.155	72
	2	3	2.6	-8.560	13.667	80

*** statistically significant difference between groups ($p<0.05$)**

5.1.4 Conclusion

It was shown that all four carriers can be used for use in CR matrix applications of highly water-soluble drugs by the melt extrusion process. Diffusion controlled drug release was identified for GDB and SUS formulations, whereas HPC formulations control release by Case II mechanisms. GPS formulations show anomalous drug release.

Due to a combination of good wetting behaviour and erosion controlled drug release, HPC formulations showed the highest dissolution rate. HPC formulations are recommended for shorter release intervals up to 12h, with duration of release depending on the drug/carrier ratio. In order to obtain slower release profiles a combination of good wettability with diffusion controlled drug release as found for SUS formulations. Considering a hypothetical eighteen-hour target release profile of theophylline for CR matrix devices, sucrose-stearate seems the most suitable carrier for once-daily theophylline formulations. Finally, GDB and GPS provide very slow drug release and may need to be combined with more hydrophilic carriers to optimize profiles.

Overall SUS and HPC may find application when formulating poorly wettable compounds in order to obtain reasonable dissolution rates, whereas the more lipophilic carriers GDB and GPS may be better suited for formulation of compounds with excellent wettability and solubility.

Finally, the batch to batch reproducibility of drug release has been demonstrated for all four carriers, with minor differences in the robustness of dissolution performance being attributed to variability of manufacture or mechanism of release.

5.2 External Factors Affecting In-Vitro Dissolution

5.2.1 Introduction

So far the proposed formulations have been tested for their potential to control drug release and the mechanisms of drug release have been investigated. Additionally, reproducibility of dissolution performance was confirmed. In this section, the impact of external factors on drug release is explored. These factors, such as changes in pH and ionic strength of dissolution media as well as storage under a variety of conditions, have been observed to affect drug release from other controlled release oral dosage forms.

After oral administration, the formulation will be exposed to both gastric and intestinal fluids during its movement through the gastrointestinal (GI) tract. The composition of these juices is subject to changes after meal intake. In the fasted state, the dosage form enters an acidic environment in the stomach, which is followed by a gradual increase in pH up to neutral values during passage of the small intestine. The pH of gastric fluids has been measured to be about pH 2 in healthy subjects (Kararli T.T. (1995), Russell T.L. (1993), Meyer M.C. et al (1995)). The pH of intestinal fluids reaches its maximum value in the distal ileum (Sasaki Y. et al (1997), Mojaveran P. (1996), Evans D.F. et al. (1988)). Ingestion of food (Kalantzi L. et al (2005)), lack of gastric acid secretion due to disease (achlorhydria) and same types of drug therapy (for example use of proton pump inhibitors) (Fallingborg J. (1999), Sasaki Y. et al (1997)) increase the gastric pH. Since both physiological and individual factors can affect pH values within the GI tract, formulations are often tested for their robustness to changes in pH (Hussein Z. et al. (1992), Rao V.M. et al. (2003), Ohara T. et al (2005), Pringels E. et al. (2005), Dressman J.B. et al. (1995)). Changes in drug release with pH are often regarded as undesirable, although in certain cases the pH dependency of drug release can be used to advantage, e.g. enteric coated formulations or localized delivery of actives distally in the GI tract (Palmieri G.F. et al. (2002), Nykänen P. et al.(1999), Patel V.R. et al. (1996)). These types of formulation provide the possibility to protect actives from acidic environments, minimize side effects or deliver drugs to a specific target in the the GI tract.

The ionic strength of gastrointestinal juices is also known to vary. In particular, differences in the ionic strength of gastrointestinal fluids between the fasted and fed state needs to be considered. Ionic strength increases with ingestion of salts and other substances in foods. Hamaguchi T. et al (1995) estimated the ionic strength of a meal to be about 0.3M. Linddahl A. et al. (1997) reported an ionic strength in human fasted stomach of about 0.1mol/l, while Johnson J.L. et al. (1993) stated that the ionic strength of gastric and intestinal fluids ranged between 0.01M and 0.166M. Galia E. et al. (1998) suggested a dissolution medium for simulating fed state with an ionic strength of 0.3M. The effects of changing the ionic strength on drug release have been examined relatively seldom in the past (e.g. Hamaguchi T. et al. (1995), Talukdar M.M. et al. (1998)).

Hydrodynamics, as another important physiological parameter with potential impact on drug release from CR matrix tablets, will be discussed at a later stage (see Chapter 5.3).

Besides the physiological factors that can impact drug release, storage can result in altered dissolution performance. Hence stability testing represents an area of intense research during formulation development. Not only is chemical stability of interest, especially for new and not fully investigated compounds, but also the physical stability of the dosage form itself must be considered. Therefore the effects of time and storage conditions on release properties of the prototype formulations were also investigated.

5.2.2 Equipment

Table 5.2.1 lists additional equipment used for characterization of CR matrix tablets.

Table 5.2.1: Additional Equipment

Device	**Source**
Sputter Coater Polaron SC500	Quorum Technologies Ltd., Newhaven, UK
Scanning Electron Microscope SM-300	Topcon (Great Britain) Ltd., Newbury, Berkshire, UK
Stability Cabinet PSC020	Sanyo Gallenkamp Plc., Leicester, UK

5.2.3 Methods

5.2.3.1 Dissolution Test

All dissolution tests were performed using USP II paddle apparatus (also see chapter 3.3) applying a rotation speed of 50 rpm. Nine hundred millilitres of the dissolution media listed in Table 5.2.1 per vessel were used for all tests (n≥3).

In order to examine pH dependency of release, results in Simulating Gastric Fluid (sine pepsin) USP 24 pH 1.2 were compared to release profiles in phosphate buffer USP 26 pH 6.8 (see chapter 5.1). The impact of ionic strength was determined using a modified version of Simulation Gastric Fluid (sine pepsin) pH 1.2, in which the ionic strength was increased by addition of sodium chloride (see Table 5.2.2).

Table 5.2.2: Dissolution media used for testing the effects of changes in pH and ionic strength on drug release

Simulating Gastric Fluid (sine pepsin)	
NaCl	2.0g
HCl conc.	7.0g
Water (Purified)	qs ad 1000ml
pH	1.20
Ionic Strength	0.097mol/l

Simulating Gastric Fluid modified (sine pepsin)	
NaCl	17.4g
HCl conc.	7.0g
Water (Purified)	qs ad 1000ml
pH	1.20
Ionic Strength	0.36mol/l

(*30min, 135min, 240min, 360min, 480min,

5.2.3.2 Scanning Electron Microscopy

The samples were prepared for scanning electron microscopy by breaking the unit into halves and placing one half on an adhesive-coated 12.5 mm diameter pin stub. Loose particles were removed by tapping the stub sharply and then gently blowing across the rear using a jet of particle-free compressed gas. The prepared specimen stub was then sputter coated with a thin (approximately 10nm) layer of gold in a Polaron SC500 coating unit at 20 mA for 3 minutes using an argon gas purge. The specimens were examined using a Topcon SM-300 scanning electron microscope (SEM). The SEM was operated at high vacuum (<10mbar) with an accelerating voltage of 5kV, a specimen working distance of 12 mm, and secondary electron images were recorded digitally at magnifications of 100x and 500x.

5.2.3.3 Stability Testing

Units were filled into brown glass containers, which were capped with polyethylene screw caps. One set of units was stored at 25°C/ 60%rh and the other one at 40°C/ 30% rh. Drug release was tested as described in Chapter 5.1 before and after twelve months.

5.2.3.4 Statistical Comparison

Unpaired t-tests were performed with SIGMASTAT® V.5.7. Selected time points and the number of tested samples are documented in their respective sections. For the unpaired t-test the significance value *p* was also set to $p=0.05$.

The f_2-test was performed according chapter 3.

5.2.4 Results and Discussion

5.2.4.1 Dissolution – Dependency on pH

All in all, no drastic changes in release behaviour with physiologically relevant changes in pH were observed for any of the formulations. Comparison of release profiles by f_2-test showed similarity of drug release in pH 6.8 and pH 1.2 for all formulations tested. Unpaired t-test showed significant differences in drug release for GDB75, GPS75 and SUS25 and SUS75, continuing the trend to overdiscriminate dissolution profiles with the t-test. Only GPS75 showed somewhat lower robustness to changes in pH of the media. Table 5.2.3 summarizes statistical comparisons of dissolution profiles obtained under different pH conditions by unpaired t-test and f_2-test for all formulations tested.

Table 5.2.3: Statistical comparisons of dissolution profiles obtained under varied pH conditions ($n \geq 3$): unpaired t-test (480min, $^{+}$135min) and f_2-test (°15min, 75min, 135min, 180min, 240min)

Formulation	**Mean Difference**	**95% Confidence Interval (t-test)**		**f_2**
	Mean pH6.8-Mean pH 1.2	**Lower bound**	**Upper Bound**	
GDB25	0.4	-0.142	0.937	96
GDB75	-5.2$^{\square}$	-7.550	-2.809	69
GPS25	5.6	-1.113	12.214	74
GPS75	12.2$^{\square}$	11.010	13.442	55
SUS25	2.2$^{\square}$	0.283	4.099	89
SUS75	-4.0$^{\square}$	-5.002	-3.064	77
HPC25^{+}	-2.6	-9.333	4.219	81
HPC75$^{+\circ}$	-2.6	-14.907	9.624	75

$^{\square}$ **t-test: $p < 0.05$ (significant difference)**

Changing the pH of dissolution media from 6.8 to 1.2 resulted in a slight increase in dissolution from formulation GDB75. Practically no change was observed for glyceryldibehenate formulation GDB25 (25% drug loading), which released 8% of the total theophylline content within eight hours (see Fig. 5.2.1) in both media. Statistical evaluation indicated similarity between profiles for both GDB25 and GDB75. Unpaired t-test indicated significant differences of level of drug release at 480min for GDB75. However, pH driven changes in drug release were moderate and similarity of profiles was suggested by f_2-test. Thus, pH-independent drug release was continued for GDB based formulations.

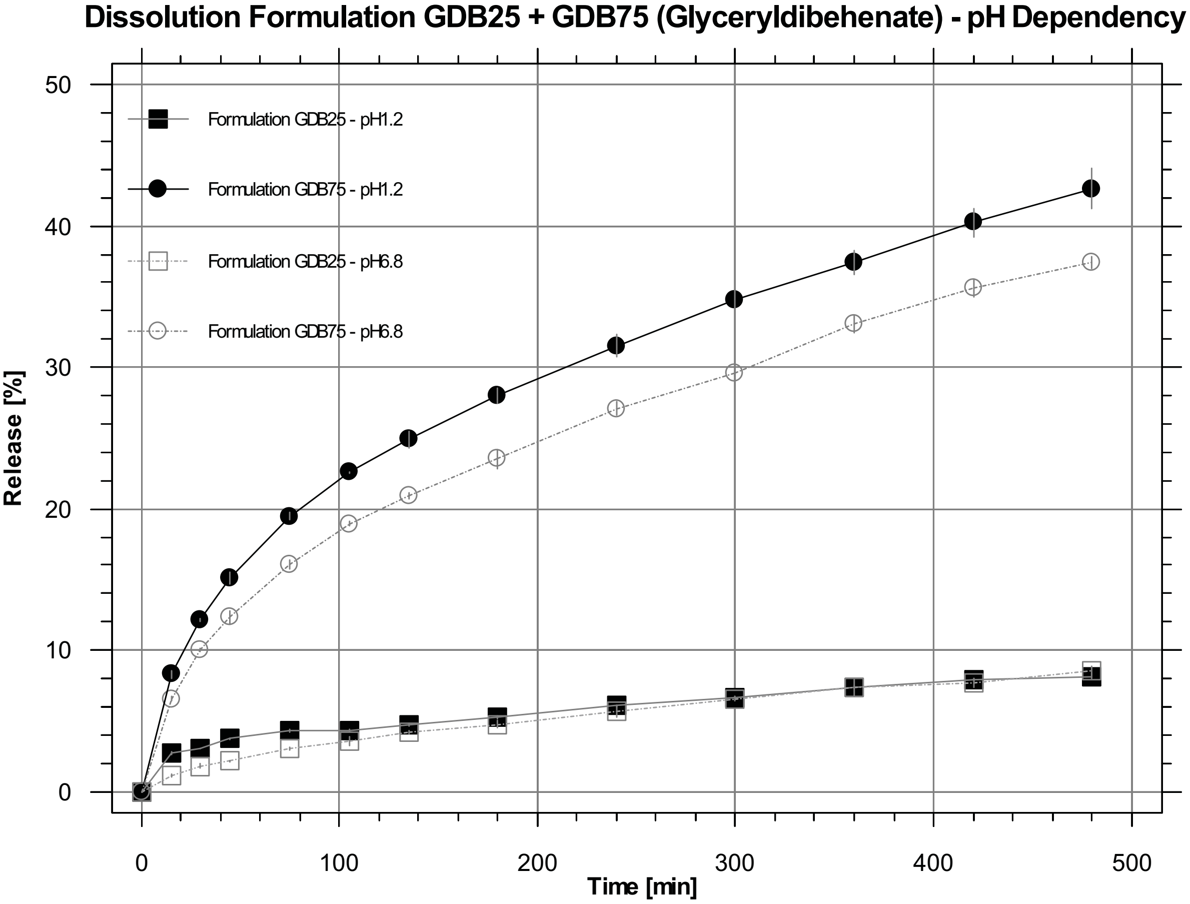


Fig. 5.2.1 Dissolution from formulation GDB25 and GDB75, simulating gastric fluid sine pepsine USP 24 pH 1.2 and phosphate buffer USP 26 pH6.8 (n≥3) - pH dependency of drug release

The other lipophilic carrier tested, glycerylpalmitostearate (GPS, see Fig. 5.2.2), showed less robust dissolution performance with change in the pH of dissolution media. At high drug loading (GPS75) slower drug release was observed in acidic conditions. GPS75 released 33.0% (±0.41) theophylline within eight hours at pH 6.8, but only 20.8% (±0.64) at pH 1.2. A comparable trend was observed for GPS25. Drug release decreased from 16.0% (±3.6) at pH 6.8 to 10.5% (±2.0) at pH 1.2 after 8h.

F_2-tests indicated less than 10% difference between profiles, for GPS25 ($f_2 = 74$) and GPS75 ($f_2 = 55$, see Table 5.2.3). Comparison by f_2-test resulted in a borderline value for GPS75 and in addition unpaired t-test indicated a significant difference in drug release at 8h for GPS75. Thus release from this formulation was considered to be prone to effects of media pH. The effect is unlikely to be caused by the physicochemical properties of theophylline, since it is highly protonated and soluble at both pH values.

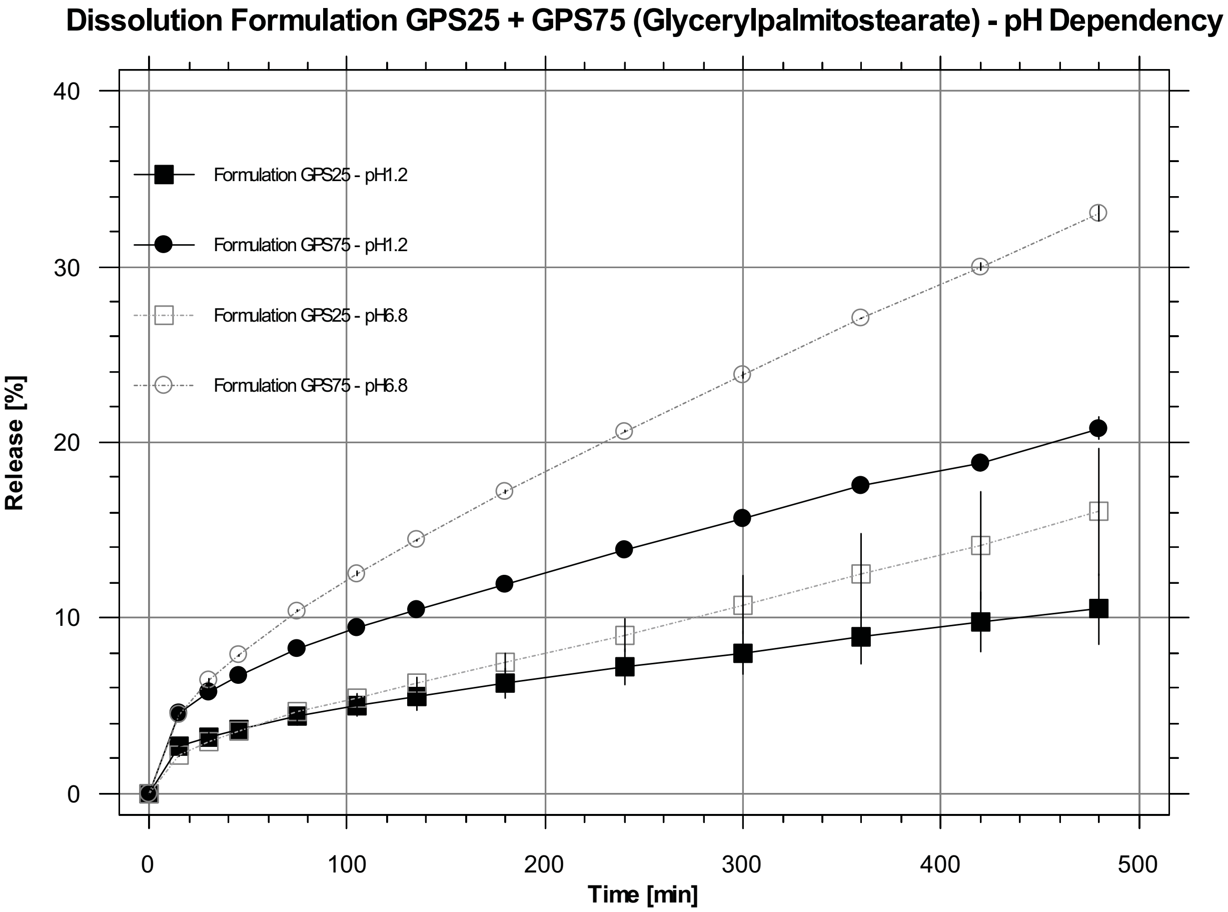


Fig. 5.2.2 Dissolution from formulation GPS25 and GPS75, simulating gastric fluid sine pepsine USP 24 pH 1.2 and phosphate buffer USP 26 pH 6.8 (n≥3) – pH dependency of drug release

Glycerylpalmitostearate may contain some amount of free fatty acids. Protonation of these acids would potentially reduce the wettability of the matrix tablets. For (partly) diffusion controlled systems like GPS75, the contact surface with dissolution media directly affects diffusion rate of the compound into the medium. If the effective contact surface is reduced, drug diffusion would be slowed. Similar effects due to protonation of excipients have been described in literature (Rohrs B.R., et al. (1999), Chang C.-M., et al. (1997)). Due to partial tablet capping during dissolution a wide variability in results was observed.

Fig. 5.2.3 shows the dissolution profiles obtained from SUS formulations at pH 1.2 and pH 6.8. Sucrose-fatty acid-ester S 1670 formulations SUS25 and SUS75 showed little pH dependency of drug release. Formulation SUS25 showed a mean decrease of 2.2% at 8h with a decrease in pH from 6.8 to 1.2. SUS75 showed slightly faster drug release at low pH (33.9% ±0.95 vs. 38.0% ±0.33). F_2-test indicated similarity of profiles for both formulations, but significant differences were suggested by the t-test at 480min (see Table 5.2.3). Overall as for GDB formulations, drug release from sucrose-stearate formulations was virtually pH-independent.

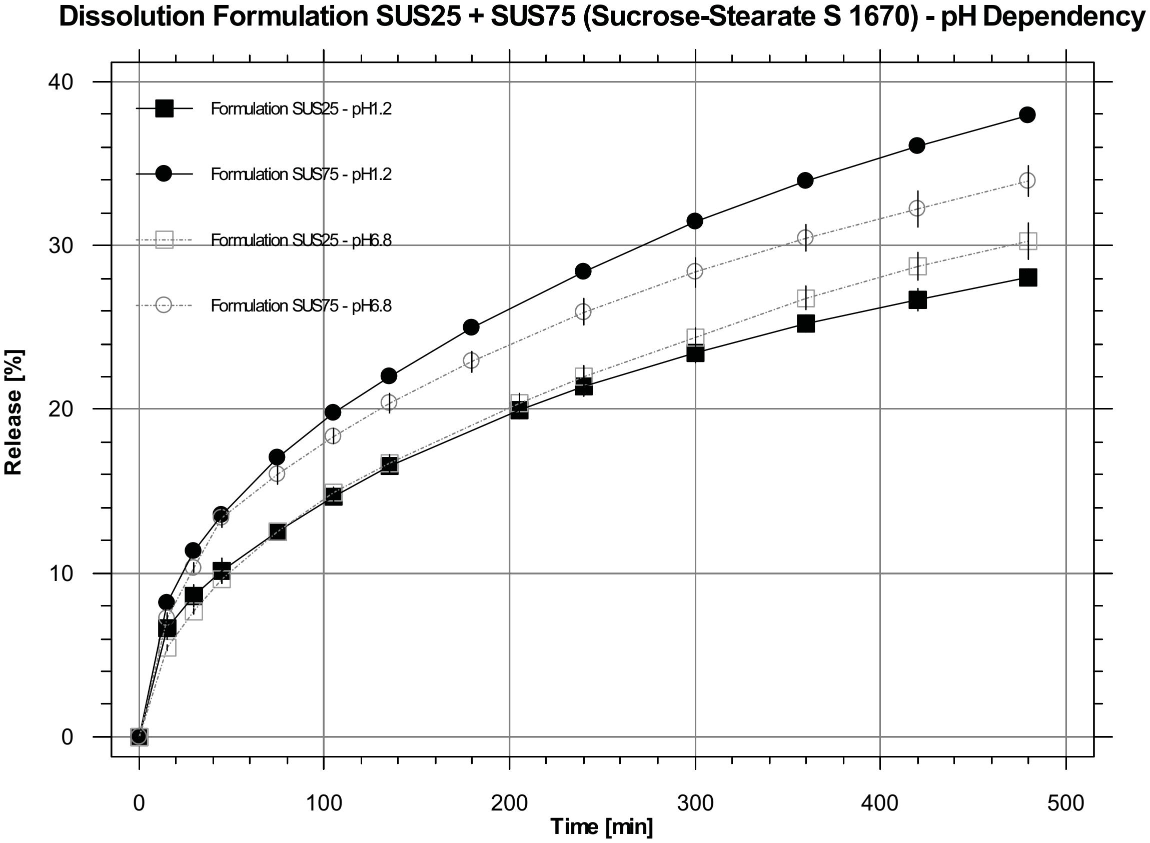


Fig. 5.2.3 Dissolution from formulation SUS25 and SUS75, simulating gastric fluid sine pepsine USP 24 pH 1.2 and phosphate buffer USP 26 pH 6.8 (n≥3) – pH dependency of drug release

For HPC25 and HPC75 a slight increase in drug release after 135min was observed with decreasing pH (see Fig. 5.2.4). The difference in mean drug release at 135min was 2.6% for both formulations. Similarity between dissolution profiles was indicated by the f_2-test values $f_2>50$ (see Table 5.2.3). The unpaired t-test also suggested insignificant differences. It was concluded that HPC formulations show pH-independent drug release. The high variability in results can be attributed to the erosion mechanism (see chapter 5.1).

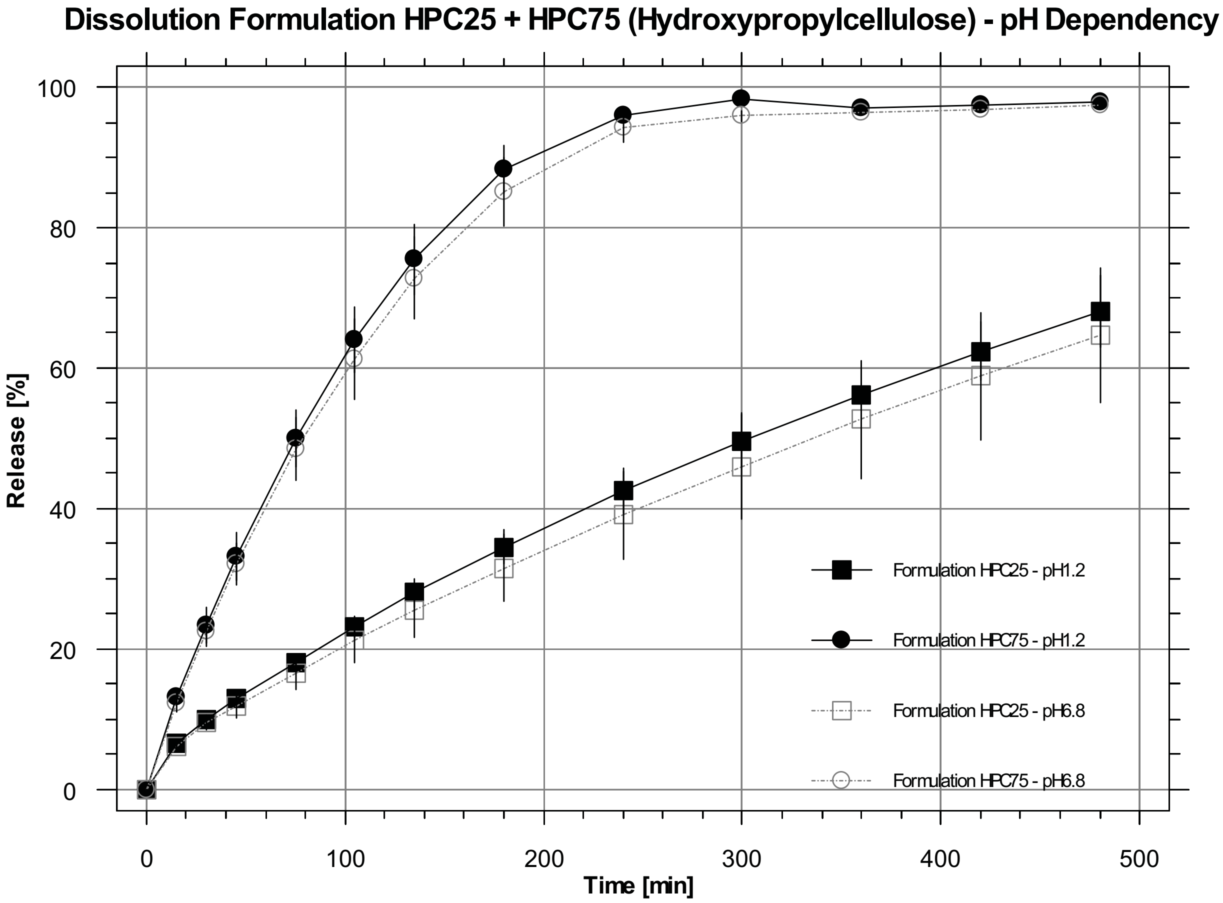


Fig. 5.2.4 Dissolution from formulation HPC25 and HPC75, simulating gastric fluid sine pepsine USP 24 pH 1.2 and phosphate buffer USP 26 pH 6.8 (n≥3) – pH dependency of drug release

5.2.4.2 Dissolution – Dependency on Ionic Strength of Dissolution Media

Drug release was tested employing two dissolution media with different ionic strength (for details see Table 5.2.2). The ionic strengths employed, 0.1 and 0.36 represent values found under fasted and fed state in the human GI tract (Linddahl A. et al. (1997), Johnson J.L. et al. (1993), Hamaguchi T. et al (1995), Galia E. et al. (1996)). Figs. 5.2.5-5.2.8 show the dissolution profiles obtained with dissolution media differing in the level of ionic strength. For all four carriers, the 25% and 75% drug loading formulations were examined (n≥3).

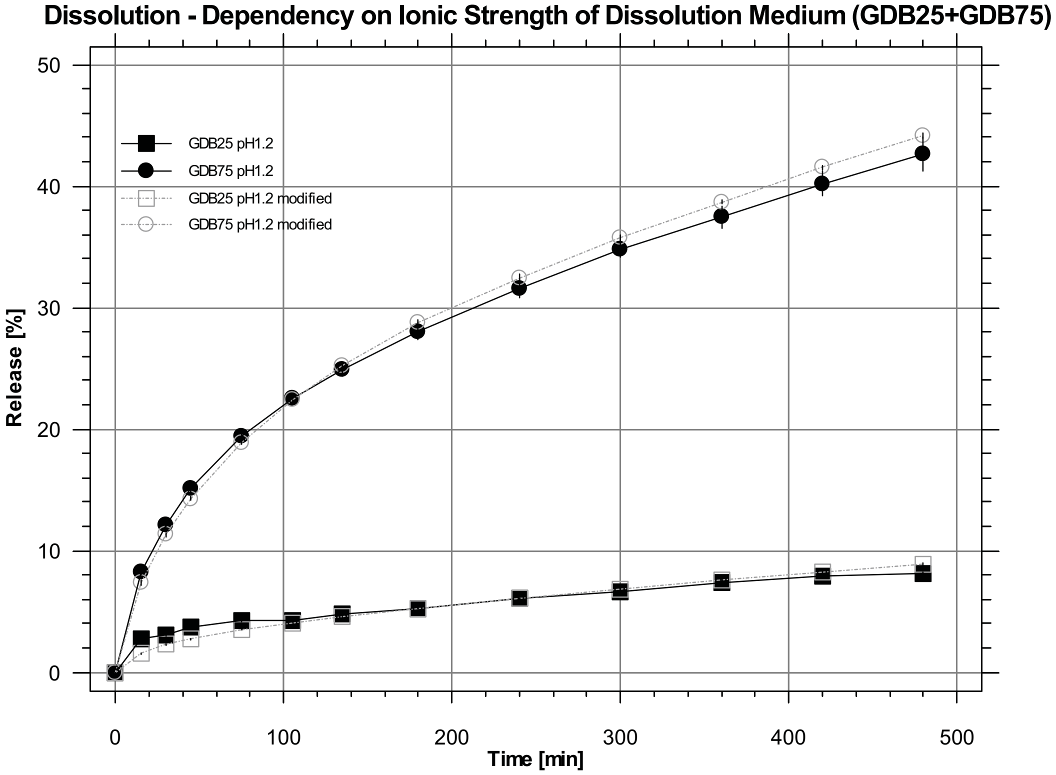


Fig. 5.2.5 Dissolution from formulation GDB25 and GDB75, simulating gastric fluid USP 24 pH 1.2 and simulating gastric fluid modified pH 1.2 (n≥3) – dependency on ionic strength of dissolution media

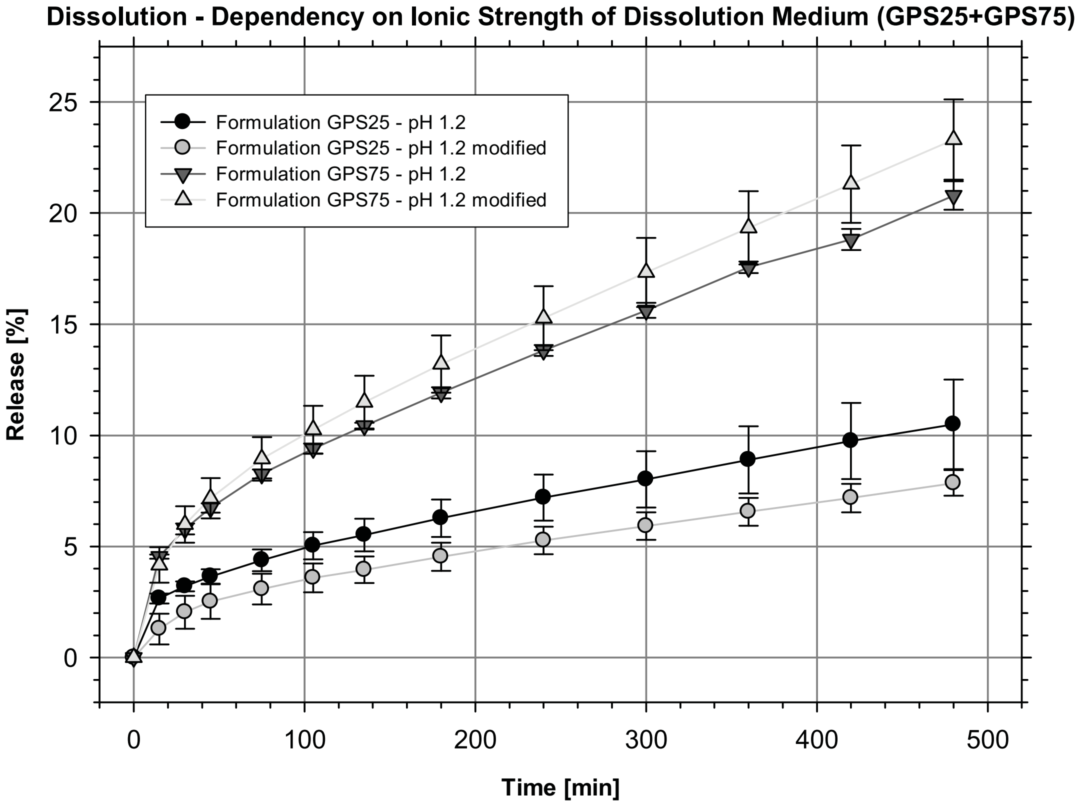


Fig. 5.2.6 Dissolution from formulation GPS25 and GPS75, simulating gastric fluid USP 24 pH 1.2 and simulating gastric fluid modified pH 1.2 (n≥3) – dependency on ionic strength of dissolution media

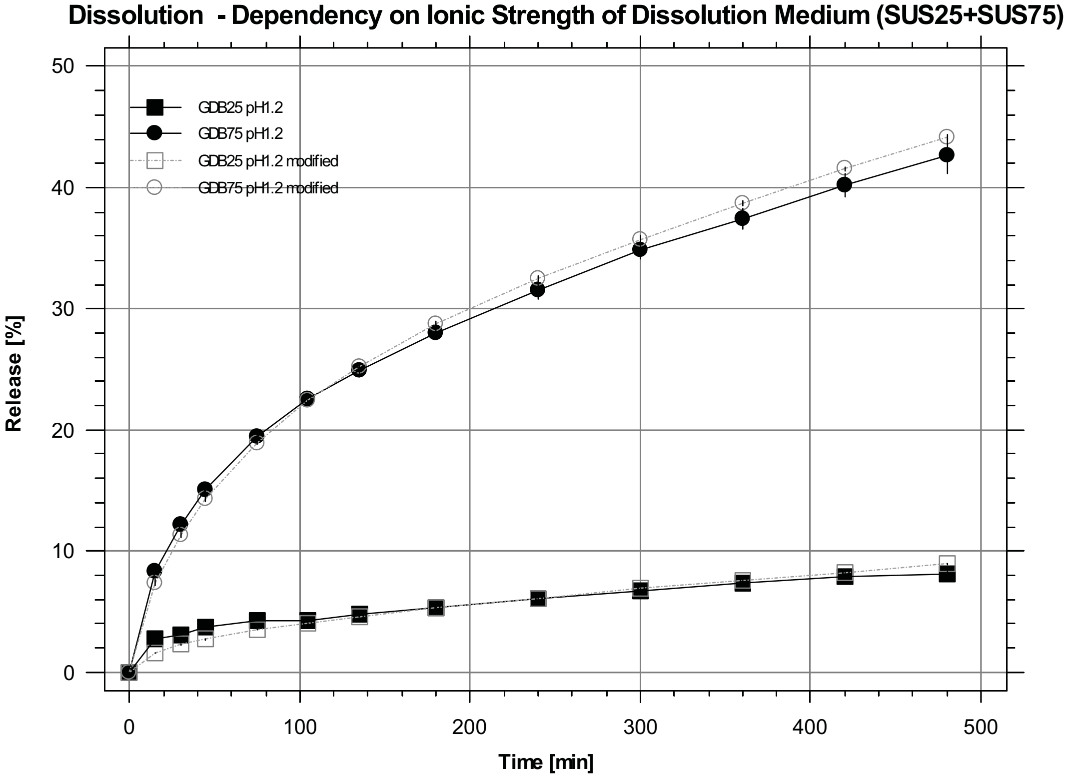


Fig. 5.2.7 Dissolution from formulation SUS25 and SUS75, simulating gastric fluid USP 24 pH 1.2 and simulating gastric fluid modified pH 1.2 (n≥3) – dependency on ionic strength of dissolution media

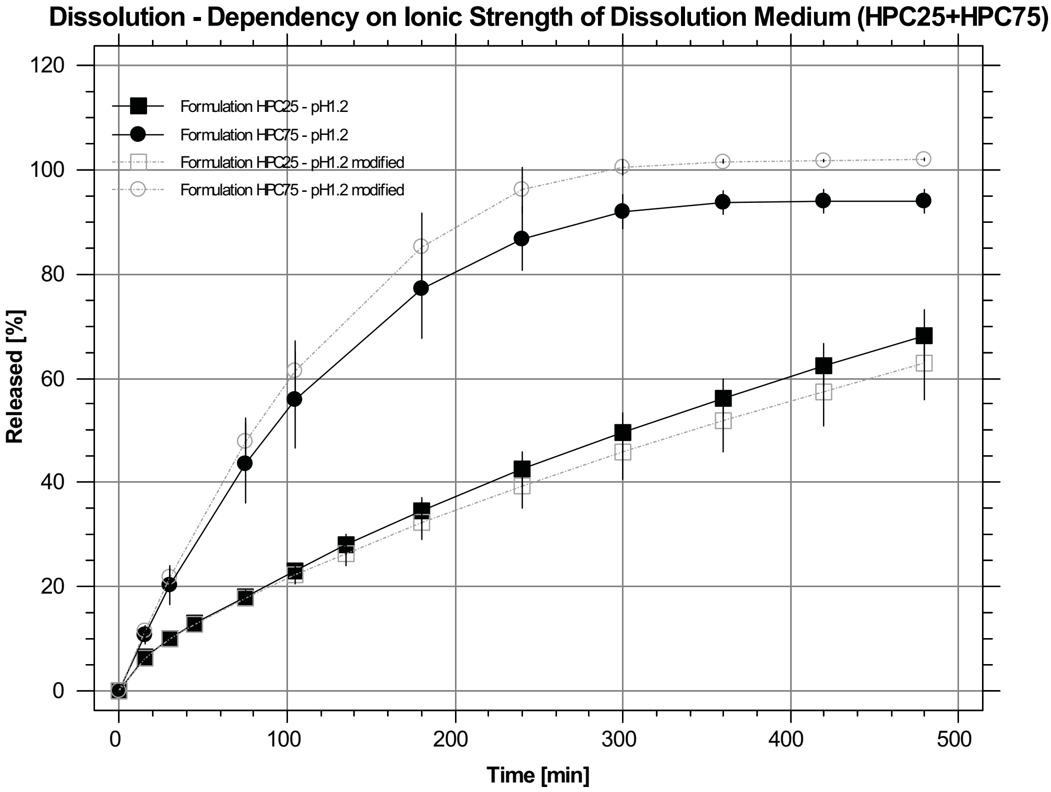


Fig. 5.2.8 Dissolution from formulation HPC25 and HPC75, simulating gastric fluid USP 24 pH1.2 and simulating gastric fluid modified pH1.2 – dependency on ionic strength of dissolution media (n≥3)

Table 5.2.4 summarizes results of statistical comparisons for all formulations tested (f_2-test, unpaired t-test). F_2-tests indicated that changes in ionic strength did not have a significant influence on drug release from any of the formulations. Comparison by unpaired t-test suggested significant differences in drug release at single time points for GDB25. Due to the small number of samples there might be an over discrimination by the t-test. Due to the comparably low absolute differences in drug release, drug release was considered to be generally independent of the level of ionic strength for all carriers tested. Therefore *in vivo* food effects based on changes in ionic strength of gastric or intestinal contents are not anticipated for any of the four carriers.

Table 5.2.4: Statistical comparisons of dissolution profiles obtained under varied ionic strength conditions ($n \geq 3$): unpaired t-test (480min, $^{+}$135min) and f_2-test ($^{\circ}$15min, 75min, 135min, 180min, 240min)

Formulation	Mean Difference	95% Confidence Interval (t-test)		f_2
	Mean pH1.2-Mean pH 1.2 modified	Lower bound	Upper Bound	
GDB25	-0.8□	-1.039	-0.494	98
GDB75	-1.5	-3.842	0.760	92
GPS25	2.6	-0.724	6.012	83
GPS75	-2.5	-5.234	0.206	86
SUS25	0.6	-1.624	2.757	85
SUS75	-2.5	-10.254	5.334	69
HPC25$^{+\circ}$	1.6	-3.446	6.632	72
HPC75$^{+\circ}$	3.0	-9.921	15.881	80

□ **t-test: $p < 0.05$ (significant difference)**

5.2.4.3 Dissolution – Stability

Stability of release from the dosage form with time is one of the most important factors for dosage form development since changes in release will limit the product shelf-life. Therefore, stability of dissolution profiles was examined for the prototype formulations. The dissolution profiles for two GDB formulations (GDB25, GDB75).are shown in Fig. 5.2.9 and Table 5.2.5 summarizes the statistical comparisons. GDB formulations showed stable dissolution profiles when stored at 25°C/60%rh, but slower drug release was found after storage at 40°C/30%rh. Compared to the initial profiles, a slight increase in mean drug release was observed for GDB75 after 360min (1.7%) and 720min (0.1%) after the formulation was stored for 365d at 25°C/60%rh. By contrast drug release slowed down when tablets were stored at elevated temperatures (365d @40°C/30%rh); for example drug release was very slow for GDB25, with 3.2% (±0.082) release in 720min. Compared to the initial values (10.8% ±(0.47) @720min) only one third of the initial percentage released was effected in the same time.

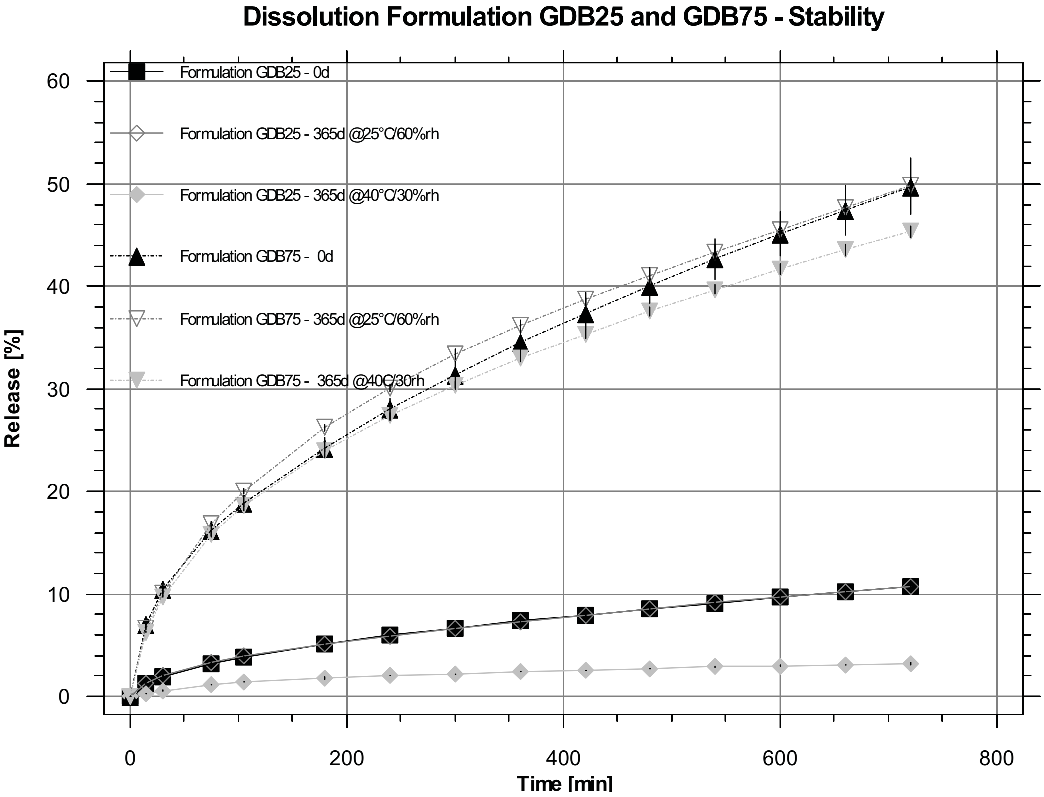


Fig. 5.2.9 Dissolution from formulations GDB25 and GDB75, phosphate buffer USP 26 pH 6.8 (n≥3) – effect of one-year-storage on dissolution

Despite the slower drug release observed, f_2 statistical comparisons indicated similarity between initial and long-term drug release for all drug loadings (see Table 5.2.5). Comparisons by t-test indicated significant differences between profiles for GDB25. The profile obtained after storage at 40°C/30%rh deviated significantly from profiles observed after other storage conditions. Significant differences were observed for both time points investigated (360min, 720min). For GDB75 comparisons by t-test indicated significant differences in level of mean drug release between profiles. Again the trend was observed that storage at 40°C/30%rh significantly decelerated drug release, but changes in drug release rate were less pronounced than for the 25% drug loading formulation.

Thus, the low drug loading formulation (GDB25) was considered prone to stability issues with respect to drug release. At higher drug loading there was less change in drug release relative to the initial profile. This was partly confirmed by statistical comparison (t-test). Thus an increase in drug loading was considered advantageous for long-term stability of GDB formulations.

Table 5.2.5: Statistical comparisons of dissolution profiles (GDB25, GDB75) obtained after varied storage conditions ($n \geq 3$): unpaired t-test and f_2-test (30min, 180min, 300min, 480min, 720min)

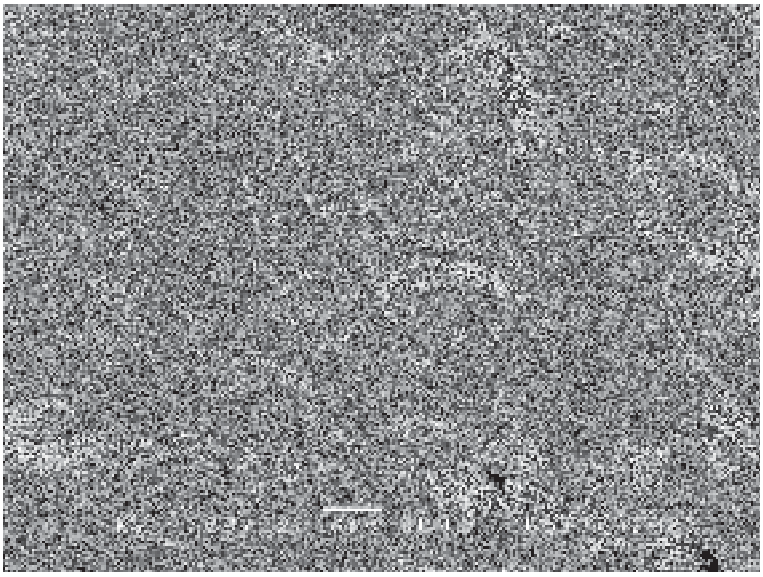
Formulation	Compared storage conditions		Time Point	Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	[min]	Mean A-Mean B [%]	Lower bound	Upper Bound	
GDB25	0d	365d 25°C/ 60%rh	360	0.1	-0.415	0.508	99
			720	0.0	-0.759	0.845	
	0d	365d 40°C/ 30%rh	360	4.9$^{\square}$	4.455	5.292	65
			720	7.6$^{\square}$	6.847	8.327	
	365d 25°C/ 60%rh	365d 40°C/ 30%rh	360	4.8$^{\square}$	4.572	5.082	
			720	7.5$^{\square}$	7.103	7.984	
GDB75	0d	365d 25°C/ 60%rh	360	-1.7	-3.795	0.417	99
			720	-0.1	-4.185	3.984	
	0d	365d 40°C/ 30%rh	360	1.5	-0.554	3.578	62
			720	4.4$^{\square}$	0.344	8.455	
	365d 25°C/ 60%rh	365d 40°C/ 30%rh	360	3.2$^{\square}$	2.074	4.328	
			720	4.5$^{\square}$	3.000	5.999	

$^{\square}$ **t-test: $p < 0.05$ (significant difference)**

Examination of the physical structure of the tablets by scanning electron microscopy indicated a loss of pores within the tablets when stored at elevated temperatures. Due to a loss of porosity, the effective surface of the tablet was decreased, resulting in a smaller contact surface with the dissolution medium. For diffusion controlled systems such as GDB25 and GDB75, a reduction of area available for diffusion can be directly correlated to slower drug release. Fig. 5.2.10 shows representative parts of cross sections of GDB50 tablets stored at different temperatures.

In order to improve the stability of GDB formulations the glyceroldibehenate content could be reduced, e.g. by increasing the drug loading or partial substitution with another excipient.

a)



b)

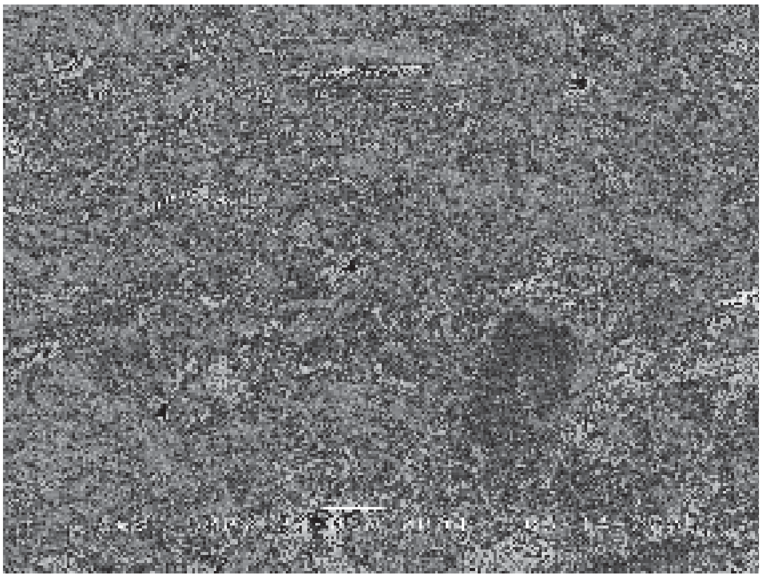


Fig. 5.2.10 Scanning electron microscopy images of tablet cross sections of GDB50- a) stored at 25°C/ 60%rh; b) stored at 40°C/ 30%rh (500x)

Fig. 5.2.11 shows dissolution profiles obtained for GPS25 and GPS75 before and after storage under different conditions for 365 days. Table 5.2.6 summarizes the statistical comparisons by f_2-test, and t-test.

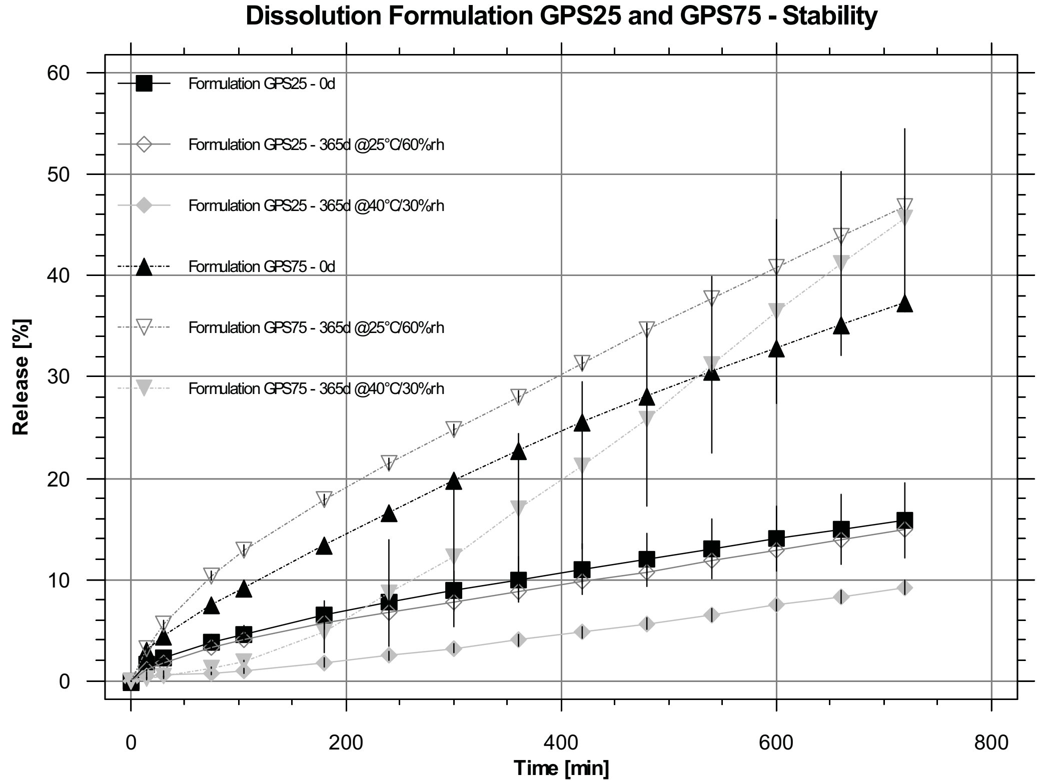


Fig. 5.2.11 Dissolution from formulations GPS25 and GPS75, phosphate buffer USP 26 pH 6.8 (n≥3) – effect of one-year-storage on dissolution

After 365 days of storage at different conditions, changes in drug release profiles were also observed for glycerylpalmitostearate formulations (GPS25, GPS75). In case of GPS25 a decrease in mean drug release was observed after one year storage at 40°C/ 30%rh. Mean drug release was decreased by 5.7% at 300min and 6.6% at 720min, respectively compared to initial values. Drug release was reasonably stable after one year storage at 25°C/60%rh. A decrease of only 1.0% was observed for both time points (300min, 720min) examined. Release profiles were similar according to f_2-tests (see Table 5.2.14), although a decreasing level of similarity was observed after storage at the higher temperature. The unpaired t-test suggested significant differences in drug release after storage at 40°C/30%rh (300min, 720min).

Table 5.2.6: Statistical comparisons of dissolution profiles (GPS25, GPS75) obtained after varied storage conditions ($n \geq 3$): unpaired t-test and f_2-test (30min, 180min, 300min, 480min, 720min)

Formulation	Compared storage conditions		Time Point	Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	[min]	Mean A-Mean B [%]	Lower bound	Upper Bound	
GPS25	0d	365d 25°C/ 60%rh	300	1.0	-1.716	3.790	93
			720	1.0	-4.267	6.228	
	0d	365d 40°C/ 30%rh	300	5.7□	2.893	8.453	63
			720	6.6□	1.391	11.887	
	365d 25°C/ 60%rh	365d 40°C/ 30%rh	300	4.6□	3.822	5.451	
			720	5.7□	4.187	7.131	
GPS75	0d	365d 25°C/ 60%rh	300	-5.0□	-5.810	-4.136	61
			720	-9.5□	-11.133	-7.933	
	0d	365d 40°C/ 30%rh	300	7.6□	0.540	14.657	59
			720	-8.3	-17.529	1.000	
	365d 25°C/ 60%rh	365d 40°C/ 30%rh	300	12.6□	1.609	23.534	
			720	1.3	-13.073	15.610	

□ t-test: $p < 0.05$ (significant difference) **◊ f_2-test: not similar**

For diffusion controlled glycerylpalmitostearate matrix tablets, such as GPS25, an impact of reduced surface and porosity on drug release has to be expected. Higher melting excipients might help to prevent softening of the matrix structure and thus ensure stable release profiles after storage at elevated temperatures.

For GPS75 faster drug release was observed after storage for 365d at 25°C/ 60%rh. At 720min drug release was increased by 9.5% compared to the initial value (37.4% ±0.9 vs. 46.9% ±1.0). A change in the drug release pattern was observed after storage at 40°C/30%rh. After a slow initial phase, the rate increased so that the amount released at 540min was similar to the initial release profile (30.6% ±0.7 vs. 31.2% ±8.8). Nonetheless, statistical comparison by the f_2-test showed similarity of profiles ($f_{2\ 25°C/60\%rh} = 93$ and $f_{2\ 40°C/\ 30\%rh} = 63$).

Storage at 40°C/30%rh resulted in a changed release profile indicating changes in the release mechanism of the dosage form. Model-dependent examination of the release mechanism confirmed this hypothesis. Table 5.2.7 summarizes the model-dependent analysis of release profiles for GPS75. Initially, drug release was mainly diffusion controlled. By contrast, the Peppas-Sahlin model suggested anomalous release from the dosage form obtained after storage at 40°C/30%rh. This conclusion was based on the observation of an increased diffusional exponent n (0.75) and an increase of the relaxational constant k_R (also see chapter 5.1).

Table 5.2.7: Theoretical examination of release mechanism using the Peppas-Sahlin model – examination of release before and after storage at different conditions

Storage condition	n	k_D	k_R	r^2
0d	0.43	0.0055	0.00099	1.00
365d, 25°C/ 60%rh	0.43	0.0083	0.00114	1.00
365d, 40°C/ 30%rh	0.75	0	0.000025	0.999

The percolation theory described by Leuenberger H., et al. (1987) provides a potential explanation for the change in profile shape. According to Leuenberger, a percolation threshold can be defined for inert matrices compressed from binary mixtures. The theoretical percolation threshold depends on the lattice formed by drug and excipient particles and indicates at which concentration one of the components starts to dominate the (release) properties of the system. In other words, the dominating component forms a continuous phase within the lattice. For example, decreasing the concentration of a release controlling excipient will result in formation of a continuous phase of the active. According to Leuenberger, drug release will then be governed by the intrinsic dissolution rate of the active. Percolation theory has been widely applied to understand and design drug release from various matrix systems (Caraballo I., et al. (1999), Gonzales-Rodriguez M.J., et al. (1997)).

Applying the percolation theory to the observations made for GPS75, glycerylpalmitostearate likely formed a continuous phase within the matrix of the formulation. During storage, the lattice underwent a significant change, with GPS forming particles and theophylline forming a continuous phase. From this point on, the release properties of the formulation were governed by the intrinsic properties of theophylline. Seventy-five percent drug loading could well exceed the percolation threshold of theophylline within a binary mixture with GPS. It is hypothesized that, due to the short melt extrusion/ granulation process, a metastable lattice was formed. Over storage time the lattice was transferred into the stable form with a continuous theophylline phase with the kinetics of the transformation were accelerated by storage at elevated temperature. The exponential release pattern are commensurate with erosion of the theophylline phase, an increase in porosity of the matrix and an increase in the contact surface of the highly water-soluble theophylline with the dissolution medium with time.

In order to improve the stability of the glycerylpalmitostearate formulations, theophylline loadings would have to be kept below the theoretical percolation threshold. For theophylline/ GPS mixtures, the percolation threshold lies between 25% and 75% drug loading: at 25% drug loading, storage effects on drug release did not indicate any changes in mechanism.

Fig.5.2.12 shows dissolution profiles of SUS25 and SUS75 obtained before and after storage under different conditions for 365 days. Table 5.2.8 summarizes the statistical comparisons by f_2-test and t-test. Sucrose-fatty acid-ester S1670 formulations (SUS25, SUS75) showed stable dissolution profiles when stored for 365d at 25°C/60%rh. For SUS25 a decrease in mean dissolution by only 0.6% after 720min compared to the initial profile was observed. For SUS75 the dissolution profile was stable after 365 days storage at 25°C/ 60%rh. After 265 days storage at 40°C/ 30%rh, slightly faster drug release was found for both formulations. For SUS75 an increase in mean fraction released of 3.2% at 720min was observed.

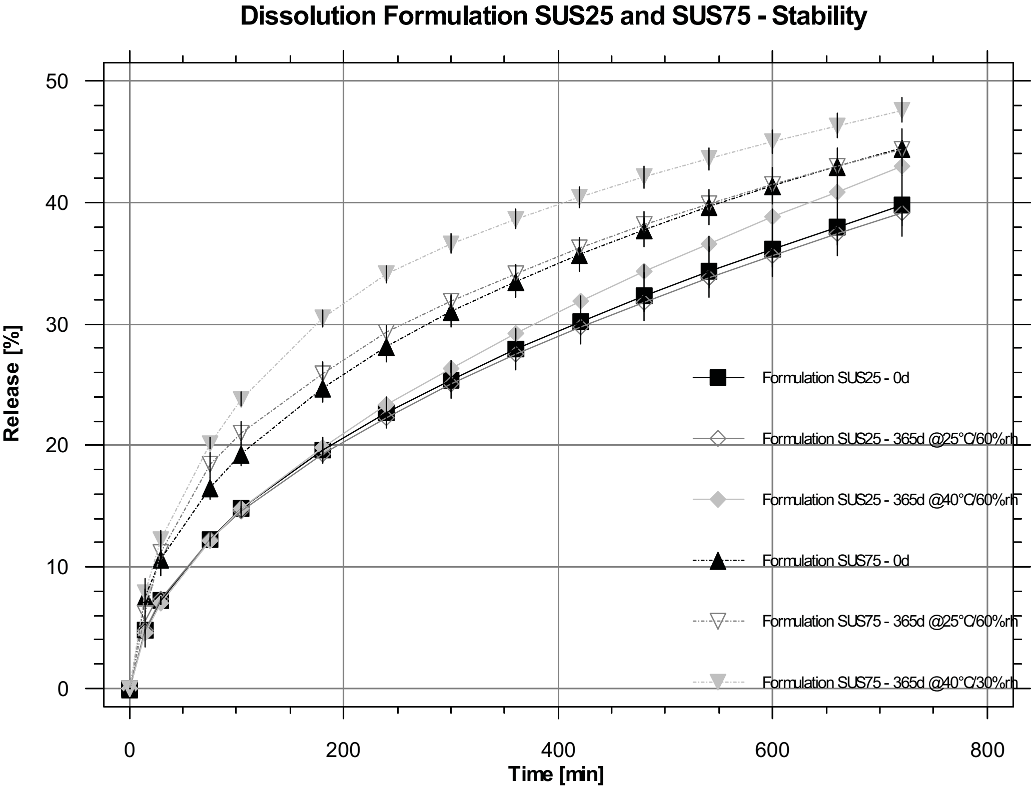


Fig. 5.2.12 Dissolution from formulations SUS25 and SUS75, phosphate buffer USP 26 pH 6.8 (n≥3) – effect of one-year-storage on dissolution

Statistical comparison by f_2-test displayed similarity of all profiles compared (see Table 5.2.5 for f_2-test). As the t-test partly indicated, stability issues may arise after storage for more than one year at elevated temperatures (40°C/30%rh). Considering the f_2-test results, dissolution of sucrose-stearate formulations were considered stable for 365 days when stored between 25°C and 40°C at drug loadings ranging from 25% to 75%.

Table 5.2.8: Statistical comparisons of dissolution profiles (SUS25, SUS75) obtained after varied storage conditions ($n \geq 3$): unpaired t-test and f_2-test (30min, 180min, 300min, 480min, 720min)

Formulation	Compared storage conditions		Time Point	Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	[min]	Mean A-Mean B [%]	Lower bound	Upper Bound	
SUS25	0d	365d 25°C/ 60%rh	360	0.4	-2.089	2.944	98
			720	0.6	-3.127	4.425	
	0d	365d 40°C/ 30%rh	360	-1.3	-3.815	1.134	85
			720	-3.2	-6.938	0.475	
	365d 25°C/ 60%rh	365d 40°C/ 30%rh	360	-1.8$^{\square}$	-3.024	-0.512	
			720	-3.9$^{\square}$	-5.922	-1.793	
SUS75	0d	365d 25°C/ 60%rh	360	-0.6	-2.880	1.769	95
			720	0.1	-2.501	2.757	
	0d	365d 40°C/ 30%rh	360	-5.1$^{\square}$	-7.466	-2.768	67
			720	-3.1$^{\square}$	-5.880	-0.357	
	365d 25°C/ 60%rh	365d 40°C/ 30%rh	360	-4.6$^{\square}$	-6.378	-2.744	
			720	-3.2$^{\square}$	-5.165	-1.327	

$^{\square}$ **t-test: $p < 0.05$ (significant difference)**

Figure 5.2.13 shows dissolution profiles obtained for HPC50 and HPC75 before and after storage for 365 days under various conditions. Table 5.2.9 summarizes the statistical comparisons for both formulations (f_2-test, t-test).

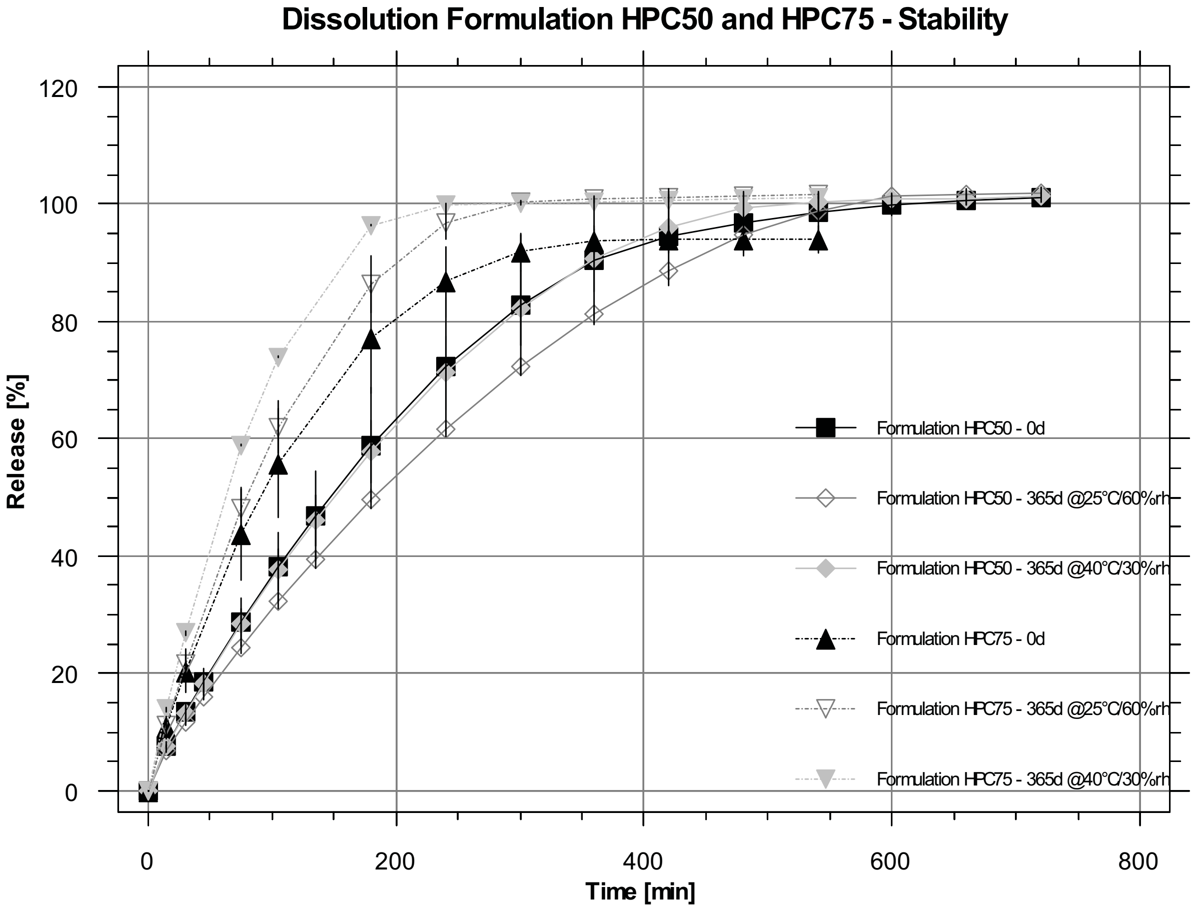


Fig.5.2.13 Dissolution from formulations HPC50 and HPC75, phosphate buffer USP 26 pH 6.8 (n≥3) – effect of one-year-storage on dissolution

Stability of drug release from hydroxypropylcellulose formulations (HPC50, HPC75) did not show a consistent trend. HPC50 showed a decrease in drug release after storage for 365 days at 25°C/60%rh compared to initial values. However, differences in means were considered insignificant based on t-test data. After storage at 40°C/30%rh stable a dissolution profile was found. Accordingly, f_2-tests certified similarity between obtained profiles for HPC50. For HPC75 evaluation of dissolution stability was also hampered by large variability in results. Despite an increase of drug release of 9.1% at 180min after 365 days storage at 25°C/60%rh, differences were considered insignificant according to the statistical comparisons by t-test. Storage at 40°C/ 30%rh resulted in a further increase in mean drug release by 14.4% at 180min. In the case of HPC75, the profile obtained after storage at 25°C/60%rh was statistically similar to the initially obtained profile (f_2 = 57), whereas the profile obtained after storage at 40°C/30%rh showed a lack of similarity to the initial profile (f_2 = 49). This was also suggested by the unpaired t-test (180min). Therefore stability of release from the HPC75 formulation seemed somewhat critical and requires further investigation.

Table 5.2.9: Statistical comparisons of dissolution profiles (HPC50, HPC75) obtained after varied storage conditions ($n \geq 3$): unpaired t-test and f_2-test (15min, 75min, 180min, 240min)

Formulation	Compared storage conditions		Time Point	Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	[min]	Mean A-Mean B [%]	Lower bound	Upper Bound	
HPC50	0d	365d 25°C/ 60%rh	105	5.8	-2.578	14.138	56
			240	10.7	-5.720	27.092	
	0d	365d 40°C/ 30%rh	105	0.5	-8.337	9.374	94
			240	1.1	-16.137	18.427	
	365d 25°C/ 60%rh	365d 40°C/ 30%rh	105	-5.3	-11.360	0.837	
			240	-9.5	-19.804	0.721	
HPC75	0d	365d 25°C/ 60%rh	75	-4.4	-16.232	7.369	57
			180	-9.1	-23.821	5.603	
	0d	365d 40°C/ 30%rh	75	-10.4	-21.057	0.290	49◊
			180	-14.4□	-26.415	-2.478	
	365d 25°C/ 60%rh	365d 40°C/ 30%rh	75	-5.9	-17.513	5.608	
			180	-5.3	-17.483	6.809	

□ t-test: $p < 0.05$ (significant difference) **◊ f_2-test: not similar**

5.2.5 Summary

Release from four types of melt extrusion matrices was examined with regard to the effects of medium pH and ionic strength. In addition, the stability of drug release after one-year of storage under two typical ICH conditions was examined.

Three of the four carriers provided pH-independent drug release, so changes in gastric or intestinal pH are not anticipated to affect drug release significantly. Only glycerylpalmitostearate showed any appreciable pH dependency of drug release, although here, too, f_2-tests still indicated similarity of release profiles. The observed decrease in drug release under low pH was attributed to the protonation of an acidic component within the applied excipient (Precirol ATO5).

Effects of dissolution media ionic strength were generally considered insignificant for all excipients tested.

With regard to stability of drug release, trends toward both acceleration and deceleration of drug release were observed. For glyceroldibehenate matrices with diffusion controlled release, a reduction in effective surface was demonstrated, resulting in decreased drug release. For glycerylpalmitostearate systems acceleration of drug release was attributed to changes in the lattice structure of the matrix according to the percolation theory for inert matrices. Results with HPC were generally favourable with respect to stability, but these systems exhibit variable release from unit to unit, which is a drawback to the use of this carrier. Sucrose-stearate matrices proved suitable for longer term stability of drug release.

5.2.6 Acknowledgement

I would like to acknowledge Dr. Gary Nichols for conducting the SEM experiments. His practical experience and efforts have been a great support to this work.

5.3 Food Effects

5.3.1 Aims of the chapter

This chapter examines the robustness of drug release from the CR matrix tablets towards the effects of food intake. Food and physiologic responses to food intake have been repeatedly reported to affect drug release from oral dosage forms (Abrahamsson, et al. (1999), Emori H., et al. (1995), Yamakita H., et al. (1995), Wonnemann N., et al. (2006), Jonkman J.H. (1989)).

To predict potential effects of lipid digestion on drug release from CR matrix carriers processed by melt extrusion *in vitro*, biorelevant dissolution media simulating conditions under fasted and fed state, were used. These media attempt to mimic conditions during fasted and fed state with regards to pH, osmolarity and activity of lipid digestion. Two different media were developed to distinguish fasted and fed state in the intestine, namely **Fa**sted **S**tate **S**imulating **I**ntestinal **F**luid (FaSSIF) and **Fe**d **S**tate **S**imulating **I**ntestinal **F**luid (FeSSIF) (Galia E. et al. (1998)). Furthermore biorelevant gastric media were suggested for use in dissolution experiments (Klein S. (2005), Klein S., et al. (2004)).

For simulation of GI passage of oral dosage forms, the method of Klein S. (2005) was applied to simulate various parts of the GI tract: (i) stomach, (ii) jejunum, (iii) ileum and (iv) colon. Standard USP3 dissolution equipment provided the technical feasibility of varying the test conditions during a dissolution experiment. During GI passage, dosage forms are exposed to different gastric and intestinal juices and hence simulation of GI passage *in vitro* ideally utilizes different media to represent conditions in various parts of GI tract. In addition to the parameters mentioned above, the experimental setup also allows simulation of changes in pH, osmolarity, residence time and volumes of dissolution media. Again, both fasted and fed state conditions have been considered.

In addition to changes in composition, eating changes the physiological motility pattern of the GI tract: postprandially, motility must support effective digestion (Davenport H.W. (1982)). Gastric motility is used to reduce size of food particles by means of mechanical stress. During the fed state, solid oral dosage forms are exposed to additional mechanical stress due to enhanced motility and presence of food particles, resulting in accelerated drug release or even damage to the dosage form. Hence, food effects on drug release caused by changes in motility can be anticipated, for example due to accelerated erosion of matrix systems or destruction of swelling layers, both of which would result in (partial) failure of the release controlling mechanism (Abrahamsson B.

(1998)). Effects of motility on drug release from CR dosage forms have been reported (Shaheem M., et al. (1995)). The USP 3 dissolution system enables variation of hydrodynamics to simulate motility under fasted and fed state conditions. Application of different dip rates during the dissolution experiment results in different hydrodynamic conditions.

Current designs of conventional dissolution equipment fail to simulate the contact between solid oral dosage forms with food particles and the gut wall during digestion well. As a result, underestimation of motility-driven food effects may result. Therefore, a novel approach to simulate enhanced food and motility driven stress on dosage forms was introduced for prediction of motility-related food effects.

5.3.2 Materials and Equipment

Ensure Plus was used as dissolution medium to simulate postprandial stomach (Klein S., 2005). Table 5.3.1 summarizes additional materials used and Table 5.3.2 gives additional equipment required for prediction of food effects on drug release in-vitro.

Table 5.3.1: Additional Materials

Material	Source
Ensure Plus Tetra Vanilla	Abbott Nutrition Ltd., Maidenhead, Berkshire, UK

Table 5.3.2: Additional Equipment

Device	Source
VanKel BioDis Dissolution Tester	VanKel Inc., Cary, NC, USA
Rotavapor R-200	Buchi UK Ltd., Chadderton, Oldham, UK
Vacuum Controller V 850	
Diaphragm Vacuum Pump V700	
Eppendorff Biofuge	Eppendorf UK Ltd., Cambridge, UK
Eppendorff Minispin	

5.3.3 Methods

5.3.3.1 Buffer Solutions used as Dissolution Media ("pH gradient methods")

Simple buffer media were used as a control to facilitate identification of the effects of bile secretions on drug release from CR matrix tablets. Media preparation was adapted from Klein S. (2005) and all control and biorelevant media were prepared accordingly. Tables 5.3.3 a)-d) show the composition and pH of the control media used.

Table 5.3.3a) –d): Buffer solutions for simulation of GI passage

a)

Simulating Gastric Fluid (sine pepsin, SGF)	
NaCl	2.0g
HCl conc.	7.0g
Water (Purified)	qs ad 1000ml
pH	1.80

b)

Simulating Colonic Fluid (SCoF)	
NaCl	6.28g
Acetic Acid glac.	10.2g
Water (Purified)	qs ad 1000ml
pH	5.80

c)

blank Fasted State Simulating Intestinal Fluid (bFaSSIF)	
$NaH_2PO_4 \times 2\ H_2O$	4.47g
NaCl	6.19g
NaOH	0.348g
Water (Purified)	qs ad 1000ml
pH	6.50-7.50

d)

blank Fed State Simulating Intestinal Fluid (bFeSSIF)	
Acetic Acid glac.	8.65g
NaCl	11.87g
NaOH	4.04g
Water (Purified)	qs ad 1000ml
pH	5.00

5.3.3.2 Biorelevant Dissolution Media

Fasted **S**tate **S**imulating **G**astric **F**luid (FaSSGF) was used for simulation of fasted state gastric conditions and the salt concentration and pH value were adjusted corresponding to physiological values under fasted state. Trition X-100 was used to reduce surface tension to a physiologic level. Table 5.3.4 shows the composition and pH of Fasted State Simulating Gastric Fluid (FaSSGF).

Table 5.3.4: Biorelevant Dissolution Media Simulating Fasted Stomach

Fasted State Simulating Gastric Fluid (FaSSGF)	
NaCl [mmol]	34.2
HCl conc. [mmol]	15.8
Triton X-100	10.0
Water purified	qs ad 1.00l
pH	1.8

Ensure® Plus was used to simulate gastric fluids during fed state. Ensure® Plus was designed for supplementary nutrition and contains approximately 16% protein, 30% fat and 54% carbohydrates.

For dissolution experiments with biorelevant media, gradients of FaSSIF were used to simulate digestive fluids in the proximal and distal jejunum and in the ileum during fasted state. In order to account for absorption of bile salts in distal parts of the small intestine, media for this region contained decreasing concentrations of bile salts. This was coupled with an increase in medium pH, simulating the typical pH profile in the human intestine.

For preparation of FaSSIF concentrate, 6.6g of taurocholic acid sodium was dissolved in 500ml of blank FaSSIF. 23.6ml of a solution of lecithin (100mg/ml) in dichloromethane (DCM) was added. DCM was removed by evaporation in a rotavap (500mbar, 40°C, 30min+ 50mbar, 40°C, 30min). Evaporated water was replaced. The clear micellar solution was brought 1.00l with blank FaSSIF to obtain FaSSIF concentrate. The various FaSSIF media were prepared by diluting FaSSIF concentrate with blank FaSSIF in different ratios according to table 5.3.5. Adjustment of pH was achieved using 1M sodium hydroxide solution for FaSSIF (adapted from Klein S. (2005)). Tables 5.3.5 to 5.3.6 show compositions and pH of biorelevant media used for simulations of intestinal fasted and fed state.

Table 5.3.5: Comparison of Biorelevant Dissolution Media Simulating Fasted Intestine (FaSSIF)

	FaSSIF 6.5	**FaSSIF 6.8**	**FaSSIF 7.2**	**FaSSIF 7.5**
pH	6.5	6.8	7.2	7.5
$c_{\text{Taurocholic Acid}}$ [mM]	3	3	1.5	-
c_{Lecithin} [mM]	0.75	0.75	0.375	-
$V_{\text{FaSSIF concentrate}}$ [ml]	350	350	175	-
V_{bFaSSIF} [ml]	1050	~1050	~1200	~1350

FeSSIF gradients were applied to simulate media in proximal and distal jejunum and ileum during fed state. Since ingestion of food activates release of enzymes and bile, higher concentrations of taurocholic acid and lecithin are needed to simulate postprandial levels. Again compositions for regions lower in the intestine contained lower concentrations of taurocholic acid and lecithin, and the pH of the media was increased.

For preparation of FeSSIF pH 5.0, 8.25g of taurocholic acid sodium were dissolved in 500ml blank FeSSIF. 59.1ml of a solution of lecithin (100mg/ml) in DCM were added. After removing DCM and replacing evaporated water, volume was brought to 1.00l with blank FeSSIF pH5.0.

For preparation of FeSSIF concentrate, 19.8g of taurocholic acid sodium was dissolved in 500ml of blank FaSSIF pH 6.5. 71.0 ml of a lecithin solution (100 mg/ml) in DCM were added. After removal of DCM and replacing evaporated water, the volume was brought 1.00 l with FaSSIF pH6.5. FeSSIF concentrate was then diluted with blank FaSSIF pH 6.5 according to Table 5.3.6 to obtain FeSSIF pH 6.5 and FeSSIF pH 6.5modified.

Table 5.3.6: Comparison of biorelevant dissolution media simulating fed intestine (FeSSIF)

	FeSSIF 5.0	**FeSSIF 6.5**	**FeSSIF 6.5 modified**
pH	5.0	6.5	6.5
$c_{\text{Taurocholic Acid}}$ [mM]	15	15	7.5
c_{Lecithin} [mM]	3.75	3.75	1.875
$V_{\text{FeSSIF pH6.5concentrate}}$ [ml]		350	175
$V_{\text{bFaSSIF pH6.5}}$ [ml]		~1050	~1200

5.3.3.3 Dissolution Test Setup

The experimental setup using USP 3 dissolution equipment permitted use of a sequence of dissolution media. Different sequences of dissolution media were used to simulate changes in pH and activity of lipid digestion. Dip times and dip rates were used to simulate conditions in the fasted and fed states. Gastric residence time was amended to be longer in the fed state. Hence the run time in gastric media was longer for *in vitro* fed state tests. In order to comply with increased intestinal motility in the fed state, dip rates for *in vitro* fed state tests were increased. control setups were used as a control. Tables 5.3.7 and 5.3.8 summarize control and biorelevant dissolution setups for fasted and fed state, including dip rates and run times.

Table 5.3.7: Dissolution setups using buffer solutions and biorelevant media to simulate the fasted state

Fasted pH gradient	**pH**	**Fasted biorelevant gradient**	**pH**	**Run Time [min]**	**Dip Rate [dpm]**
SGF	1.8	FaSSGF	1.8	60	10
bFaSSIF	6.5	FaSSIF 6.5	6.5	15	10
bFaSSIF	6.8	FaSSIF 6.8	6.8	15	10
bFaSSIF	7.2	FaSSIF 7.2	7.2	30	10
bFaSSIF	7.5	FaSSIF 7.5	7.5	120	10
SCoF	5.8	SCoF	5.8	600 (60+3x120+180)	10
bFaSSIF	6.5	bFaSSIF	6.5	360 (180+180)	10

Table 5.3.8: Dissolution setups using buffer solutions and biorelevant media to simulate the fed state

Fed pH gradient	**pH**	**Fed biorelevant gradient**	**pH**	**Run Time [min]**	**Dip Rate [dpm]**
bFeSSIF	5.0	Ensure Plus	1.8	240 (120+120)	15
bFeSSIF	5.0	FeSSIF 5.0	5.0	15	15
bFaSSIF	6.5	FeSSIF 6.5	6.5	15	15
bFaSSIF	6.5	FeSSIF 6.5 modified	6.5	30	15
bFaSSIF	7.5	bFaSSIF	7.5	120	15
SCoF	5.8	SCoF	5.8	600 (2x120+2x180)	15
bFaSSIF	6.5	bFaSSIF	6.5	180	15
		bFaSSIF (Infinity Point)	6.5	180 + Ultraturrax	15

5.3.3.4 Modified Dissolution Setup (“Disc System”)

The standard USP3 dissolution system was modified to better simulate collision of the dosage form with food particles and the gut wall during the *in vitro* test.

The modification combined a conventional USP apparatus 3 dissolution tester (USP 2003) with discs used for conventional disintegration testing (Ph.Eur. 1997). Each disc had an approximate weight of 3g. Fig. 5.3.1 shows a schematic picture of the disc. The disc method was used with the control fed state dissolution setup.

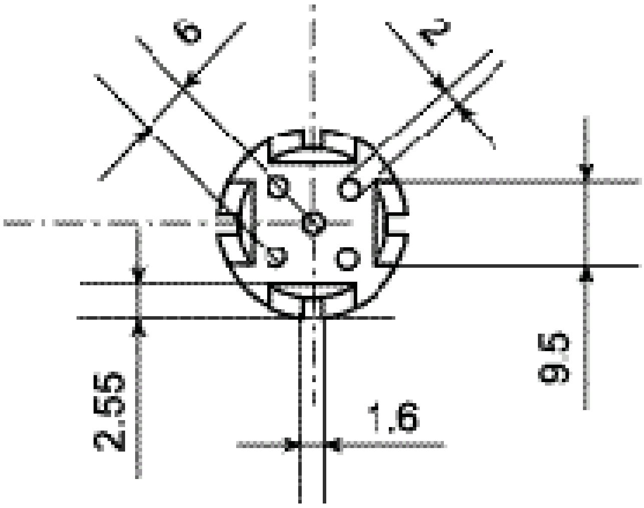


Fig. 5.3.1 Disc for disintegration testing (Ph.Eur. 1997)

5.3.3.5 HPLC Sample Preparation for Ensure® Plus Samples

Prior to performance of HPLC assays, dissolution samples containing Ensure® Plus had to be processed. Removal of proteins and lipids was required to reduce interferences during HPLC assays and damage of HPLC columns.

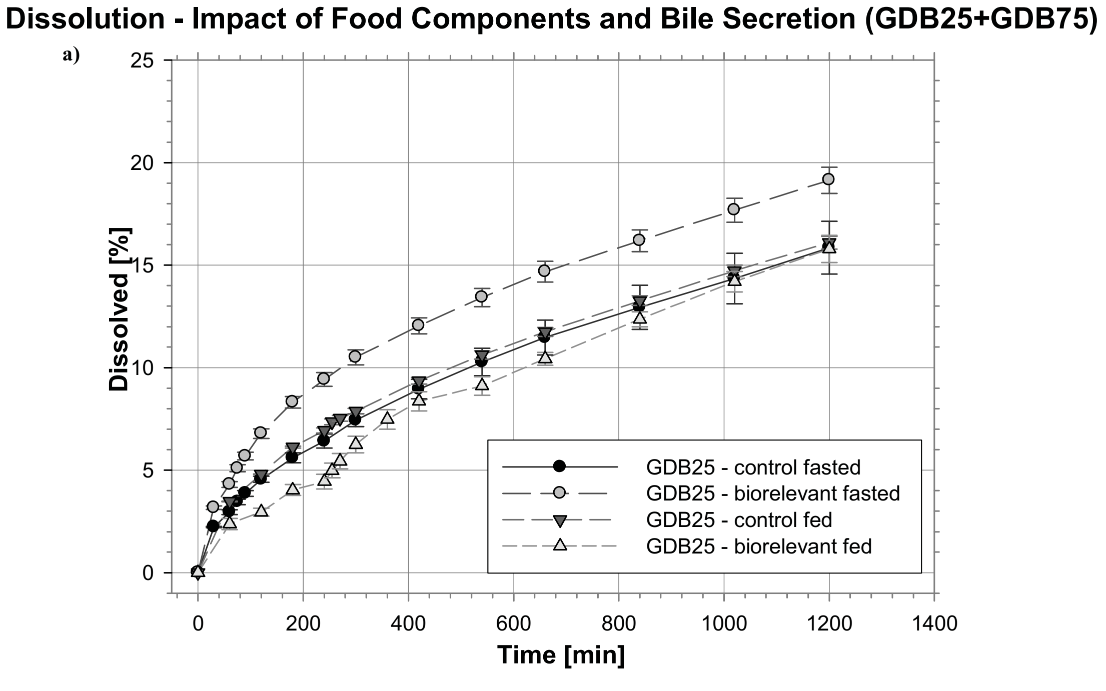
0.25ml of sample was diluted with 1.25ml of demineralised water. Diluted samples were centrifuged at 4400rpm for 90min (25°C). The aqueous supernatant was carefully collected and centrifuged at 13200rpm for 90min (25°C). Again, the aqueous supernatant was collected and filtered with a 0.45µm PTFE syringe filter. Processed samples were diluted with blank FeSSIF pH5.0 according to the HPLC assay described in chapter 3.3.3. Method validation confirmed that theophylline was fully dissolved in the aqueous phase of samples. Theophylline was recovered within ±5% of the true value over the concentration range 2mg/ 200ml to 55mg/ 200ml.

5.3.4 Results and Discussion

5.3.4.1 Impact of Nutrition Components and Bile Secretions on Drug Release of CR Matrix Tablets

The prototype formulations showed different sensitivities to the presence of lecithin and bile salts in dissolution media. Whilst drug release from GDB was fairly robust, GPS and SUS formulations suffered significant changes in drug release. HPC formulations showed highly accelerated drug release in the USP 3 dissolution tester and therefore no controlled release of theophylline was observed.

Fig. 5.3.2 shows dissolution profiles obtained for GDB25 and GDB75 using control and biorelevant setups. Table 5.3.9 summarizes the statistical comparison of the dissolution profiles obtained.



b)

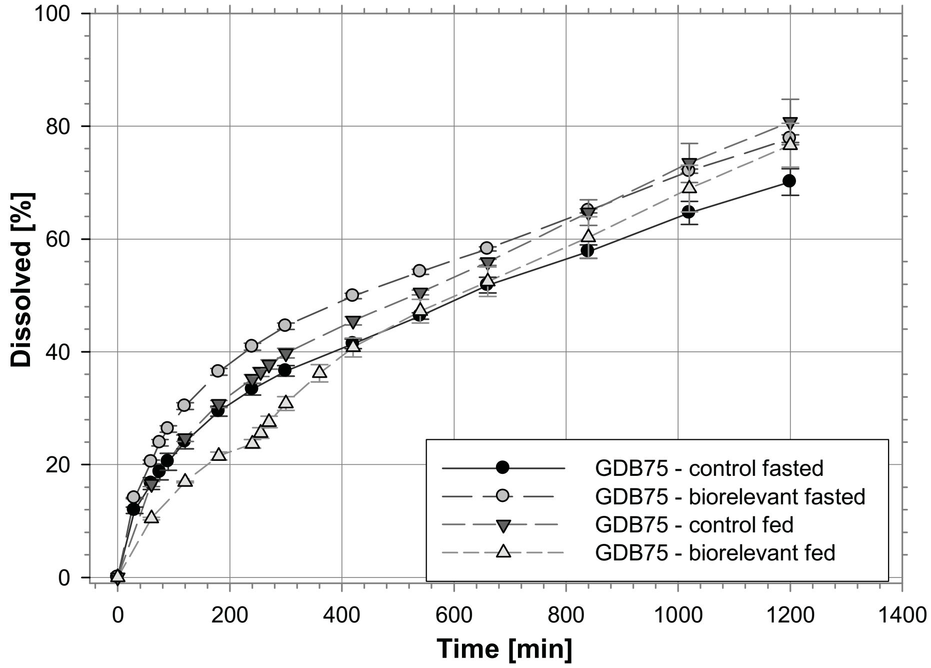


Fig. 5.3.2: Impact of bile secretions on drug release from glyceryldibehenate (GDB) formulations (n=3); control vs. biorelevant setups simulating fasted and fed state: a) GDB25, b) GDB75

For both glyceryldibehenate (GDB) formulations (GDB25/ GDB75), the addition of lecithin and bile salts increased mean drug release after 20h in the fasted state. An increase in mean drug release by 3.3% (GDB25) and 7.7% (GDB75), respectively, after 20h was observed with the biorelevant fasted state setup compared to control. Statistical similarity of the dissolution profiles (see Table 5.3.9) was suggested by f_2-test in both cases. However, comparison by unpaired t-test indicated differences in release profiles of both formulations, since significant deviations in mean drug release were found at 180min and 1200min.

With the biorelevant fed state conditions, only a little difference in mean drug release after 20h was observed compared to control. This was also supported by the t-test, not showing significant differences between mean values after 1200min for both formulations. Further, similarity criteria (f_2-test) were fulfilled. However, t-test still suggested significant differences in mean drug release at 180min compared to control.

Compared to the biorelevant fasted setup, drug release under biorelevant fed conditions was slower (GDB25) and comparable after 20h (GDB75), respectively. Accordingly, statistically significant differences in mean drug release were found for GDB25 at 180min and 1200min, while GDB75 differed significantly only after 180min.

Looking at the figures, the accelerating effect of bile salts and lecithin on drug release, as suggested by the fasted setups, seemed to be masked by slower release in the biorelevant gastric medium (Ensure® Plus) with the fed conditions. Suppression or delay of drug release of rosiglitazone by the Ensure® Plus medium have been reported by Fischbach M. (2006). Therefore, viscosity of dissolution media may be another important parameter to predict food effects from GDB matrix dosage forms. Drug release in the biorelevant intestinal media was faster compared to control, indicated by the steeper slope of the release curve in the second part. The effect of increased viscosity was dominating for GDB25. For GDB75, both effects cancelled each other out after 20h and mean drug release was comparable to control.

Changing the dissolution device from USP 2 to USP 3 had only little impact on the dominating drug release mechanism (data not shown). Further, the absolute drug release was comparable to USP2 experiments. This may be a first indication that GDB formulations are robust towards changes in agitation.

Table 5.3.9: Statistical comparisons of dissolution profiles (GDB25, GDB75) obtained with control and biorelevant setups simulating fasted and fed states (n=3): unpaired t-test and f_2-test (30min, 180min, 300min, 540min, 1200min)

Formulation	Compared setups		Time Point	Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	[min]	Mean A-Mean B [%]	Lower bound	Upper Bound	
GDB25	fasted control	fasted biorelevant	180	-2.7□	-3.312	-2.109	77
			1200	-3.3□	-5.601	-0.990	
	fed control	fed biorelevant	180	2.1□	1.668	2.528	86
			1200	0.2	-0.690	1.156	
	fasted biorelevant	fed biorelevant	180	4.3□	3.660	4.904	70
			1200	3.3□	1.994	4.569	
GDB75	fasted control	fasted biorelevant	180	-7.0□	-8.684	-5.298	58
			1200	-7.7□	-11.604	-3.780	
	fed control	fed biorelevant	180	9.2□	7.739	10.745	56
			1200	4.1	-4.882	13.1	
	fasted biorelevant	fed biorelevant	180	14.9□	13.479	16.364	50
			1200	1.2	-5.168	7.478	

□ t-test: $p < 0.05$ (significant difference)

In conclusion, GDB formulations seemed to be modestly prone to food effects driven by food and (i) bile components with and (ii) viscosity of gastric and intestinal contents.

Fig. 5.3.3 shows dissolution profiles of GPS25 and GPS75 under *in vitro* fasted conditions and the statistical evaluation of the dissolution profiles is summarized in Table 5.3.10. Mean drug release from GPS25 decreased by 1.9% at 20h under biorelevant fasted conditions (30.2% (±1.4) vs. 28.3% (±3.2)). A high degree of similarity was suggested by f_2-test ($f_{2\ \mathrm{Fasted}}$=80), but a statistically significant difference in mean release at 180min was suggested by t-test. For simulated fed conditions, mean drug release decreased significantly by 16.1% at 20h in biorelevant fed state conditions. Although statistical examination by f_2-test indicated similarity between dissolution profiles (see Table 5.3.10), the unpaired t-test showed significant differences in mean drug release at 180min and 1200min.

For GPS75 mean drug release at 20h increased significantly by 8.2% with the fasted biorelevant setup compared to control. By contrast, increase in mean drug release in the *in vitro* fed state setup after 20h was only 2.8%. For GPS75, statistical comparison indicated non-similarity of release profiles under fasted state conditions, but similar dissolution profiles under fed state conditions ($f_{2\ \text{Fasted}}$=47/ $f_{2\ \text{Fed}}$=80). The unpaired t-test confirmed the non-similarity and suggested a significant difference in mean drug release at 180min under fed conditions.

Based on fasted state experiments, little change in drug release was expected by the addition of bile salts and lecithin to the dissolution media. However, significant decrease in drug release was observed for both GPS25 and GPS75, and thus other parameters must have affected drug release from GPS formulations. Statistically, a significant reduction in mean drug release was expected for both formulations (t-test). F2-testing confirmed the non-similarity of dissolution profiles obtained with biorelevant fasted and fed setups for GPS75, while similarity was shown for GPS25. However, absolute drug release was only <20% for GPS25 and thus f_2=62 was considered to indicate quite some difference between profiles.

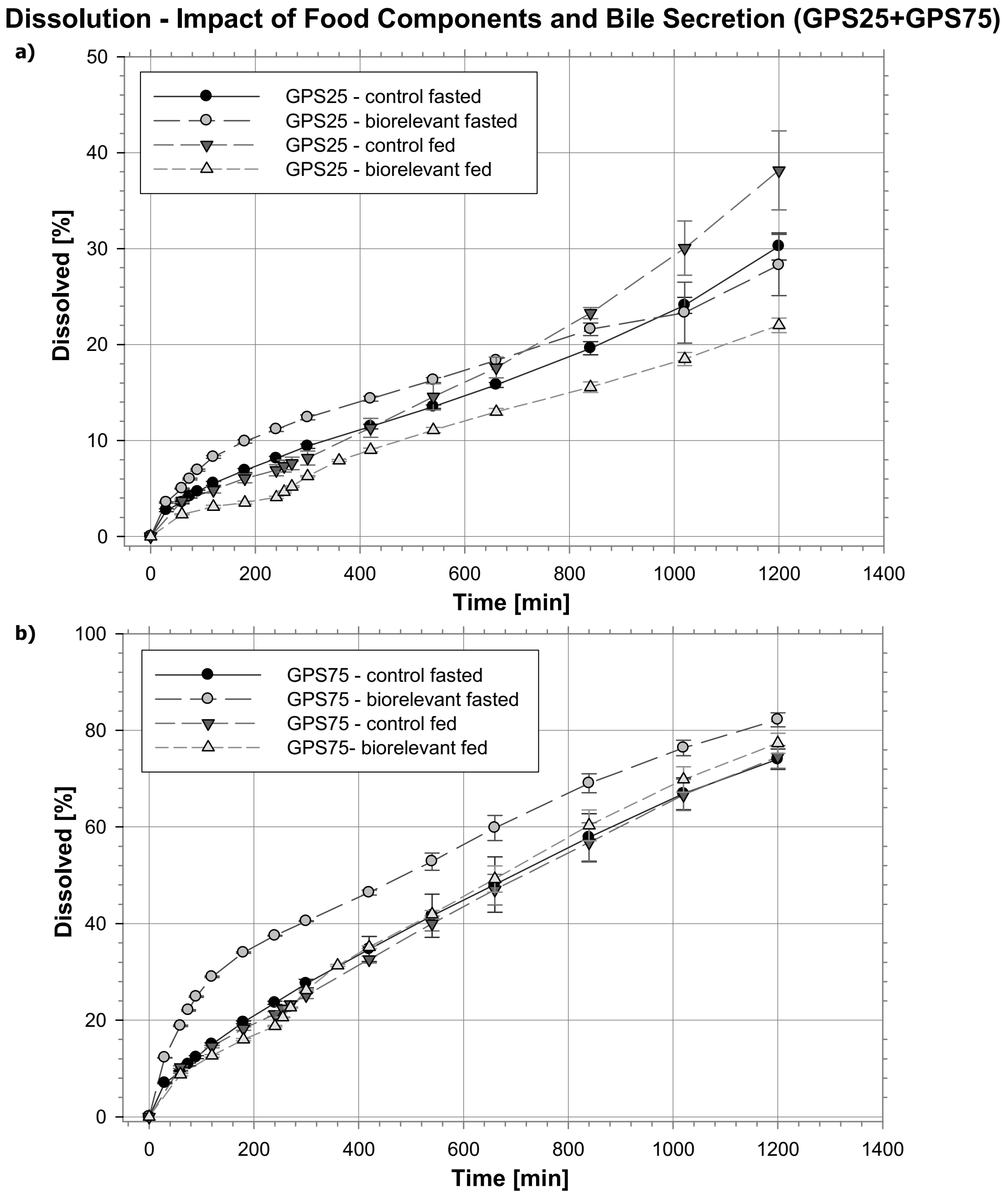


Fig. 5.3.3: Impact of bile secretions on drug release from glycerylpalmitostearate (GPS) formulations (n=3); control vs. biorelevant setups simulating fasted and fed state: a) GPS25, b) GPS75

Table 5.3.10: Statistical comparisons of dissolution profiles (GPS25, GPS75) obtained with control and biorelevant setups simulating fasted and fed states (n=3): unpaired t-test and f_2-test (30min, 180min, 300min, 540min, 1200min)

Formulation	Compared setups		Time Point	Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	[min]	Mean A-Mean B [%]	Lower bound	Upper Bound	
GPS25	fasted control	fasted biorelevant	180	-3.0$^{\square}$	-3.467	-2.560	80
			1200	1.9	-3.647	7.545	
	fed control	fed biorelevant	180	2.5$^{\square}$	1.772	3.290	60
			1200	16.1$^{\square}$	9.422	22.858	
	fasted biorelevant	fed biorelevant	180	6.4$^{\square}$	5.992	6.763	62
			1200	6.3$^{\square}$	1.002	11.534	
GPS75	fasted control	fasted biorelevant	180	-9.4$^{\square}$	-9.919	-8.871	47$^{\Diamond}$
			1200	-8.2$^{\square}$	-12.268	-4.076	
	fed control	fed biorelevant	180	2.3$^{\square}$	1.576	3.012	80
			1200	-2.8	-7.902	2.255	
	fasted biorelevant	fed biorelevant	180	13.0$^{\square}$	12.516	13.445	45$^{\Diamond}$
			1200	4.9$^{\square}$	0.768	8.946	

$^{\square}$ t-test: $p < 0.05$ (significant difference) **$^{\Diamond}$ f_2-test: not similar**

Major differences between release profiles obtained with biorelevant fasted and fed setups were found in (i) a decrease in mean drug release with biorelevant fed setup and (ii) a change in the release pattern for GPS25. The decrease in drug release may be attributed to the increased viscosity of biorelevant gastric dissolution medium (Ensure® Plus). However, drug release from GPS formulations seemed less sensitive to the presence of bile and food components and thus did not make up for the initial decrease in drug release.

To investigate the cause for the changed release pattern for GPS25, a model-dependent analysis of the drug release mechanism was performed. The results are summarized in Table 5.3.11. The analysis indicated an increased level of erosion-controlled drug release for GPS25 and GPS75. As erosion prevailed in both control and biorelevant fed state setups, this change may be attributed to the changes in the dissolution apparatus. Hence, the impact of hydrodynamics on drug release needs to be investigated separately (see chapter 5.3.4). It seemed that the changes in hydrodynamics caused significant changes in the release mechanism, extent of drug release and profile shape. The increased variability of drug release could also be attributed to the prevailing erosion mechanism.

Table 5.3.11: Theoretical Examination of Drug Release Mechanism with Biorelevant Fed and Fasted State Conditions (GPS25 and GPS75)

Formulation	Dissolution Setup	Higuchi Model		Power-Law Model			Peppas-Sahlin Model		
		k	r^2	k’	n	r^2	k_D	k_R	r^2
GPS25	pH gradient fed state	0.759	0.873	0.018	1.07	0.989	0.089°	0.001°	0.993°
GPS25	biorelevant fed state	0.489	0.923	0.035	0.91	0.993	<0.001*	0.035*	0.993*
GPS75	pH gradient fasted state	1.884	0.980	0.505	0.70	0.999	0.939	0.124	0.999
GPS75	biorelevant fasted state	2.372	0.996	2.637	0.48	0.996	3.133	0.036	0.997

***m=0.454 °m=0.706**

In conclusion, a reduction of drug release under fed state conditions is expected for GPS formulations. The decrease seemed mainly driven by changes in viscosity of the dissolution media and thus changes in viscosity of gastric and intestinal contents are considered likely to affect drug release *in vivo*. The effect of bile salts and lecithin seemed to be of subordinate importance for the dissolution profile compared to motility and potentially viscosity. Potential effects of changed changes in motility will be addressed in the following section.

Fig. 5.3.4 shows dissolution profiles from SUS25 and SUS75 under fasted and fed state conditions. With fasted state conditions, no significant change in mean drug release was found (42.1% (±0.7) vs. 40.6% (±1.0)) for SUS25. By contrast, mean drug release increased by 17.9% at 20h with a biorelevant fed setup. Statistical examination revealed that only with the biorelevant fed state setup, significant differences in mean drug release were found (unpaired t-test, see Table 5.3.12). The increase was also coupled with a change to a biphasic release profile.

For SUS75, mean drug release was significantly increased in presence of bile salts. Under fasted state conditions, presence of bile components affected mean drug release in particular in the first phase of drug release in which media contained the highest concentrations of taurocholic acid and bile salts. After 180min drug release was significantly increased by 11.2% with the biorelevant fasted setup. However, after 20h only an insignificant difference was found.
In fed state conditions, drug release was increased by 22.6% at 11h with the biorelevant fed state setup, resulting in non-similar release profiles ($f_{2\ fed}$=42) for SUS75. Further, t-test indicated a significant difference in mean drug release at 180min and 660min.

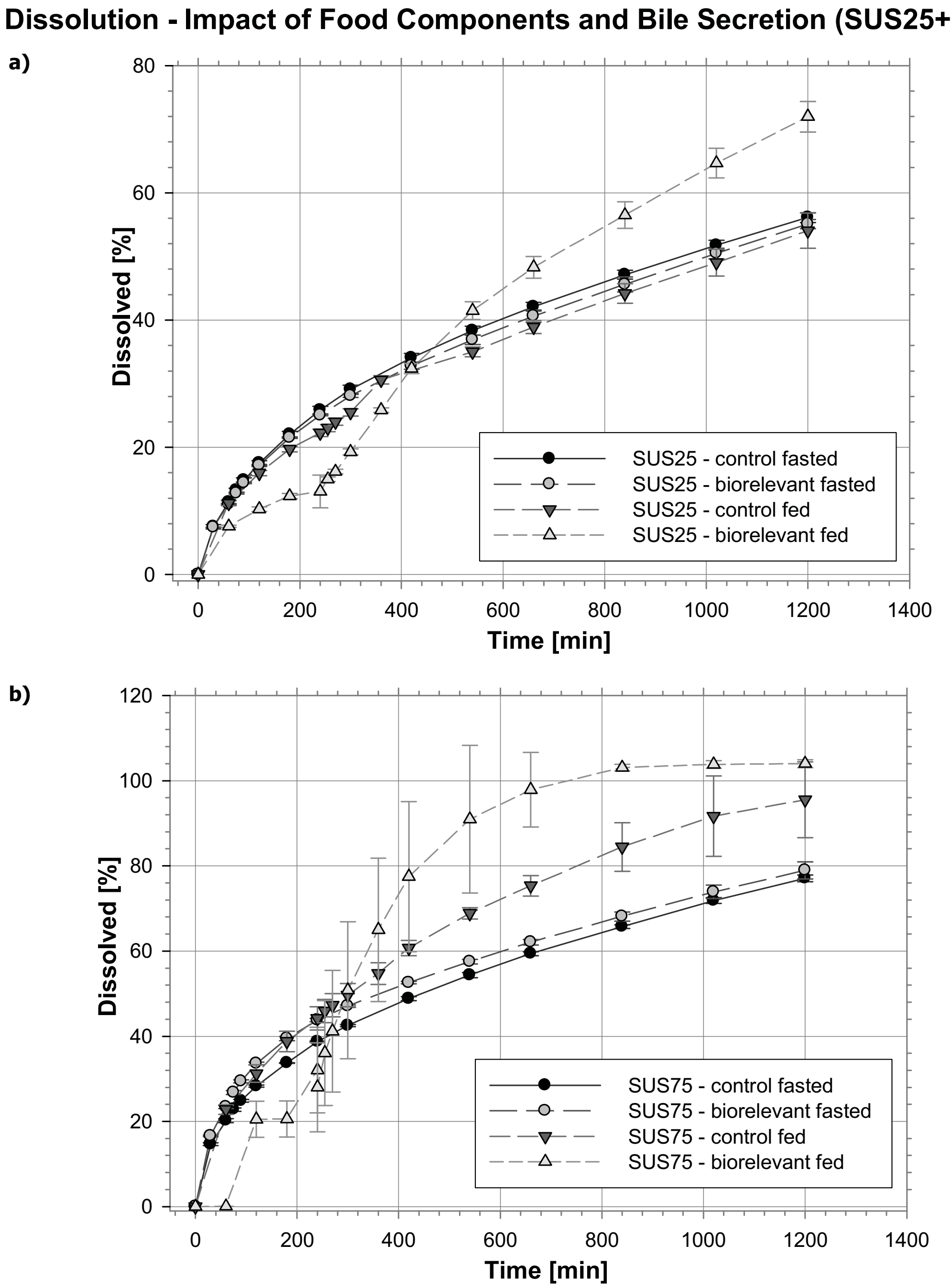


Fig. 5.3.4: Impact of bile secretions on drug release from sucrose stearate (SUS) formulations (n=3); control vs. biorelevant setups simulating fasted and fed state: a) SUS25, b) SUS75

In both cases, a significant increase in mean drug release was suggested and supported by statistical analyses. Hence, significantly increased mean drug release was observed after 1200min and 660, respectively. However, a decreased drug release under biorelevant fed conditions was observed in the initial part of the experiment simulating gastric environment. Similar to GPS formulations, this resulted in a biphasic release pattern under biorelevant fed conditions.

Model-dependent analysis of the release mechanism indicated that the change in the release pattern was attributed to change in the dominating release mechanism. Table 5.3.13 summarizes the evaluation of drug release mechanisms obtained with the biorelevant fasted and fed setups (also see chapter 5.1). The analysis showed a change to erosion controlled drug release under biorelevant fed state conditions. Likely, agitation was increased due to an increase in dip rate. Therefore, selected prototype formulations will be examined in more detail regarding their robustness towards changes in hydrodynamics (see 5.3.4).

Similar to GDB and GPS formulations, drug release in Ensure Plus was significantly slower compared to control. In the case of SUS75, even a lag-time of approximately 120min was observed with the biorelevant fed setup. Based on these results, drug release from SUS formulations seemed severely affected by the comparably high viscosity of the Ensure® Plus medium.

Drug release from SUS formulations showed little sensitivity to the addition of bile secretions to dissolution media. Effects of motility and viscosity were considered to predominate.

Table 5.3.12: Statistical comparisons of dissolution profiles (SUS25, SUS75) obtained with control and biorelevant setups simulating fasted and fed states (n=3): unpaired t-test, and f_2-test (30min, 180min, 300min, 540min, 1200min) / $^{+}$(30min, 180min, 300min, 660min)

Formulation	Compared setups		Time Point	Mean Difference	95% Confidence Interval		f_2
	No. A	**No. B**	**[min]**	**Mean A-Mean B [%]**	**Lower bound**	**Upper Bound**	
SUS25	fasted control	fasted biorelevant	180	0.5	-0.229	1.263	93
			1200	1.0	-0.702	2.747	
	fed control	fed biorelevant	180	7.4□	6.438	8.320	51
			1200	-17.9□	-23.792	-12.039	
	fasted biorelevant	fed biorelevant	180	9.2□	8.491	9.881	51
			1200	-16.9□	-20.893	-12.857	
SUS75^{+}	fasted control	fasted biorelevant	180	-11.2□	-12.044	-10.355	70
			1200	-1.9	-5.311	1.588	
	fed control	fed biorelevant	180	18.2□	10.398	26.037	42◊
			660	-22.6□	-37.113	-7.991	
	fasted biorelevant	fed biorelevant	180	18.9□	12.054	25.773	34◊
			660	-35.8□	-49.894	-21.726	

□ t-test: $p < 0.05$ (significant difference) **◊ f_2-test: not similar**

In conclusion, SUS formulations seemed prone to food effects mainly driven by changes in gastrointestinal motility and viscosity of gut contents. Dissolution experiments suggested an increase in drug release for both SUS25 and SUS75. Similar as for GDB formulations, the physiologic relevance of *in vitro* experiments with respect to medium viscosity is questionable. *In vivo*, the effect of viscosity may become more pronounced, potentially resulting in a decrease in drug release. A more reliable *in vitro* assessment will require a series of dissolution experiments applying media with varied viscosities.

Table 5.3.13: Theoretical Examination of Drug Release Mechanism with Biorelevant Fed and Fasted State Conditions (SUS25 and SUS75)

Formulation	Dissolution Setup	Higuchi Model		Power-Law Model			Peppas-Sahlin Model		
		k	r^2	k’	n	r^2	k_D	k_R	r^2
SUS25	biorelevant fasted state	1.59	0.999	1.48	0.511	0.990	1.94	0.033	0.998
SUS25	biorelevant fed state	1.69	0.920	0.089	0.958	0.960	0°	0.130°	0.983
SUS75	biorelevant fasted state	2.47	0.984	5.21	0.383	0.990	3.87	0	0.995
SUS75	biorelevant fed state	3.09	0.857*	0.038*	1.24	0.929	0	0.371	0.956

***0-660min °m=0.449**

Fig. 5.3.5 shows the dissolution profiles of HPC formulations with control (fasted and fed) and biorelevant fasted setups. The statistical comparison of mean drug release from HPC25 is summarized in Table 5.3.14.

For Hydroxypropylcellulose (HPC) formulations (HPC25/ HPC75), insignificant changes in mean drug release were observed in presence of taurocholic acid and lecithin. For HPC25, an insignificant increase in mean drug release by 2.7% at 240min was found with the biorelevant fasted state setup.

Similarly, HPC75 showed an insignificant increase in mean drug release under biorelevant fasted conditions after 1h (91.0% ±3.4 vs. 91.7% ±1.3).

In both cases, theophylline was released much faster compared to previous tests using a USP 2 dissolution tester. Changes in agitation are likely to have caused the significant increase in drug release. This was supported the statistical significant difference in mean drug release obtained with biorelevant fasted and control fed conditions. Therefore a more detailed investigation on the effects of motility will be conducted (see chapter 5.3.4.2).

Due to fast release profiles and hydrophilic character of the polymer under simulated fasted state conditions, the effects of bile and food components were considered of subordinate importance for the *in vivo* performance of HPC formulations. This was statistically confirmed by the similarity of profiles and the insignificant differences in mean drug release according to the t-test.

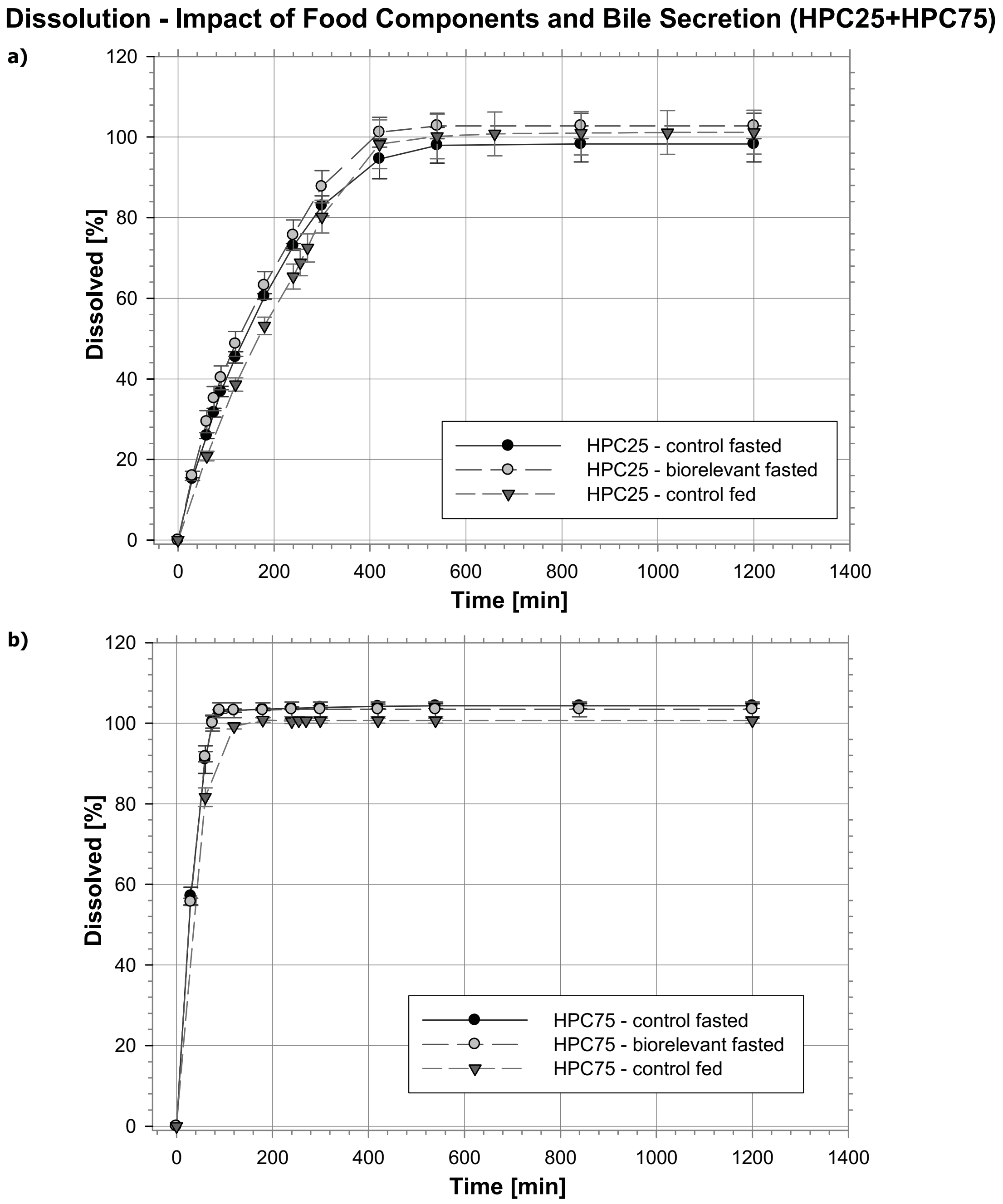


Fig. 5.3.5: Impact of bile secretions on drug release from hydroxypropylcellulose (HPC) formulations (n=3); controls vs. biorelevant setups simulating fasted state: a) HPC25, b) HPC75

The suitability of high drug loading HPC formulations for CR release profiles was thrown into question by these results. For a low drug loading formulation, HPC may work as a carrier for semi-retard retard formulations. Due to the fast drug release, experiments with biorelevant fed setups were omitted.

In conclusion, HPC formulations are considered prone to food effects. Changes in motility seemed to be the major cause for an increase in drug release. Therefore an increase in drug release is expected *in vivo* under fed conditions.

Table 5.3.14: Statistical comparisons of dissolution profiles (HPC25) obtained with control and biorelevant setups simulating fasted state (n=3): unpaired t-test and f_2-test (30min, 60min, 120min, 240min)

Formulation	**Compared setups**		**Time Point**	**Mean Difference**	**95% Confidence Interval**		**f_2**
	No. A	**No. B**	**[min]**	**Mean A-Mean B [%]**	**Lower bound**	**Upper Bound**	
HPC25	fasted control	fasted biorelevant	60	-3.4	-8.007	1.109	73
			240	-2.7	-8.829	3.473	
	fasted biorelevant	fed control	60	-9.2$^{\square}$	-14.357	-4.097	51
			240	10.2$^{\square}$	2.437	18.057	

$^{\square}$ t-test: $p < 0.05$ (significant difference)

5.3.4.2 Impact of Motility on Drug Release from CR Matrix Tablets

Drug release from GDB25 and GPS25 proved to be robust with respect to changes in hydrodynamics. Similarity of drug release was found after changing dip rate and addition of a disc. For all other formulations, drug release was sensitive to changes in hydrodynamic conditions.

Fig. 5.3.6 shows the dissolution profiles obtained for GDB formulations with varying hydrodynamic conditions. For GDB25, acceleration of dip rate from 10dpm to 15dpm resulted in little increase in mean drug release at 20h (15.8% ±1.3 vs. 16.1% ±0.3). Likewise, applying a disc barely increased mean drug release at 20h compared to a 15dpm test (16.1% ±0.3 vs. 17.5% ±1.1). Therefore GDB25 was considered robust towards hydrodynamic stress.

By contrast, drug release from GDB75 was impacted by increase in dip rate and more so by enhanced stress using a disc. Acceleration of the dip rate from 10dpm to 15dpm resulted in an increase in mean drug release of 10.6% at 20h. When a disc was applied, complete drug release was achieved within approximately 10h. The mean drug release at 20h was increased by 23.0%. Table 5.3.15 summarizes the statistical analysis of mean drug release obtained for comparison of dissolutions tests demonstrating the impact of changes in hydrodynamics on drug release from GDB75 matrix tablets, as well as for all other excipients. F_2 comparison indicated similarity of dissolution profiles with dip rate 10dpm vs. 15dpm, but showed lack of similarity when the disc was applied (15dpm vs. 15dpm with disc). Unpaired t-test also indicated a significant difference in mean drug release for GDB75.

The disc method discriminated formulations with regard to lack of robustness towards changes in hydrodynamics. Based on the disc method results, a significant impact of the hydrodynamic conditions *in vivo* on drug release from GDB75 would be anticipated. Low tablet hardness and unfavourable shape with low tablet thickness were considered potential reasons. Due to the physical instability of GDB75 tablets, mechanical stress caused a fast disintegration of the matrix and resulted in faster drug release.

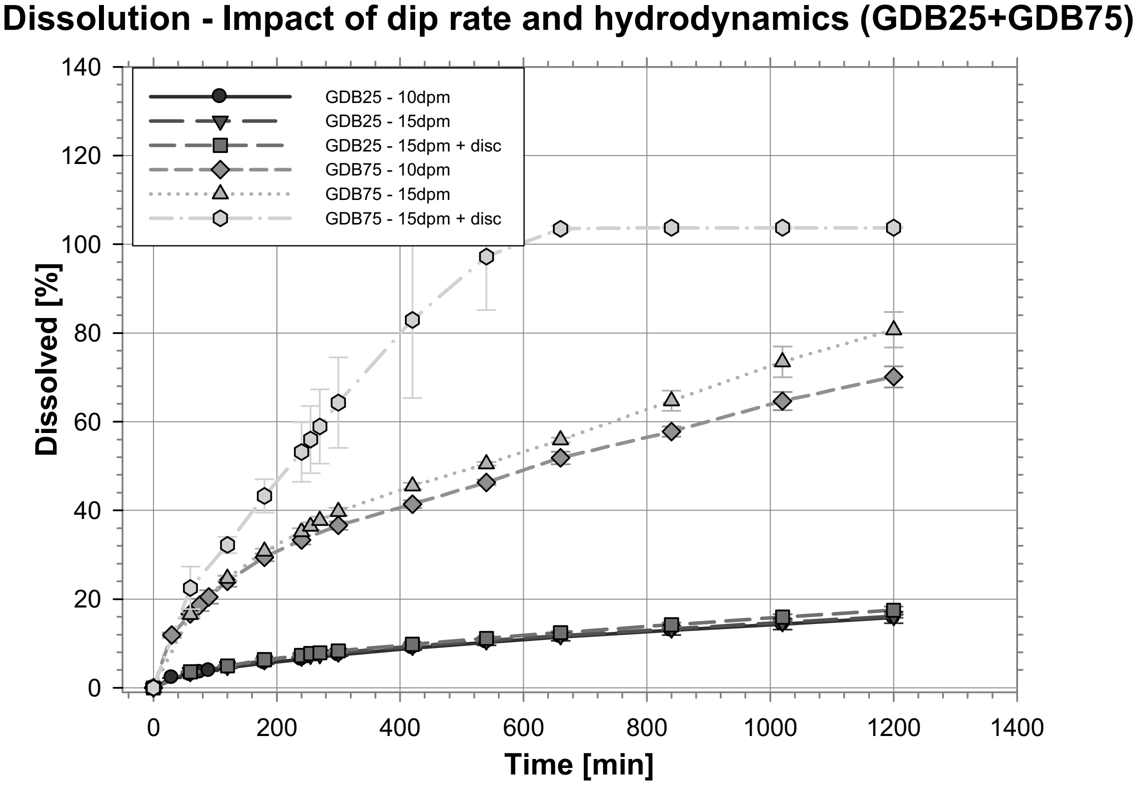


Fig. 5.3.6: Impact of hydrodynamic stress on drug release from glyceryldibehenate (GDB) formulations

Fig. 5.3.7 shows the dissolution profiles for GPS formulations obtained with varying hydrodynamic conditions. For GPS25 acceleration of dip rate from 10dpm to 15dpm resulted in an increase in mean drug release at 20h by 7.9% (30.2% (±1.4) vs. 38.2% (±4.1)), but statistical comparisons indicated general similarity between release profiles (see Table 5.3.15). Applying a disc resulted in a slight change in mean drug release at 20h (38.2% ±4.1 vs. 34.2% ±4.9). This was also confirmed by statistical comparison of profiles and mean drug release. Overall, there was no significant difference in drug release between 10dpm, 15dpm and disc experiments. Therefore GPS25 was considered robust against hydrodynamic stress.

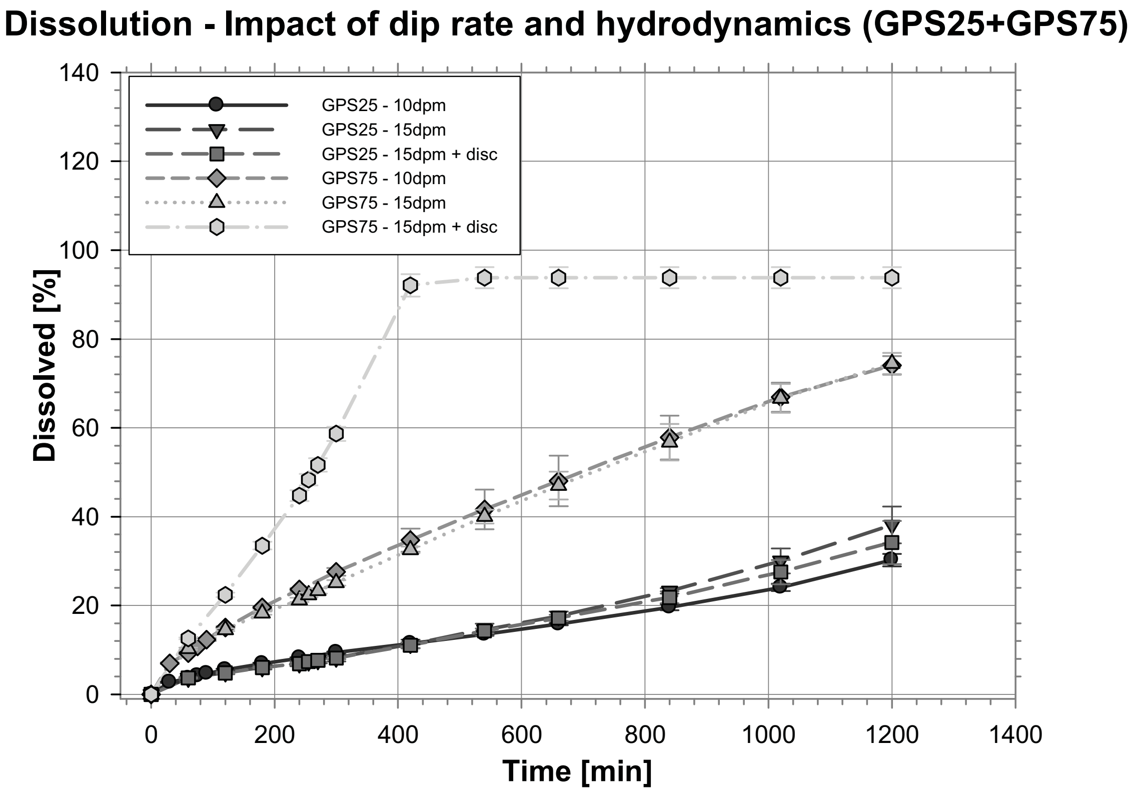


Fig. 5.3.7: Impact of hydrodynamic stress on drug release from glycerylpalmitostearate (GPS) formulations

For GPS75, acceleration of dip rate from 10dpm to 15dpm, resulted in little or no increase in mean drug release at 20h (74.0% ±2.1 vs. 74.5% ±2.4). The f_2-test value of 87.5 indicated similarity between profiles. By contrast, application of a disc accelerated drug release, resulting in an increase of mean drug release by 19.3% compared to a test at 15dpm without disc. Based on this result, a significant impact of the hydrodynamic conditions in vivo on drug release from GPS75 was anticipated. For GPS75, an erosion-controlled CR matrix dosage system, mechanical stress might result in faster matrix erosion. Low tablet hardness and unsuitable tablet thickness may also have contributed to the lack of robustness to hydrodynamics.

Similar to GDB formulations, the disc method was capable of discriminating formulations with regard to their robustness of drug release to hydrodynamic conditions.

As described in chapter 5.3.4.1 for the biorelevant fed state setup, enhancing hydrodynamics again caused a change in the release profile to a biphasic release for GPS25. This confirmed that the change in release mechanism was driven by the changed hydrodynamics rather than be presence of bile components.

For SUS25 acceleration of dip rate from 10dpm to 15dpm resulted in little or no change in mean drug release at 20h (56.1% ±0.8 vs. 54.1% ±2.8). Similarity of dissolution profiles was continued by statistical comparison (see Table 5.3.15). However, application of a disc increased mean drug release at 20h by 42.0% compared to a standard 15dpm setup. Statistical analysis confirmed lacking similarity between release profiles (f_2=26.1) and mean drug release (unpaired t-test). Similarly, SUS75 showed significantly higher drug release with increased in dip rate from 10dpm to 15dpm (59.4% ±0.5 (10dpm) vs. 75.3% ±2.4 (15dpm)). A further increase in drug release was observed with the disc setup at 11h (102.6% ±1.3 (15dpm, disc) vs. 75.3% ±2.4 (15dpm, no disc)). Statistical comparison confirmed significant differences in mean drug release (unpaired t-test) (see Table 5.3.15).

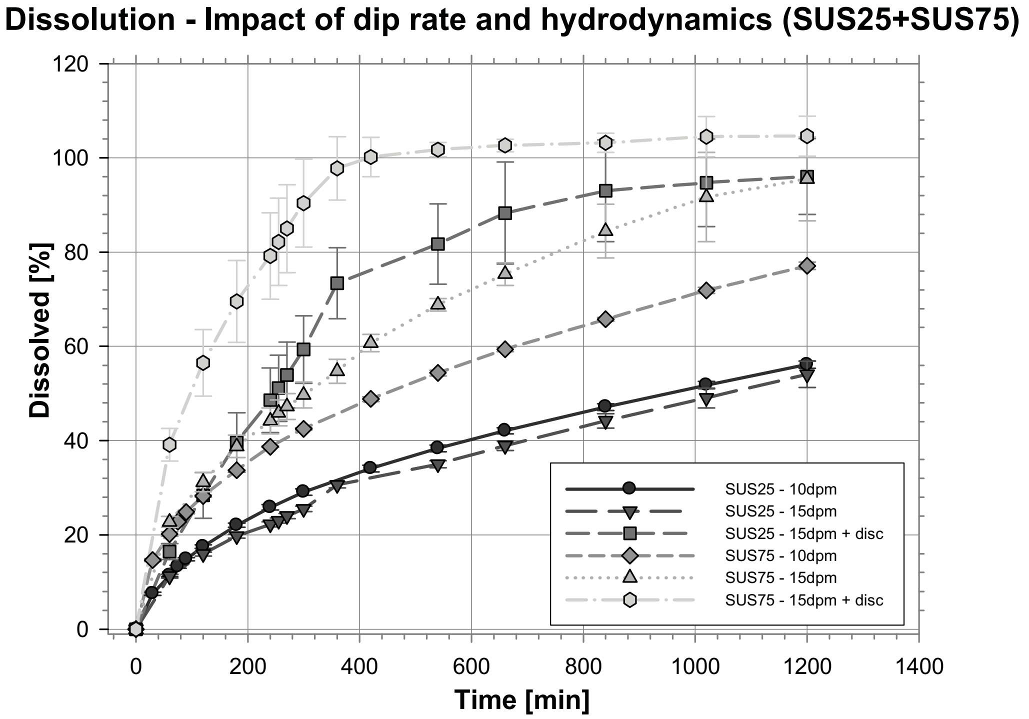


Fig. 5.3.8: Impact of hydrodynamic stress on drug release from sucrose-stearate (SUS) formulations

Thus, drug release from SUS25 and SUS75 proved highly susceptible to hydrodynamic or mechanical stress. As observed during dissolution experiments, the tablets lacked physical robustness, softening upon contact with water. Under mechanical stress this resulted in disintegration. The experiments also confirmed that the change release mechanism and release profile seen with the biorelevant fed state setup (see chapter 5.3.4.1) was mainly driven by changes in hydrodynamics. Therefore sucrose-stearate itself might be unsuitable as a single matrix forming agent and the use of additional excipients may be needed.

In the case of HPC25, modifications of hydrodynamic dissolution setups no trends in mean drug release. Whilst an increase of dip rate from 10dpm to 15dpm reduced mean drug release at 4h by 7.7% (73.0% ±0.6 (10dpm) vs. 65,4% ±3.6 (15dpm)), application of disc setup had little effect on drug release (80.2% ±13.2 (15dpm, disc) vs. 65.4% ±3.6 (15dpm, no disc)). Mean drug release differed statistically significant (t-test) only when the dip rate was increased from 10dpm to 15dpm. Nevertheless, changes in hydrodynamics appear to have a great impact on drug release, since changing the dissolution setup from USP2 to USP3 apparatus resulted in much faster drug release from HPC25.

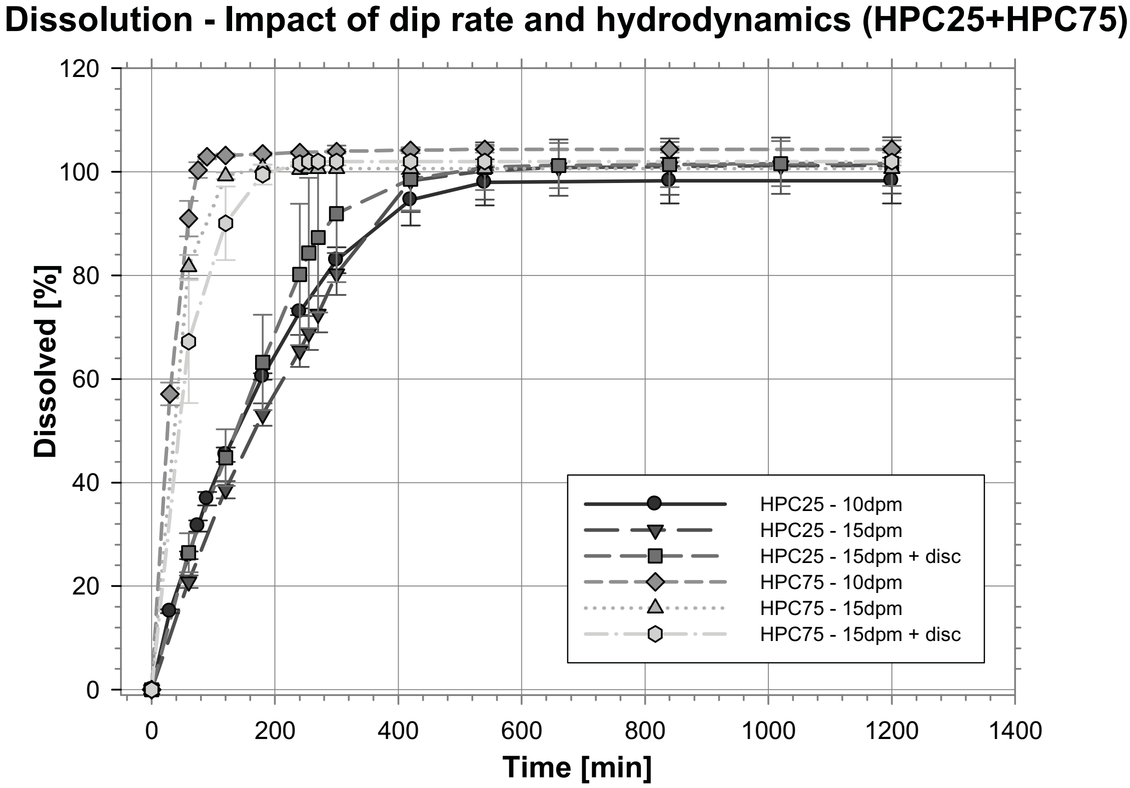


Fig. 5.3.9: Impact of hydrodynamic stress on drug release from hydroxypropylcellulose (HPC) formulations

Similarly, in two of the USP 3 dissolution experiments, HPC75 released more than 80% of contained theophylline within 60min. indicating that the controlled release function had been lost and rendering f_2-test comparison inappropriate.

Table 5.3.15: Statistical comparisons of dissolution profiles obtained with control setups with varying hydrodynamic setups ($n\geq3$): unpaired t-test and f_2-test (30min, 180min, 300min, 480min, 720min)

Formulation	Dip Rate		Time Point	Mean Difference	95% Confidence Interval		f_2
	No. A	No. B	[min]	Mean A-Mean B [%]	Lower bound	Upper Bound	
GDB25	10dpm	15dpm	1200	-0.2	-2.370	1.877	98
	15dpm	15dpm with disc	1200	$-1.4^{\square}$	-3.408	0.544	96
GDB75	10dpm	15dpm	1200	$-10.6^{\square}$	-18.099	-3.156	65
	15dpm	15dpm with disc	1200	$-23.0^{\square}$	-30.859	-15.148	$34^{\Diamond}$
GPS25	10dpm	15dpm	1200	$-7.9^{\square}$	-19.497	3.652	73
	15dpm	15dpm with disc	1200	4.0	-5.044	12.983	89
GPS75	10dpm	15dpm	1200	-0.5	-5.576	4.592	88
	15dpm	15dpm with disc	1200	$-19.3^{\square}$	-23.957	-14.561	$27^{\Diamond}$
SUS25	10dpm	15dpm	1200	2.1	-2.559	6.685	77
	15dpm	15dpm with disc	1200	$-42.0^{\square}$	-54.631	-29.313	$26^{\Diamond}$
SUS75	10dpm	15dpm	660	$-16.0^{\square}$	-19.882	-12.025	$48^{\Diamond}$
	15dpm	15dpm with disc	660	$-27.3^{\square}$	-30.907	-23.692	$26^{\Diamond}$
HPC25	10dpm	15dpm	240	$7.7^{\square}$	2.536	12.601	60
	15dpm	15dpm with disc	240	-14.8	-35.859	6.347	50

$^{\square}$ t-test: $p < 0.05$ (significant difference) **$^{\Diamond}$ f_2-test: not similar**

5.3.4.3 Prediction of Food Effects Based on Dissolution Data

The four carriers were examined with regard to their susceptibility to food effect *in vivo*. The study investigated effects of (i) bile components and (ii) changes in hydrodynamics on drug release. A qualitative assessment of effects of medium viscosity on drug release was made. The prediction of food effects is thus based on a combined evaluation of these parameters.

GDB formulations seemed prone to food effects. Major parameters causing changes in drug release were (i) bile components, (ii) viscosity of gastric and intestinal contents and (iii) motility.
For low drug loading (≤25% w/w drug/carrier), changes in viscosity of gut contents seemed to dominate potentially resulting a decreased drug release. However, the physiologic relevance of the *in vitro* experiments with respect to viscosity of gut contents is questionable. Hence, the effects of viscosity of gastrointestinal contents may be more or less pronounced *in vivo*.
Changes in drug release due to bile components seemed more pronounced at drug loadings >25% [w/w] drug/ carrier. At low drug loading (≤25% w/w drug/carrier), GDB seemed more robust towards these factors.
Diffusion controlled systems may also be affected by the higher viscosity of gastric contents. As seen with Ensure Plus as the dissolution medium, a slight reduction of release rate was observed. Due to the inverse proportional relation between Fickian diffusion constant D and the viscosity of the surrounding medium (Bauer K.H., et al. (1997)), increased viscosity may result in a smaller diffusion constant. Slower diffusion then correlates to slower drug release from diffusion controlled systems. Therefore increased viscosity of gastrointestinal contents may decelerate drug release from glyceryldibehenate formulations. Further, slower hydration due to slower diffusion might affect drug release from the dosage forms (Marabi, et al. (2005)).

Recently alternative media to simulate gastric fluids in fed state have been disclosed (Vertzoni M., et al. (2005), Jantratid E., et al. (2007)).

Motility became more dominating for high drug loading formulations (>>25% [w/w] drug/ carrier).
Susceptibility to changes in hydrodynamics was only revealed when the newly designed disc setup was used. Both increase in dip rate (10dpm vs. 15dpm) and increase in viscosity (biorelevant fed state setup) had only little effect on drug release. Therefore potential food effects may be underestimated by the standard setup.

In conclusion, the possibility of food effects *in vivo* from glyceryldibehenate appeared to depend on the drug loading of the formulations. A high drug loading enhances the risk of food effects, especially under enhanced hydrodynamic conditions. At low drug loading (≤25%) formulations are expected to be more robust to changes in hydrodynamics and bile secretions. However, potential effects of viscosity have to be investigated.

Drug release from glycerylpalmitostearate (GPS) formulations was sensitive to (i) presence of bile components, (ii) motility and (iii) viscosity of the gastrointestinal content.

Bile components accelerated drug release for both low and high drug loading formulations (25% [w/w] ≤ drug/ carrier ≤ 75% [w/w]). However, compared to other parameters, bile secretion seemed of subordinate importance for changes in drug release *in vivo*.

For high drug loading (>>25% [w/w] drug/ carrier) enforced mechanical stress caused a great increase in mean drug release. Increase in hydrodynamics forced a change in the prevailing drug release mechanism and thus erosion controlled drug release became more pronounced. However, at low drug loading (≤25% [w/w] drug/ carrier) mean drug release was not or only little sensitive to increased hydrodynamics, but indicated a change in the shape of the release profile.

Similar to GDB matrices, changes in viscosity of gut contents may decrease drug release. Dissolution experiments suggested medium viscosity to have a very significant impact on the *in vivo* performance of the formulation.

Food effects are expected for sucrose-stearate formulations. While bile and food components showed little effect, hydrodynamics caused changes in mean drug release, release mechanism and even affected the shape of the release profile. As for GDB and GPS, effects of medium viscosity were anticipated, but cannot be quantified at this stage. Increasing the viscosity of the dissolution medium resulted in slower or even delayed drug release.

Release profiles from both formulations underwent changes when hydrodynamics were changed, e.g by increasing dip rate. Increasing the hydrodynamic stress by means of dip rate caused a great increase in mean drug release. Similar to GPS formulations, a change in the prevailing release mechanism was observed. With the biorelevant fed state setup erosion prevailed as the drug release mechanism.

In conclusion, drug release from sucrose-stearate formulations seems prone to increased drug release under fed state mainly driven by increased motility. It is anticipated that *in vivo* the impact hydrodynamics will dominate due to the poor physical stability of the dosage forms. In contrast to

GDB and GPS, low drug loading of the formulation was not considered to reduce the tendency to food effects. At this stage, *in vivo* effects of viscosity on drug release cannot be quantified, but are anticipated to potentially invert the effect of hydrodynamics in the fed state.

For hydroxypropylcellulose (HPC) formulations food effects were also expected. Drug release seemed robust towards bile and food components, but a major effect by enhanced motility was expected. This corresponded to mainly erosion controlled release mechanism of HPC formulations. In fact, drug release accelerated greatly by changing from USP 2 to USP 3 dissolution devices, so that for low drug loading (<25% [w/w]) only a semi-retard drug release was observed.

5.3.5 Summary of Excipient Properties

Regarding processing, all four carriers are suitable for melt extrusion to prepare matrix dosage forms. All carriers have been well suited for melt extrusion processes applying drug loadings up to 75% [w/w]. In all cases suitable setting of extrusion parameters has been the key to successful melting extrusion processes. Main differences between the carriers have been observed in the preparation of granulates. While GDB, GPS and SUS extrudates have shown favourable granulation properties, the elasticity of HPC extrudates made granulation difficult. Only a high drug loading resulted in suitable brittleness of the extrudates. All four carriers possess poor compression properties, so that excipients to facilitate compression would be necessary to achieve a product suitable for modern-day processing.

The four different carriers were examined regarding their suitability to prepare CR matrix tablets and *in vitro* drug release was compared from these dosage forms. Robustness of *in vitro* drug release towards different parameters was investigated: (i) pH, (ii) ionic strength of dissolution medium, (iii) storage, (iv) presence of bile components and (v) hydrodynamics.

Regarding drug release, the four carriers provide the potential to cover a wide range of release profiles. While GDB and GPS allow controlling drug release over more than 20h, SUS formulations support drug release within 10 to 12h. Low drug loading HPC formulations cover the range of semi-retard formulations with 100% drug release within <6h.

HPC and SUS formulations showed their superiority with regard to the stability of drug release. After 365d storage at 25°C and 40°C, respectively, drug release was unchanged. By contrast drug release from GPS and GDB formulations are susceptible to storage effects. Storage at 40°C for 365d resulted in slower drug release for all formulations tested. For GPS formulations, the shape of the release profile also changed after storage at 40°C. For GDB, the effect was less pronounced for the high drug loading formulation [75% w/w].

All four carriers showed reasonable robustness towards changes in pH and ionic strength of the dissolution media. SUS and HPC formulations seem slightly advantageous over the lipid carriers (GDB, GPS), which showed a slight change in mean drug release with decreasing pH. However, all release profiles showed statistical similarity (f_2-test) for all pH values examined.

All exploratory formulations seem prone to food effects. Due to the different chemical nature and release mechanisms prevailing, food effects are based on the presence of bile components, motility, changes in viscosity of gut contents or combinations thereof. Low drug loading GDB formulations (<25% w/w) showed best robustness towards these parameters (GDB25). Drug release from HPC formulations was not affected by the presence of bile and food components, while all other carriers (GDB, GPS and SUS) showed at least a slight effect. Hydrodynamics proved to dominate generation of food effects. For all carriers, drug release increased depending on the intensity of the hydrodynamics. Only GDB25 showed robustness to intense hydrodynamic conditions. HPC formulations failed to control drug release at all when tested in USP3 dissolution device and may only be considered for semi-retard formulations at low drug loading.

The novel disc system was able to discriminate between physically robust and sensitive formulations, e.g. for GDB25 and GDB75, which did not show motility driven effects under previously established conditions (Klein S. (2005). The disc system indicated that motility might have effects on drug release from GDB75 in contrast to GDB25. Therefore this novel approach could be used to rank formulations with regards to their robustness of drug release towards motility, mechanical stress and hydrodynamics.

At this stage a more quantitative assessment of viscosity effects would be desirable. All carriers proved sensitive to an increase medium viscosity, resulting in a significantly decreased drug release in these media.

Overall, GDB and SUS seemed most favourable as carriers for CR matrix dosage forms among the four carriers tested. Based on the experience with the exploratory formulations, the major area of improvement with GDB formulations is seen in the extension of long-term stability. For SUS formulations, although possessing favourable properties in many respects, further work needs to be done to address robustness towards hydrodynamics.

6 *In vivo* Performance of CR Matrix Tablets processed by Melt-Extrusion

6.1 Aims of Chapter

The main goal of this chapter is to evaluate the *in vivo* performance of two selected CR matrix formulations. Sucrose-stearate formulations SUS 25 and SUS 75 were chosen for *in vivo* testing due to their drug release characteristics. Both formulations show controlled release over a longer period of time. As drug release was found to be sensitive towards changes in hydrodynamics, food components and viscosity of dissolution media *in vitro*, SUS25 and SUS75 are suitable to assess how well the *in vitro* test results predict these *in vivo*.

The performance of these two formulations was examined under fasted and fed state in a dog study. Deconvolution of *in vivo* data provided an *in vivo* drug release profile. Based on these results, an *in vitro-in vivo* correlation (IVIVC) was established. IVIVC was then used to evaluate the correctness of the *in vitro* predictions and the suitability of applied *in vitro* methods.

6.2 Materials and Equipments

Table 6.1 summarizes all additional materials required for in vivo characterization of SUS25 and SUS75.

Table 6.1: Additional Materials

Material	Source
Lithium-Heparinate Monovette	Fisher Scientific UK Ltd., Loughborough, Leicstershire, UK
Standard Microcentrifuge Tube	
Mobile Phase Romil MF4	Romil Ltd., Cambridge, UK
Mobile Phase Romil MF5	

Table 6.2 lists all additional equipment and software used for in vivo performance of SUS25 and SUS75.

Table 6.2: Additional Equipments and Software

Device	Source
Microcentrifuge Eppendorf 5424	Eppendorf UK Ltd., Cambridge, UK
Thermomixer Eppendorf Comfort	
Eppendorf Biofuge	
PK/ PD Modelling Software WinNonLin® Professional V.4.1 Build 200307301056	Pharsight Corp., Mountain View, Ca, USA

Table 6.3 shows the HPLC equipment used for quantification of theophylline plasma concentrations.

Table 6.3: HPLC Equipment

Device	Source
Binary LC Module Agilent 1100	Agilent Technologies Ltd., Stockport, Cheshire, UK
HPLC column Pursuit® Diphenyl 5µm, 150 x 4.6mm	Varian Ltd., Oxford, UK
Flow Splitter Acurate	Dionex (UK) Ltd., Camberley, Surrey, UK
Masspectrometer API2000	Applied Biosystems Ltd., Warrington, Cheshire, UK

6.3 Methods

6.3.1 Canine Study

6.3.1.1 Animals

Two female and two male beagle dogs, aged 2-6 years and weighing between 12 and 14kg were used in the present pharmacokinetic study. The study was performed at an animal facility of Pfizer Ltd., Sandwich, Kent, UK. The study was carried out under the authority of the Home Office project license PPL 70/5592. The details of the work were submitted and approved by the Pfizer Ethical Review Panel prior to submission to the Home Office. The study was carried out according to protocol No. UK2350/DD/001/05.

6.3.1.2 Formulations Tested

One hundred milligrams of anhydrous theophylline were dosed orally. As an intravenous control, theophylline anhydrous was dissolved in isotonic saline at a concentration of 5mg/ml.
Low and high drug loading CR matrix formulations SUS25 (batch AD00AN02a) and SUS75 (batch AD00AR00b) were selected for oral dosing. They consisted of a 25% [w/w] and 75% [w/w] binary mixture of anhydrous theophylline with sucrose stearate (Ryoto S 1670). The binary mixtures were melt extruded followed by a granulation process. Granulates were compressed to 10mm and 9mm matrix tablets, respectively. One percent [w/w] magnesium stearate was used as a glidant for compaction. For further details see chapter 4.1.

6.3.1.3 Study Protocol

A two way crossover study was performed, in which each dog received 50mg of theophylline as an intravenous infusion or 100mg as CR matrix tablet in the fasted and fed states. Table 6.4 shows dosing schedules for each dog.

For fasted state examinations, dogs were fasted overnight, but had free access to water. Eight hours after dosing, dogs were fed with a standard meal (pellets, water). For fed state examinations, dogs received an FDA breakfast prior to dosing (FDA 2002).

Table 6.4: Five week dosing schedule for canine study

	Dog ID			
	Female 1	**Female 2**	**Male 1**	**Male 2**
Week 1	i.v.	i.v.	i.v.	i.v.
Week 2 - Fasted	SUS25	SUS75	SUS25	SUS75
Week 3 - Fasted	SUS75	SUS25	SUS75	SUS25
Week 4 - Fed	SUS25	SUS75	SUS25	SUS75
Week 5 - Fed	SUS75	SUS25	SUS75	SUS25

For intravenous application, 10ml of the intravenous formulation were infused over 10minutes. For oral dosing, tablets were swallowed followed by 5ml of tap water.

Blood samples were collected from a temporary catheter, inserted into the saphenous vein. Approximately 2ml of blood were taken per sample using a LiHep Monovette. Plasma was prepared by centrifugation immediately after sampling. Plasma was then stored at -80°C until sample assay. Samples were taken according to Table 6.5.

Table 6.5: Collection times for canine study

Route of Administration	**Collection Times [min]**														
i.v.	PD	0	5	10	15	20	30	45	60	90	120	180	300	600	1440
p.o.	PD	15	30	45	60	90	120	150	180	240	300	360	600	1440	

Eight hours after dosing, dogs were returned to their cages, where they had free access to food (pellets, water). Catheters were removed after the last samples were taken (24h). A one week washout period was granted after each dose.

6.3.1.4 Sample Assay

Plasma samples were processed prior to the HPLC/ ECD assay. Two hundred microliters of sample were diluted with an aqueous solution of an internal standard (0.1ml, 4µg/ml) and ethylacetate (1.0ml). Samples were then mixed for five minutes at 37°C at 1400rpm using a thermomixer. After centrifugation the organic phase was transferred into a fresh microcentrifuge tube and evaporated to dryness under nitrogen at 37°C. Residues were redissolved in HPLC mobile phase MF5 (10% methanol, 90% Water, 2mM ammonium acetate, 0.027% formic acid). Eighty microliters were injected into the HPLC. Theophylline standards were prepared by dissolving Theophylline anhydrous in dog plasma, followed by treatment as described above. Typically, linear regression of linearity plots obtained by above method showed a squared regression coefficient of at least 0.999. The limit of quantification was 10ng/ml. Fig 6.1 shows a typical chromatogram for Theophylline anhydrous.

Plasma samples containing Theophylline were assayed by HPLC/ MS/ MS. A Pursuit® Diphenyl column (5µm, 150mm x 4.6mm) was used for separation. The components of the chromatographic system are described in Table 6.2. The mobile phase consisted of MF4 (90% methanol, 10% Water, 2mM ammonium acetate, 0.027% formic acid) and MF5 (10% methanol, 90% Water, 2mM ammonium acetate, 0.027% formic acid). For separation an eluent gradient was run according to Table 6.5 at 1ml/min. Eluate was split 1:4 and 250µl were injected into the masspectrometer. Theophylline showed typical retention time of 4.2min.

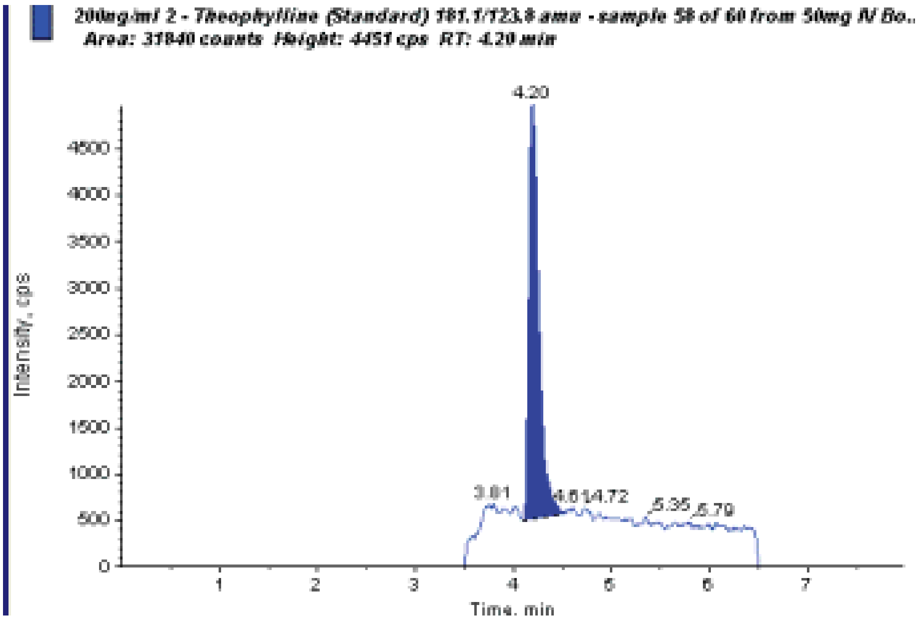


Fig. 6.1: Typical chromatogram obtained for theophylline from HPLC/ MS assay

6.3.2 Pharmacokinetic Calculations

6.3.2.1 *In vivo* Data Analysis

Deconvolution analysis was used to calculate the theophylline fraction absorbed from the gastrointestinal tract. Calculations were performed by WinNonLin® Pharmacokinetic Software. A one-compartment model with absorption phase and first-order elimination was applied (Bach J.E., et al. (2004)). The Gauss-Newton algorithm was used for deconvolution. The dose-normalized intravenous infusion was used as reference for all required pharmacokinetic parameters.

6.3.2.2 *In vitro-in vivo* Correlation

A level A *in vitro-in vivo* correlation (IVIVC) was performed (FDA 1997, USP 2003a). A point-to-point relationship between *in vitro* drug release and the absorbed theophylline fraction was established. Linear regression of the obtained plots was applied to describe the goodness of fit of the IVIVC. Correlations were ranked by means of squared correlation coefficient (RSQ) and the slope of linear regression. *In vitro* predictions were considered superior the closer linear correlation coefficient and slope approximated a value of 1.00. In this case drug release rate and absorption rate were directly superimposible.

Further, *in vivo* fraction absorbed and *in vitro* release profiles were fit to the Weibull (RRSBW) function between 0 and 300min (see chapter 5.1 for details). The goodness of the prediction was evaluated by comparison of the sum of square residuals. The calculation was based on the eleven time points as indicated in Table 6.5 (p.o.).

Table 6.6 summarizes the dissolution methods used for IVIVC. For further details see chapter 5.3.3.

Table 6.6: Summary of dissolution Setups used for IVIVC

Dissolution Apparatus	Media Type	Simulated State	Disc Applied
USP 3	pH gradient	Fasted	No
USP 3	biorelevant gradient	Fasted	No
USP 3	pH gradient	Fed	No
USP 3	pH gradient	Fed	Yes
USP 3	biorelevant gradient	Fed	No
USP 2	Phosphate Buffer pH6.8	-	No

6.4 Results and Discussion

6.4.1 Calculation of Pharmacokinetic Parameters

Intravenous infusion of 50mg of theophylline anhydrous as 10mg/ml solution was used as the reference for all further calculations. Fifty milligrams of theophylline corresponded to a mean dose of 4.0mg/kg. A mean half-life of 4.88h (±0.46) and a mean clearance of 1.97ml/min/kg were observed. Mean distribution volume was found 0.78l/kg (±0.09). The mean $AUC_{0\text{-}t}$ was 33255ng*h/ml (±6053.9). All results corresponded well with values found in the literature (Shiu G.K. et al. (1989), Nosaka H., et al (1986), McKiernan B.C., et al. (1981)). Table 6.7 shows all important pharmacokinetic parameters obtained from four dogs after i.v. administration of 50mg theophylline.

Table 6.7: Pharmacokinetic Parameters after i.v. Administration of 50mg Theophylline

Parameter	Female 1	Female 2	Male 1	Male 2	Mean (±SD)
Dose [mg/kg]	4.00	4.17	3.85	3.97	4.00 (±0.13)
t½ [h]	5.0	5.20	5.10	4.20	4.88 (±0.46)
CL [ml/min/kg]	2.14	1.57	2.05	2.12	1.97 (±0.27)
VSS [l/kg]	0.89	0.68	0.82	0.73	0.78 (±0.09)
AUC1-t [ng*h/ml]	29874	42319	30083	30745	33255 (±6053.9)

6.4.2 In-vivo Performance of CR Matrix Tablets

For SUS25, lower mean c_{Max} (3246ng/ml) and relative bioavailability was observed in the fasted state compared to fed state (c_{Max} = 5620ng/ml). For both fasted and fed state, individual t_{Max} was typically observed between 3h and 5h resulting in mean t_{Max} of 5h (fasted state) and 4h (fed state), respectively. Fig. 6.2 shows the mean theophylline plasma profiles obtained from SUS25.

Reverse results were obtained for SUS75. Lower c_{Max} and relative bioavailability was observed in the fed state. The highest plasma concentration (c_{Max}) decreased from 5735ng/ml to 4225ng/ml when the dose was administered with food. C_{Max} was reached after 5h under fed state and after 3h under fasted state, respectively. Fig 6.3 shows plasma profiles obtained from SUS75 under fasted and fed state conditions.

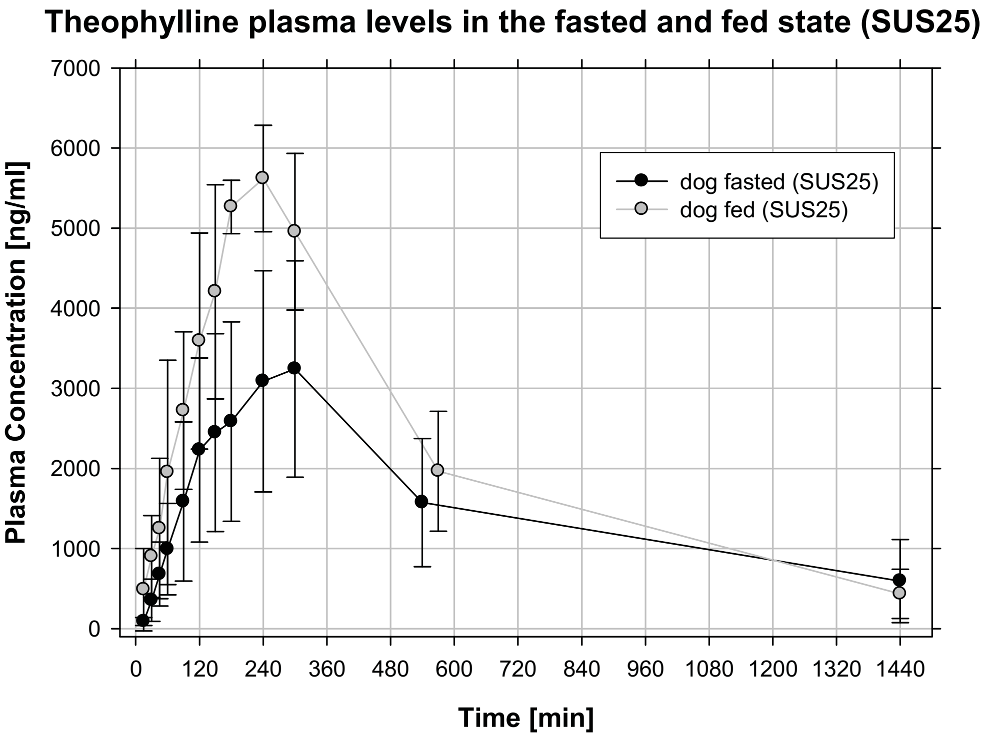


Fig. 6.2: Theophylline plasma profiles from SUS25 in the fasted and fed state (dog)

For both formulations tested (SUS25, SUS75), an impact of the nutritional state on mean plasma was observed. Alterations of c_{Max} and bioavailability were of concern. Increases in c_{Max}, as observed for SUS25, potentially cause toxic side effects. With large inter-individual differences, as observed in the present study, these side effects were considered likely and potentially dangerous. In particular theophylline, with a narrow therapeutic window, will tend to show toxic side effects caused by food effects.

On the other hand, if there is a decrease in c_{Max} and exposure, as seen for SUS75, sub-therapeutic plasma levels might result, negatively affecting drug therapy. Obviously, neither formulation was able to achieve robustness to food intake.

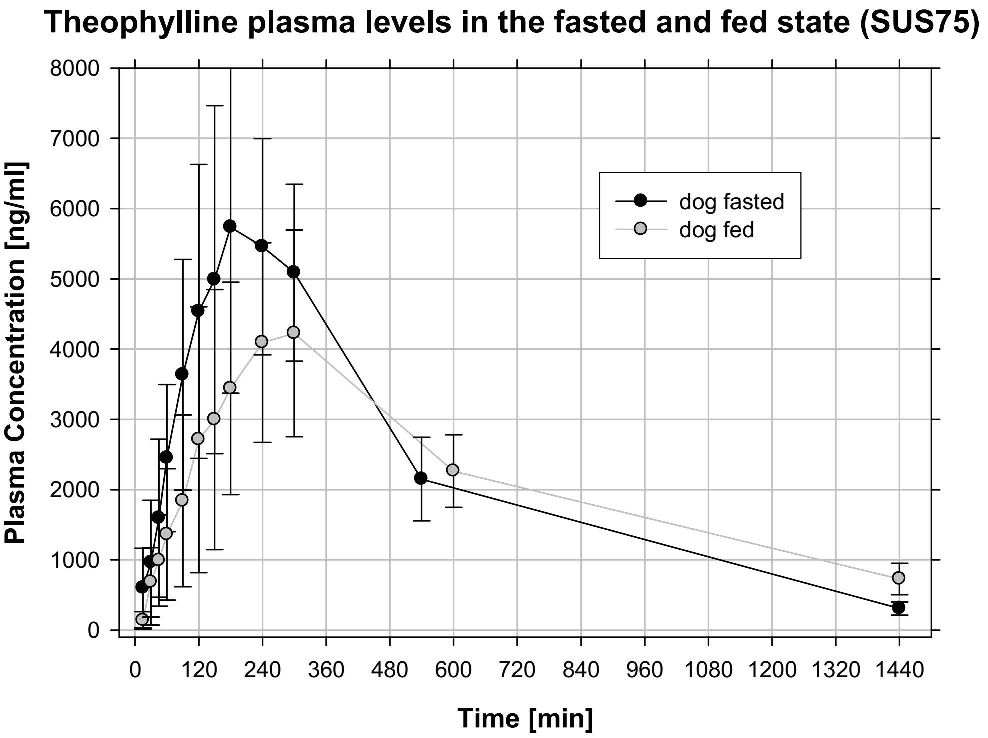


Fig. 6.3: Theophylline plasma profiles from SUS75 in the fasted and fed state (dog)

6.4.3 IVIVC

For the present study, theophylline, a well absorbed drug (Brouwers J., et al (2005)), was used. Therefore drug release was considered the rate limiting step to the absorption process.

Drug release from SUS25 and SUS75 had indicated robustness towards changes in pH and ionic strength *in vitro*. Therefore, differences in plasma levels and bioavailability between fasted and fed state were mainly attributed to (i) bile and food components and (ii) hydrodynamics. Correlation of *in vitro* with *in vivo* data will indicate the suitability of applied *in vitro* methods to predict the effect of bile, food and hydrodynamics on drug release.

Fig. 6.4 shows the cumulative F_a vs. time profiles for SUS25 and SUS75 for fasted and fed state obtained by deconvolution of theophylline plasma concentration profiles. Biphasic profiles were obtained in all four cases. Within the first 4-6h, theophylline was absorbed fast from the gut. In the second phase, only slow absorption was observed.

Sutton S.C., et al. (2006) reported colonic absorption of theophylline in dogs. Thus it was concluded that after the dosage form left the small intestine as the main drug absorption window, there still was a slow theophylline absorption in the colon. Slowed theophylline absorption occurred after 3-5h in the fasted state and after 4-5h in the fed state, respectively. Prolonged gastrointestinal transit time may have been the result of an increased gastric residence time in the fed state. These results correlated well to previously published gastric and small intestinal transit times in dogs (Dressman J.B. (1986), Sutton S.C. (2004)).

As the colonic mucosal uptake process was much slower, drug release was not considered the rate limiting step to absorption in the colon. Therefore only the first phase (0-300min) was used for the IVIVC.

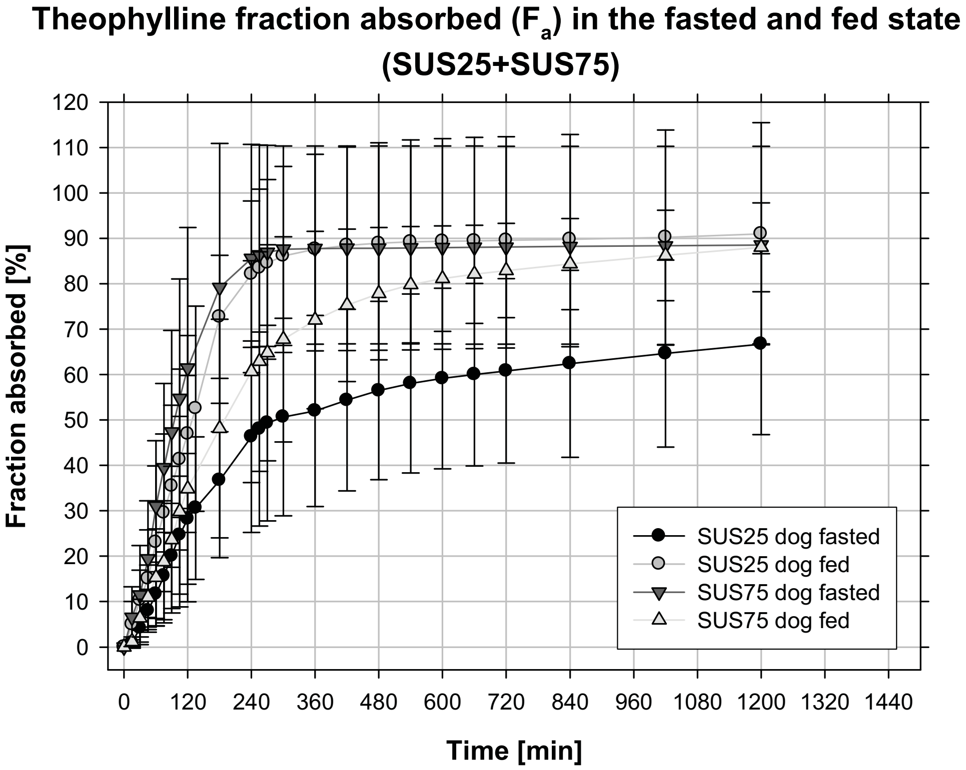


Fig. 6.4: Theophylline fraction absorbed (F_a) vs. time profiles obtained from SUS25 and SUS75 in the fasted and fed state (dog)

Table 6.8 summarizes the IVIVC for SUS25 and SUS75 for fasted and fed state in dog. The correlations are indicated in Fig.6.5. Examination of SUS25 in the fasted state, the relationship between fraction absorbed (F_a) and fraction released (F_r) showed reasonable to good linear fit. For all dissolution methods correlated to *in vivo* data, the squared correlation coefficient was >0.9 (0.926 < RSQ <0.986). The control fed with disc setup showed the best correlation to fasted state *in vivo* results for SUS25 (RSQ=0.986) and the slope of the linear regression was closest to 1.00 (effective 0.97). Slopes of linear regression of drug release profiles obtained from other methods ranged from 1.9 to 2.6, indicating a significant underestimation of the fraction absorbed *in vivo*. Especially the USP2 and the biorelevant fed setup deviated from the *in vivo* performance (2-3fold).

In the fed state, goodness of fit was similar for the IVIVC of cumulative f_a with *in vitro* results. Correlation coefficients ranged between 0.911 and 0.974. The control fed with disc setup again indicated the best correlation to *in vivo* data (RSQ=0.974). Also with respect to slope, the control fed with disc setup came closest to a value of 1 (effective 1.6). All other methods significantly underestimated the F_a with slope values ranging from 3.5 to 5.3. Again, the USP2 and biorelevant fed setup deviated most from a quantitative perspective.

Table 6.8: Summary of IVIVC regression analysis parameters (0-300min): drug release from SUS25 and SUS75 tested with several dissolution setups vs. F_a (dog, fasted and fed state)

	SUS25 dog fasted		SUS25 dog fed		SUS75 dog fasted		SUS75 dog fed	
	Slope	**RSQ**	**Slope**	**RSQ**	**Slope**	**RSQ**	**Slope**	**RSQ**
USP 2*	2.6	0.957	4.5	0.956	3.3	0.950	2.4	0.926
fasted control	1.9	0.965	3.4	0.961	2.4	0.942	1.8	0.901
fasted biorelevant	1.9	0.966	3.5	0.962	2.1	0.945	1.5	0.880
fed control	2.2	0.958	3.8	0.959	1.9	0.868	1.5	0.952
fed control with disc	0.9	0.986	1.6	0.974	1.0	0.875	0.8	0.958
fed biorelevant	3.1	0.926	5.3	0.911	1.8	0.927	1.3	0.905

*** Phosphate Buffer pH 6.8**

For a summary of the linear regression parameters for IVIVC of SUS75 see Table 6.8. The correlations are indicated in Fig. 6.6. Examination of SUS75 in the fasted state partly resulted in reasonable correlations. Correlation coefficients ranged between 0.868 and 0.950. The USP 2 dissolution experiment provided the best correlation coefficient (RSQ=0.950), but significantly underestimated the F_a (slope=3.3). The control fed with disc setup provided the best quantitative prediction (slope=1.0). With respect to correlation coefficient biorelevant fasted setup provided results comparable to USP 2. Overall there was trend of better quantitative prediction of the F_a. Slopes ranged from 1.0 to 2.4 for USP 3 methods.

Similar results were found for correlations with *in vivo* fed state data. The best correlation was found with the control fed with disc setup (RSQ=0.958). In this case, the dissolution method overestimated the F_a (slope=0.8). Overall, reasonable predictions of F_a were obtained with slopes ranging from 1.3 to 2.4.

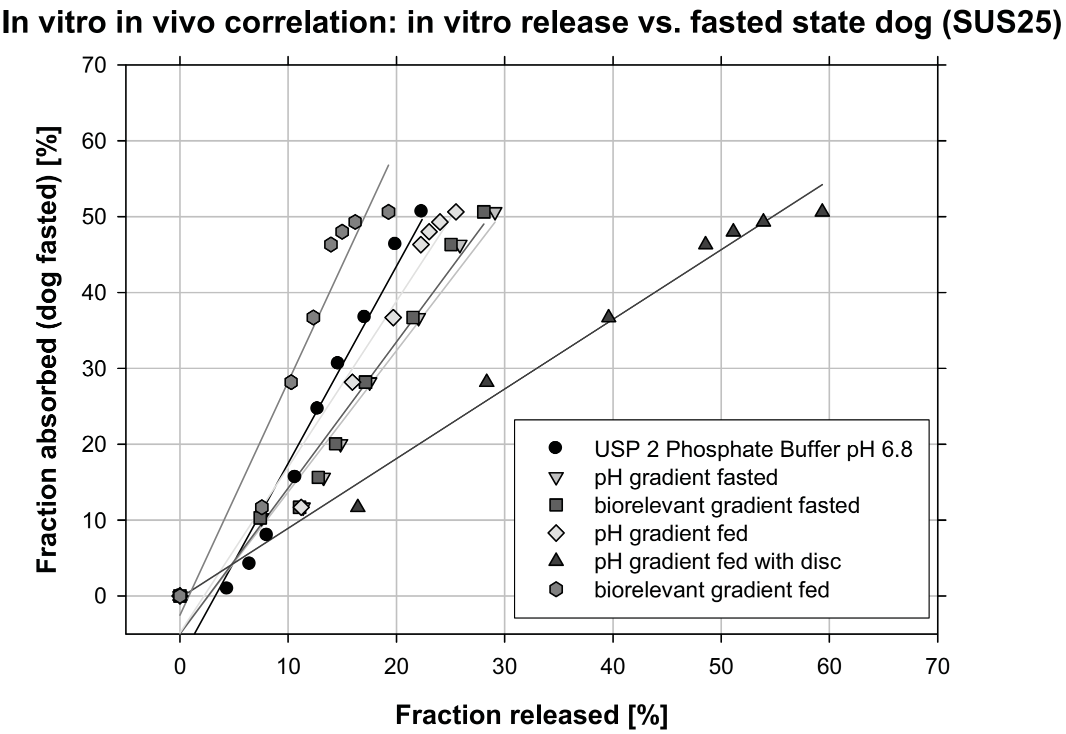


Fig. 6.5a: IVIVC SUS25 cumulative fraction absorbed (F_a) (fasted state) vs. mean fraction released (F_r) with several dissolution setups

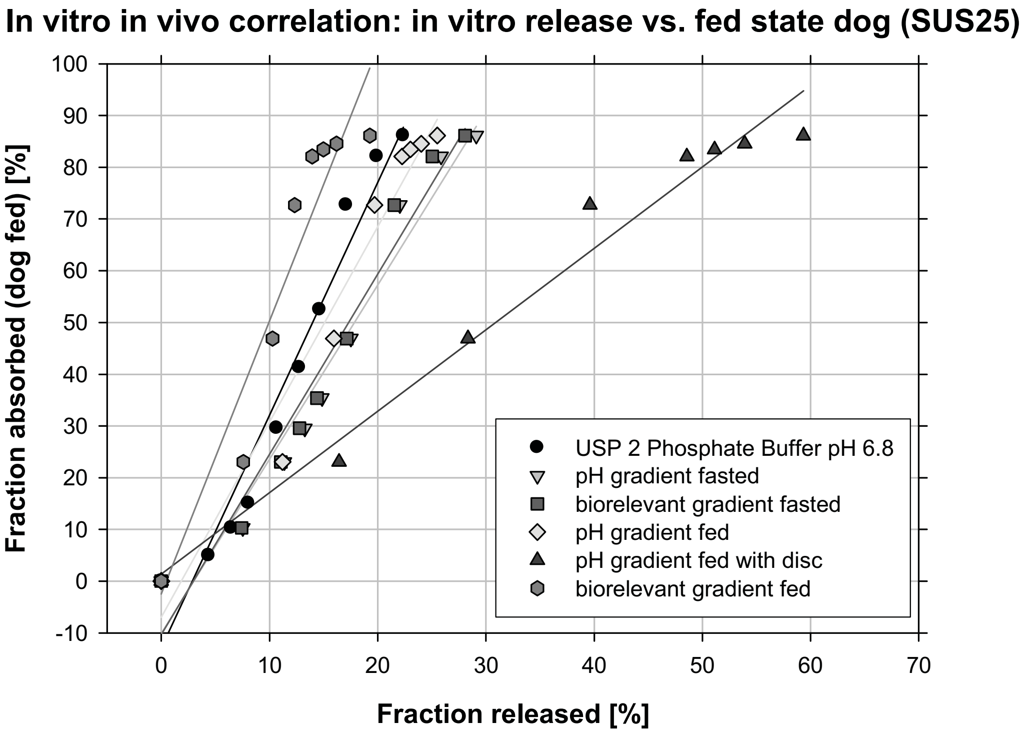


Fig. 6.5b: IVIVC SUS25 cumulative fraction absorbed (F_a) (fed state) vs. mean fraction released (F_r) with several dissolution setups

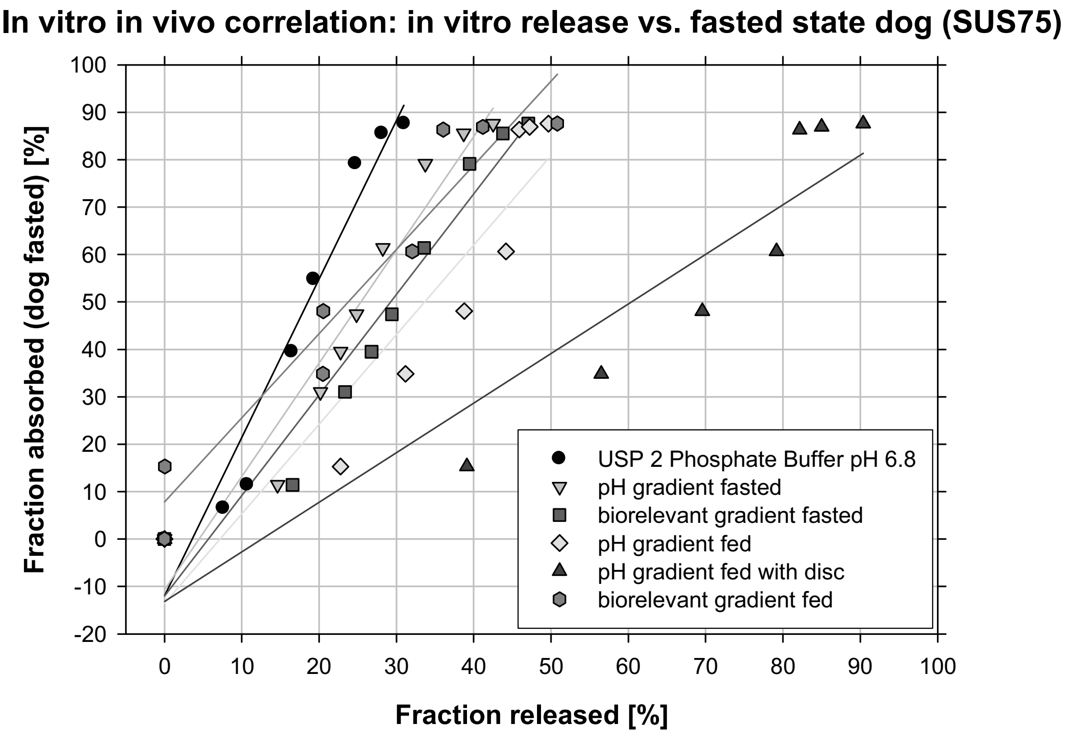


Fig. 6.6a: IVIVC SUS75 cumulative fraction absorbed (F_a) (fasted state) vs. mean fraction released (F_r) with several dissolution setups

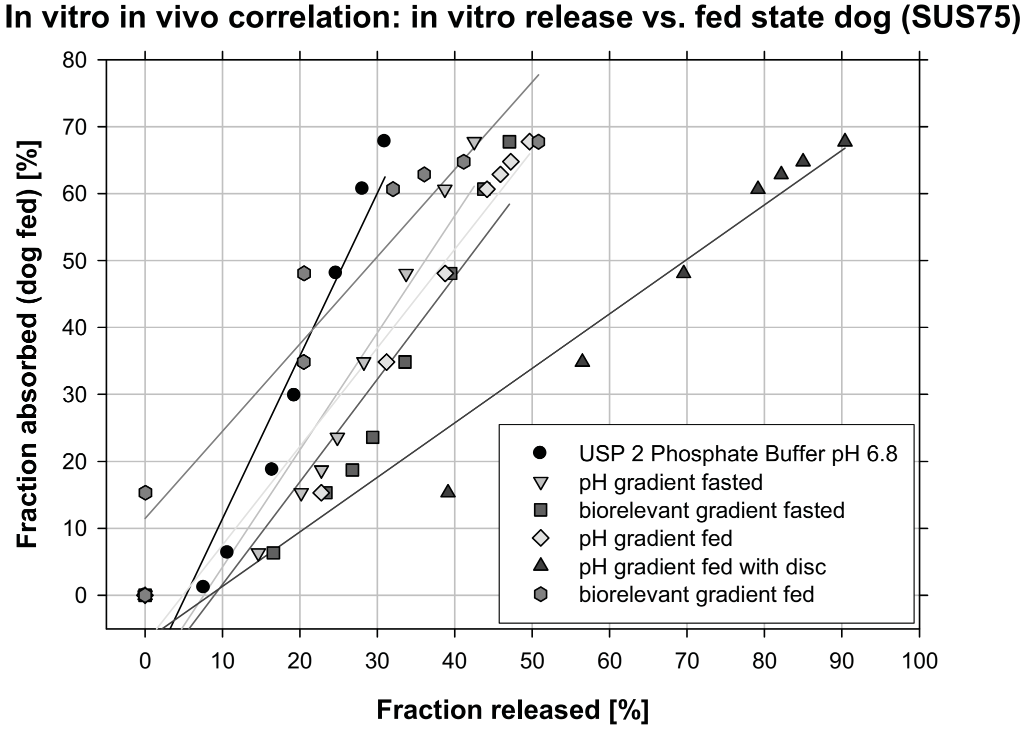


Fig. 6.6b: IVIVC SUS75 cumulative fraction absorbed (F_a) (fed state) vs. mean fraction released (F_r) with several dissolution setups

Surprisingly, the biorelevant fed setup provided for SUS75 a qualitatively and quantitatively better prediction of the *in vivo* performance than for SUS25. The USP 2 setup significantly underestimated F_a significantly in all cases.

6.4.4 Comparison of Profiles by Weibull function

The previous section assessed IVIVC based on the linearity of the correlation indicating the potential of *in vivo* and *in vitro* release profiles to be superimposed. However, a scaling factor might be required to make profiles superimposible (FDA 1997). So far, only the qualitative aspect, i.e. the shape of the release profiles, was addressed. Hence, the quantitative relation between *in vitro* and *in vivo* needs to be examined.

The relevant Weibull parameters are summarized in Table 6.9. The statistical comparison of *in vitro* with *in vivo* profiles from SUS25 is given in Table 6.10. Fig. 6.7 and Fig.6.8 show the theophylline release *in vitro* and *in vivo* from SUS25 and SUS75 based on data fitted to the Weibull function.

The goodness of fit of the *in silico* profiles was indicated by the high correlation to the respective measured profiles (RSQ$\geq$0.989).

For SUS25, the control fed with disc gave by far the best prediction for *in vivo* drug release for fasted and fed state. This corresponded to the observation regarding the linearity and slope of the correlation. *In vitro* drug release was similar to release in the fasted state *in vivo*. However, there was a lack of similarity between *in vitro* profiles and *in vivo* release in the fed state. Overall, there was good agreement in the ranking of qualitative and quantitative correlation. There was a trend that USP 3 methods were more accurate compared to the USP 2 method. Again, the release profile obtained with the biorelevant fed setup deviated most from *in vivo* results.

By contrast to SUS25, different rankings of *in vitro* drug release were obtained depending on the correlation method for SUS75. While the control fed with disc setup provided the least sum of square residuals compared to *in vivo* fasted state, the control fed (without disc) gave the best quantitative prediction of drug release *in vivo* in the fed state. The USP 2 method, providing the best correlation in terms of linearity, underestimated drug release in both cases.

While for the fasted state only the pH fed with disc setup provided a similar release, in the fed state similarity of release profiles was found for three dissolution setups (pH gradient fasted, pH gradient fed, biorelevant gradient fasted).

Table 6.9: Summary of Weibull parameters for in vitro and in vivo release profiles and correlation to measured data: a) SUS25, b) SUS75

a)

SUS25				
Experiment	**R_{Max}**	**t_D**	**β**	**RSQ (with real data)**
USP 2	100.0	2695	0.618	0.999
pH gradient fasted	100.0	1689	0.626	1.000
biorelevant gradient fasted	100.0	1804	0.625	0.999
pH gradient fed	98.7	1804	0.659	0.997
pH gradient fed with disc	97.1	311	1.149	0.995
biorelevant gradient fed	99.9	968	1.224	0.990
cumulative release dog fasted	62.2	197	1.191	0.993
cumulative release dog fed	89.8	139	1.532	0.998

b)

SUS75				
Experiment	**R_{Max}**	**t_D**	**β**	**RSQ (with real data)**
USP 2	99.9	1993	0.522	1.000
pH gradient fasted	99.9	734	0.616	0.996
biorelevant gradient fasted	100.0	645	0.556	0.996
pH gradient fed	100.0	432	0.861	0.989
pH gradient fed with disc	100.0	139	1.024	0.990
biorelevant gradient fed	100.0	358	2.158	0.990
cumulative release dog fasted	88.1	106	1.530	1.000
cumulative release dog fed	84.3	207	1.266	0.998

Table 6.10: Comparison of calculated in vitro release profiles with calculated in vivo profiles by sum of squared residuals [%^{2}]

Formulation	**SUS25**		**SUS75**	
Experiment	**dog fasted**	**dog fed**	**dog fasted**	**dog fed**
USP 2	2292	14619	14688	3371
pH gradient fasted	1328	11927	9527	1348
Biorelevant gradient fasted	1459	12329	7539	1029
pH gradient fed	1771	13249	8082	641
pH gradient fed with disc	149	3958	232	4160
biorelevant gradient fed	3522	17522	16741	3724

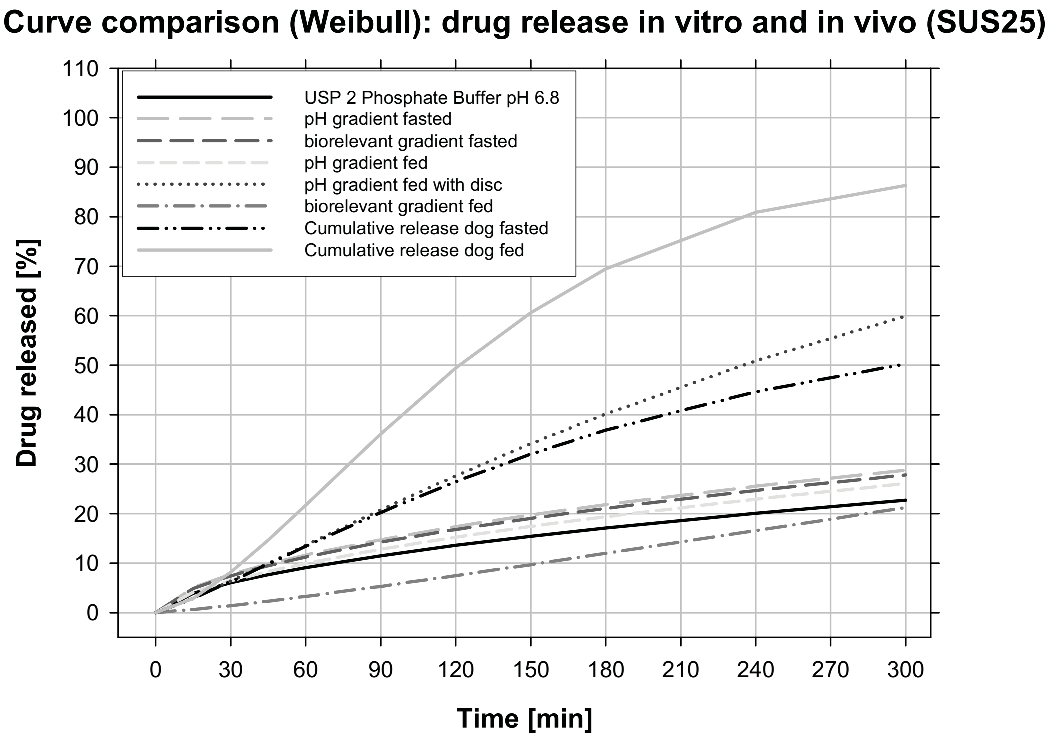


Fig. 6.7: Comparison of drug release profiles obtained for SUS25 in vitro and in vivo (fasted and fed state)

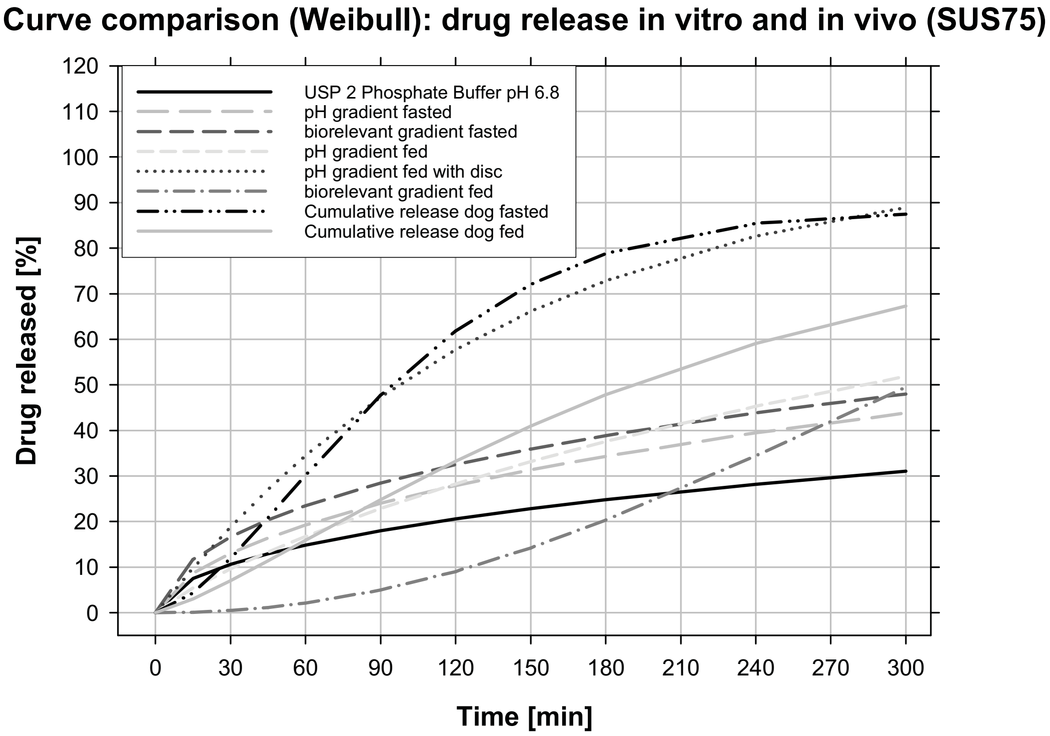


Fig. 6.8: Comparison of drug release profiles obtained for SUS75 in vitro and in vivo (fasted and fed state)

6.5 Discussion

Three main parameters were identified *in vitro* to trigger changes in drug release: (i) presence of bile and food components, (ii) hydrodynamics and (iii) changes in viscosity of dissolution media. In particular the latter two parameters seemed to have major impact on drug release. The novel disc method demonstrated accelerating effects of hydrodynamics, while a decreased drug release was seen in dissolution medium with increased viscosity (Ensure® Plus).

IVIVC confirmed the great effect of hydrodynamics on the drug release from SUS25 as the best correlation was obtained for both fasted and fed state when dissolution testing applied enhanced hydrodynamic conditions (pH gradient fed with disc). Further enhancement of hydrodynamics was seen as the driving force for the increase in drug release in the fed state, as indicated by dissolution experiments.

However, dissolution methods mostly underestimated the motility *in vivo*, i.e. dogs, as the dissolution method applying harshest hydrodynamic conditions (control fed disc) provided the best IVIVC for *in vivo* fasted and fed state. This was observed for both SUS25 and SUS75 as the control fed with disc setup provided the most accurate prediction of the release profile in the fasted state. For the fed state, an underestimation of drug release prevailed also for the disc method. The novel “disc method” may therefore be a suitable approach to realistically simulate hydrodynamics in the *in vivo* fasted state. Further enhancement of conditions will be necessary to realistically simulate canine *in vivo* conditions in the fed state.

In conclusion, dissolution experiments were capable of indicating motility as a relevant parameter for generation *in vivo* food effects, but need to be optimized with respect to hydrodynamic conditions to allow a better quantitative *a priori* prediction. However, motility-driven dosage form “failures” are known to occur more often in dogs than humans. For interpretation of IVIVC data, also physiological differences between humans and dogs should be taken into consideration, when selecting CR carrier for development.

For SUS75 *in vitro* experiments also suggested increased drug release in the fed state. However, the reverse effect was observed resulting in an incorrect prediction of the *in vivo* food effect.

Based on *in vitro* results, both hydrodynamics and increased viscosity were identified as potential causes generating food effects. The major difficulty was seen in a lacking quantification of viscosity effects. This hindered an accurate evaluation on the dominance of either factor. There

was a clear indication that the viscosity of the dissolution medium will have a decelerating effect on drug release, but the observation was not put into correct relation to the effects of hydrodynamics.
When using Ensure® Plus to simulate gastric contents in the fed state (biorelevant fed), a delayed onset of drug release from SUS75 was observed. The effect seemed more pronounced for SUS75 compared to SUS25. Thus for SUS75 drug release was potentially dominated by the change in viscosity of the gut contents, while for SUS25 hydrodynamics were the dominating parameter. For SUS75, effects of hydrodynamics on drug release may have been compensated by an increased viscosity of the gut content in the fed state.

Improvements of dissolution methods are required to improve the *a priori* prediction of food effects driven by hydrodynamics and viscosity of gut contents. Application of discs in dissolution test proved to be potential tool to adjust hydrodynamic conditions in dissolution experiments. Furthermore, a wider range of dip rates could be used with USP 3 apparatus to enhance agitation. Also, investigations on alternative dissolution apparatus for assessment of food effects for CR matrix dosage forms should be considered.
Additionally, dissolution media need to be modified to address effects of viscosity. A set of dissolution media providing a physiologically relevant range of viscosities would enable a more quantitative assessment of viscosity effects. Recently alternative media to simulate gastric fluids in fed state have been disclosed (Vertzoni M., et al. (2005), Jantratid E., et al. (2007)).
Finally, only a combination of both parameters in dissolution experiments will allow an adequate prediction of *in vivo* performance of a CR matrix dosage form in fasted and fed state.

In conclusion, the dissolution methods allowed identification of carriers prone to food effects and identified the parameters causing changes in drug release. However, a quantitative comparison of different factors, in particular viscosity of dissolution medium, was not achieved with current methods. As still not all relevant parameters were appropriately covered by the *in vitro* methods, incorrect predictions of *in vivo* performance resulted.
There was a trend, at least for the tested formulations, to underestimate *in vivo* drug release. USP 3 methods seemed advantageous compared to USP 2 methodology. The novel disc method indicated its potential to identify formulations prone to food effects triggered by hydrodynamics.

6.6 Conclusion

For SUS25 and SUS75, *in vitro* experiments provided reasonable predictions of drug release *in vivo*. For fasted state correlations were better compared to the fed state. Food effects, anticipated from *in vitro* tests, have been confirmed *in vivo* for SUS25. For SUS75 the reduction of drug release in the fed state was not anticipated by the *in vitro* results.

Hydrodynamics have been confirmed as the main factor to cause food effects for SUS25. For SUS75, hydrodynamics may also have impacted drug release *in vivo*, but other parameters dominated *in vivo* release.

The novel “disc method” has been identified as valuable tool to check robustness of drug release towards mechanical stress. Also, it has been useful to quantitatively predict drug release in the fasted state for both formulations. For fed state further enhancement of in vitro hydrodynamics seemed necessary due to the underestimation of drug release. Therefore, the use of a disc may be a valuable supplement for modification of USP 3 dissolution experiments to improve *in vitro* characterization of CR matrix dosage forms.

6.7 Acknowledgement

The dog study was kindly supported and conducted by Pfizer Ltd., Sandwich, UK. I would like to acknowledge Gerry James and Kelly Jones for their support and contribution to this work.

7 Summary

Melt extrusion provides a wide range of potential applications for pharmaceutical purposes. So far its application to controlled release delivery has been modest, chiefly because there is a lack of suitable excipients. The present work aimed at identifying such release-controlling carriers on the basis of physical, processing and release properties.

Both standard and novel excipients were evaluated with respect to their applicability to melt extrusion and general suitability for controlling drug release. Three important parameters were considered: (i) suitability as a fusible binder, (ii) process temperature range and (iii) drug release properties. Thirteen different excipients were evaluated and ranked according to these parameters. Based on these results, four excipients were chosen for further investigations. An additional consideration for selection was the chemical classification, as the aim was to identify as wide a range a range of carriers as possible. Excipients found most suitable were glyceryldibehenate (GDB), glycerylpalmitostearate (GPS), sucrose stearate (SUS) and hydroxypropylcellulose (HPC).

All four excipients were melt-extruded as binary mixtures with a model drug, theophylline. For each excipient three different drug/carrier ratios were used: 25:75% [w/w], 50:50% [w/w] and 75:25% [w/w]. All (binary) mixtures of the four selected excipients with theophylline could be successfully processed by melt extrusion and functioned as a matrix carrier in release experiments. Only HPC formulations required plasticizers to facilitate the melt extrusion processes. Generally process temperatures below 130°C were sufficient, although the carriers differed in their process temperature range. Flow properties of the intermediate suspensions were found to be either pseudoplastic (GBD, GPS, HPC) or dilatant (SUS). All processes proved to be reproducible using parameter sets based on the predictions of process temperatures, drug loading, requirement of plasticizers and general suitability made from the lab scale feasibility study.

Solid state characterization of the granulates obtained showed that the model drug (theophylline) is present in a crystalline state in all melt-extruded formulations. This was expected, as the processing temperatures were in all cases much lower than the drug's melting point (271°C). An increase in thermal input would have been required in order to achieve amorphisation or formation of solid dispersions.

The granulates were examined with regards to pharmaceutical quality parameters such as particle size, flowability and compactibility. GDB, GPS and SUS formulations exhibited flowability and particle size characteristics in the acceptable pharmaceutical range. All three proved flexible with regard to manufacture of matrix tablets over a wide range of drug loading. Due to the binary nature of compositions, compactibility was rather poor in all cases and resulted in low tensile strength of tablets. Despite the low tensile strength, most formulations fulfilled pharmacopeial requirements of friability. HPC formulations produced the hardest tablets, but the poor flowability and particle shape of granulates also affected the quality of the prepared tablets, with HPC75 providing the best compromise between flowability and tablet hardness.

Compaction simulation revealed that melt extrusion/granulation improved the compression properties by increasing plastic deformation. This resulted in an increase in tablet hardness. GDB and GPS formulations provided best compression properties due to highest extent of plastic deformation. By contrast, for HPC25, processing resulted in a deterioration of compression properties due to a decrease in plasticity and an increase in elasticity.

Regarding drug release, the four carriers provide the potential to cover a wide range of release profiles. While GDB and GPS facilitate control of drug release over more than 20h, SUS formulations support drug release within 10 to 12h. Low drug loading HPC formulations cover the range of semi-retard formulations with 100% drug release within <6h.

The possibility of modifying drug release was investigated with respect to processing and drug loading. All SUS formulations released drug by a diffusion controlled mechanism. Therefore addition of pore formers would be a potential way to modify drug release. By contrast to all other carriers examined, drug release from SUS formulations showed less variability with changes in drug loading. Therefore changes in drug loading seemed a less powerful tool to achieve the desired dissolution profile from SUS formulations.

Several parameters were investigated to demonstrate robustness of drug release: (i) long term stability, (ii) variation in pH of dissolution media, (iii) variation of ionic strength of dissolution media, (iv) effects of food components and bile secretions and (v) changes in motility/ hydrodynamics. As a basis for these examinations, the reproducibility of drug release was examined and all SUS formulations showed reproducibility of drug release under standardized conditions. Sucrose-stearate matrices showed long term stability of drug release (1 year). Further, drug release from sucrose-stearate (SUS) formulations was robust to changes of pH and ionic strength of dissolution media.

Similar to SUS formulations, GDB and GPS formulations showed reproducible dissolution profiles under standardized conditions. HPC formulations exhibited variable release from unit to unit, which was a drawback to the use of this carrier. With regard to stability of drug release, trends toward both acceleration and deceleration of drug release were observed for glyceroldibehenate and glycerylpalmitostearate. For GDB matrices with diffusion controlled release, a reduction in effective surface was demonstrated, resulting in decreased drug release. For GPS systems with high drug loading acceleration of drug release was attributed to changes in the lattice structure of the matrix according to the percolation theory for inert matrices. Results with HPC were generally favourable with respect to stability of drug release. Only GPS showed any appreciable pH dependency of drug release. The observed decrease in drug release under low pH was attributed to the protonation of an acidic component within the applied excipient (Precirol ATO5). Similar to SUS formulations, effects of dissolution media ionic strength were generally considered insignificant for the three other excipients tested.

Food effects are expected for sucrose-stearate formulations. While bile and food components showed little effects, hydrodynamics caused changes in mean drug release, release mechanism and even affected the shape of the release profile. As for GDB and GPS, effects of medium viscosity are anticipated, but cannot be quantified at this stage. Increasing the viscosity of the dissolution medium resulted in slower or even delayed drug release.

The other three carriers tested also seemed prone to food effects. For GDB, sensitivity of drug release to food effects appeared to depend on the drug loading of the formulations. A higher drug loading increased the risk of food effects, especially under enhanced hydrodynamic conditions. At lower drug loading (≤25%) formulations are expected to be more robust to changes in hydrodynamics and bile secretions. For GPS formulations, bile components accelerated drug release for both low and high drug loading formulations (25% [w/w] ≤ drug/ carrier ≤ 75% [w/w]). However, compared to other parameters, bile secretion seemed of subordinate importance for changes in drug release *in vivo*. For high drug loading (>>25% [w/w] drug/ carrier) enforced mechanical stress caused a great increase in mean drug release. As for SUS formulations, effects of medium viscosity on drug release are anticipated for both lipid carriers (GDB, GPS), but cannot be quantified at this stage. For HPC formulations food effects are also expected. Drug release seemed robust towards bile and food components, but a major effect by enhanced motility is expected. This results from the mainly erosion controlled release mechanism of HPC formulations.

In order to verify the *in vitro* predictions, *in vivo* drug release from SUS25 and SUS75 in dogs was investigated. *In vitro* experiments provided reasonable predictions of drug release *in vivo*. Fasted state correlations were better than fed state. Food effects, anticipated from *in vitro* tests, have been confirmed *in vivo* for SUS25. For SUS75 the reduction of drug release in the fed state was not anticipated by the *in vitro* results. Hydrodynamics have been confirmed as the main factor to cause food effects for SUS25. For SUS75, while hydrodynamics may have impacted drug release *in vivo*, other parameters dominated.

The novel "disc method" has been identified as valuable tool to check robustness of drug release towards mechanical stress. Also, it has been useful to quantitatively predict drug release in the fasted state for both formulations. For fed state further enhancement of *in vitro* hydrodynamics seems necessary due to the underestimation of drug release. Therefore, the use of a disc may be a valuable supplement for modification of USP 3 dissolution experiments to improve *in vitro* characterization of CR matrix dosage forms.

In conclusion, three carriers (GDB, GPS, SUS) were identified as suitable for use as carriers for CR oral dosage forms processed by melt extrusion. SUS has not been studied previously for this application. In addition, HPC was found to function as a semi-retard excipient in melt-extrusion formulations.

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9 Appendices

Table 9.1.1: Process Monitor Melt-Extrusion Formulation GDB25, Mean Values during Steady State

	Rotation Speed $[min^{-1}]$	Torque [Nm]	Feeding Rate [g/min]	Specific Mechanical Energy [J/g]
Mean run 1	45	13	34	106
sd	45	29	64	-
Mean run 2	50	26	40	202
sd	4	6	1	-
Mean run 3	50	22	40	172
sd	0	5	1	-
Mean	**48**	**20**	**38**	**160**
sd	**2.8**	**6.8**	**3.7**	**49.5**

Table 9.1.2: Process Monitor Melt-Extrusion Formulation GDB50, Mean Values during Steady State

	Rotation Speed $[min^{-1}]$	Torque [Nm]	Feeding Rate [g/min]	Specific Mechanical Energy [J/g]
Mean run 1	100	3	22	70
sd	0	0.4	23	-
Mean run 2	100	6	50	75
sd	0	3	0	-
Mean run 3	100	7	49	88
sd	0	3	4	-
Mean	**100**	**5.2**	**40**	**78**
sd	**0.0092**	**2.3**	**16**	**9.4**

Table: 9.1.3: Process Monitor Melt-Extrusion Formulation GDB75, Mean Values during Steady State

	Rotation Speed $[min^{-1}]$	Torque [Nm]	Feeding Rate [g/min]	Specific Mechanical Energy [J/g]
Mean run 1	200	9	34	318
sd	0.47	1	12	-
Mean run 2	200	8	39	253
sd	0.46	1	2	-
Mean run 3	200	9	40	294
sd	0.46	1	1	
Mean	**200**	**9**	**38**	**288**
sd	**0.01**	**0.7**	**3.3**	**33**

Table 9.1.4: Process Monitor Melt-Extrusion Formulation GPS25, Mean Values during Steady State

	Rotation Speed [min^{-1}]	Torque [Nm]	Feeding Rate [g/min]	Specific Mechanical Energy [J/g]
Mean run 1	70	6	40	70
sd	0.14	1	0	-
Mean run 2	70	5	40	53
sd	0.14	1	0	-
Mean run 3	70	6	40	61
sd	0.14	1	0	-
Mean	**70**	**6**	**40**	**61**
sd	**0.0017**	**0.8**	**0.039**	**8.3**

Table 9.1.5: Process Monitor Melt-Extrusion Formulation GPS50, Mean Values during Steady State

	Rotation Speed [min^{-1}]	Torque [Nm]	Feeding Rate [g/min]	Specific Mechanical Energy [J/g]
Mean run 1	90	6	40	79
Sd	2	0.2	0	
Mean run 2	90	6	41	81
sd	2	1	2	-
Mean run 3	90	6	40	83
sd	0.18	2	1	-
Mean	**90**	**6**	**40**	**81**
sd	**0.26**	**0.1**	**0.35**	**2.2**

Table 9.1.6: Process Monitor Melt-Extrusion Formulation GPS75, Mean Values during Steady State

	Rotation Speed [min^{-1}]	Torque [Nm]	Feeding Rate [g/min]	Specific Mechanical Energy [J/g]
Mean run 1	200	20	50	508
sd	0.49	1	0	-
Mean run 2	200	17	50	421
sd	0.48	2	1	
Mean run 3	200	17	50	436
sd	0.48	2	1	-
Mean	**200**	**18**	**50**	**455**
sd	**0.026**	**2**	**0.2**	**47**

Table 9.1.7: Process Monitor Melt-Extrusion Formulation SUS25, Mean Values during Steady State

	Rotation Speed [min^{-1}]	Torque [Nm]	Feeding Rate [g/min]	Specific Mechanical Energy [J/g]
Mean run 1	100	16	40	248
sd	0.19	2	2	-
Mean run 2	100	19	40	293
sd	0.21	1	0	-
Mean run 3	100	17	40	264
sd	0.20	1	0	-
Mean	**100**	**17**	**40**	**268**
sd	**0.0057**	**1.5**	**0.15**	**23**

Table 9.1.8: Process Monitor Melt-Extrusion Formulation SUS50, Mean Values during Steady State

	Rotation Speed [min^{-1}]	Torque [Nm]	Feeding Rate [g/min]	Specific Mechanical Energy [J/g]
Mean run 1	80	10	20	244
sd	0.3	7	1	-
Mean run 2	70	16	20	342
sd	0.2	1	1	-
Mean run 3	70	14	20	301
sd	0.1	1	0	-
Mean	**73**	**13**	**20**	**296**
sd	**5.7**	**3.1**	**0.18**	**49**

Table 9.1.9: Process Monitor Melt-Extrusion Formulation SUS75 Mean Values during Steady State

	Rotation Speed [min^{-1}]	Torque [Nm]	Feeding Rate [g/min]	Specific Mechanical Energy [J/g]
Mean run 1	60	31	29	410.6532
sd	0.2	11	10	-
Mean run 2	60	39	30	493.0134
sd	0.0	3	0	-
Mean run 3	60	36	30	450.6737
sd	0.2	3	1	-
Mean	**60**	**36**	**30**	**451**
sd	**0.18**	**4.1**	**0.94**	**41**

Table 9.1.10: Process Monitor Melt-Extrusion Formulation HPC25, Mean Values during Steady State

	Rotation Speed [min^{-1}]	**Torque** [Nm]	**Feeding Rate** [g/min]	**Specific Mechanical Energy** [J/g]
Mean run 1	100	10	40	156
sd	0.19	1	0	-
Mean run 2	100	9	40	147
sd	0.19	1	0	-
Mean run 3	100	8	41	117
sd	0.19	2	23	-
Mean	**100**	**9.0**	**40**	**140**
sd	**0.0072**	**1.1**	**0.85**	**20**

Table 9.1.11: Process Monitor Melt-Extrusion Formulation HPC50, Mean Values during Steady State

	Rotation Speed [min^{-1}]	**Torque** [Nm]	**Feeding Rate** [g/min]	**Specific Mechanical Energy** [J/g]
Mean run 1	100	15	40	238
sd	0.20	1	1	-
Mean run 2	100	14	40	224
sd	0.20	1	1	-
Mean run 3	100	15	40	235
sd	0.21	1	1	-
Mean	**100**	**15**	**40**	**232**
sd	**0.012**	**0.46**	**0.018**	**7.2**

Table 9.1.12: Process Monitor Melt-Extrusion Formulation HPC75, Mean Values during Steady State

	Rotation Speed [min^{-1}]	**Torque** [Nm]	**Feeding Rate** [g/min]	**Specific Mechanical Energy** [J/g]
Mean run 1	200	75	29	3198
sd	0.49	3	4	-
Mean run 2	200	74	30	3109
sd	0.49	3	1	-
Mean run 3	200	67	30	2793
sd	0.49	4	1	-
Mean	**200**	**72**	**30**	**3033**
sd	**0.0014**	**4.6**	**0.27**	**213**

Table 9.1.13: Powder Flow Formulation GDB25

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.45	0.51	0.58	0.58	22	12
2	0.45	0.42	0.56	0.48	20	13
3	0.45	0.42	0.56	0.48	20	13
Mean	0.45	0.45	0.57	0.51	21	12
SD	0.00	0.052	0.012	0.058	1.6	0.25

Table 9.1.14: Powder Flow Formulation GDB50

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.50	0.49	0.61	0.55	18	11
2	0.46	0.45	0.58	0.52	21	14
3	0.47	0.45	0.57	0.52	18	14
Mean	0.48	0.46	0.59	0.53	19	13
SD	0.021	0.023	0.021	0.017	1.7	1.5

Table 9.1.15: Powder Flow Formulation GBD75

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.47	0.60	0.59	0.67	20	10
2	0.46	0.57	0.58	0.64	21	11
3	0.46	0.57	0.57	0.63	19	10
Mean	0.46	0.58	0.58	0.65	20	10
SD	0.0058	0.017	0.010	0.021	0.72	0.72

Table 9.1.16: Powder Flow Formulation GPS25

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.43	0.46	0.50	0.54	14	15
2	0.36	0.39	0.43	0.44	16	11
3	0.37	0.42	0.44	0.48	16	13
Mean	0.39	0.42	0.46	0.49	15	13
SD	0.038	0.035	0.038	0.050	1.2	1.759

Table 9.1.17: Powder Flow Formulation GPS50

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.43	0.51	0.51	0.58	16	12
2	0.37	0.46	0.45	0.53	18	13
3	0.39	0.46	0.46	0.52	15	12
Mean	0.40	0.48	0.47	0.54	16	12
SD	0.031	0.029	0.032	0.032	1.4	0.85

Table 9.1.18: Powder Flow Formulation GPS75

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.44	0.55	0.56	0.62	21	11
2	0.39	0.53	0.48	0.6	19	12
3	0.40	0.5	0.48	0.56	17	11
Mean	0.41	0.53	0.51	0.59	19	11
SD	0.026	0.025	0.046	0.031	2.4	0.48

Table 9.1.19: Powder Flow Formulation SUS25

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.52	0.60	0.73	0.70	29	14
2	0.53	0.58	0.72	0.67	26	13
3	0.55	0.55	0.72	0.63	24	13
Mean	0.53	0.58	0.72	0.67	26	13
SD	0.015	0.025	0.0058	0.035	2.6	0.79

Table 9.1.20: Powder Flow Formulation SUS50

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.57	0.64	0.69	0.72	17	11
2	0.56	0.60	0.70	0.70	20	14
3	0.56	0.61	0.72	0.69	22	12
Mean	0.56	0.62	0.70	0.70	20	12
SD	0.0058	0.021	0.015	0.015	2.4	1.7

Table 9.1.21: Powder Flow Formulation SUS75

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.53	0.66	0.68	0.75	22	12
2	0.53	0.62	0.66	0.69	20	10
3	0.53	0.61	0.65	0.72	18	15
Mean	0.53	0.63	0.66	0.72	20	12
SD	0.000	0.026	0.015	0.030	1.8	2.6

Table 9.1.22: Powder Flow Formulation HPC25

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.41	0.24	0.51	0.32	20	25
2	0.41	0.22	0.53	0.29	23	24
3	0.42	0.19	0.55	0.26	24	27
Mean	0.41	0.22	0.53	0.29	22	25
SD	0.0058	0.025	0.020	0.030	2.1	1.4

Table 9.1.23: Powder Flow Formulation HPC50

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.43	0.28	0.55	0.35	22	20
2	0.42	0.24	0.54	0.31	22	23
3	0.42	0.26	0.54	0.32	22	19
Mean	0.42	0.26	0.54	0.33	22	20
SD	0.0058	0.020	0.0058	0.021	0.23	2.0

Table 9.1.24: Powder Flow Formulation HPC75

Test No.	Bulk Density [g/ml]		Tapped Density [g/ml]		Compressibility Index	
	Powder Blend	Granulate	Powder Blend	Granulate	Powder Blend	Granulate
1	0.40	0.43	0.54	0.51	26	16
2	0.41	0.48	0.55	0.57	25	16
3	0.39	0.51	0.54	0.57	28	11
Mean	0.40	0.47	0.54	0.55	26	14
SD	0.010	0.040	0.0058	0.035	1.2	3.0

Table 9.1.25: Particle Size Distribution Formulation GDB25, a) Powder Blend, b) Granulate

a)

Mesh Size [μm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	21.7	13.5	21.8
75	62.0	57.9	54.0
125	13.4	20.9	18.2
180	1.4	4.2	3.5
250	0.7	2.3	1.1
355	0.5	0.5	0.5
500	0.4	0.7	0.9
	Blend 1	**Blend 2**	**Blend 3**
d_{10} [μm]	35	56	34
d_{50} [μm]	98	107	101
d_{90} [μm]	151	174	168
σ [%]	119	111	132

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	22.6	13.4	14.5
180	7.4	7.8	8.6
250	12.4	12.0	12.1
355	16.8	16.6	16.2
500	23.5	23.5	20.6
710	15.5	19.4	16.4
1000	1.7	7.3	11.7
	Granulate 1	**Granulate 2**	**Granulate 3**
d_{10} [μm]	80	135	124
d_{50} [μm]	420	502	488
d_{90} [μm]	845	960	1018
σ [%]	182	164	183

Table 9.1.26: Particle Size Distribution Formulation GDB50, a) Powder Blend, b) Granulate

a)

Mesh Size [μm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	23.1	60.9	47.7
75	43.7	27.1	40.9
125	18.2	5.9	4.7
180	9.6	3.6	2.0
250	2.3	0.7	3.0
355	1.5	0.7	1.0
500	1.6	1.1	0.8
	Blend 1	**Blend 2**	**Blend 3**
d_{10} [μm]	32	12	16
d_{50} [μm]	106	62	78
d_{90} [μm]	216	143	142
σ [%]	174	213	162

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	26.1	26.4	21.7
180	10.4	10.0	9.0
250	14.0	13.6	14.5
355	16.3	17.7	18.7
500	20.5	21.5	24.3
710	11.9	10.5	11.5
1000	0.8	0.3	0.3
	Granulate 1	**Granulate 2**	**Granulate 3**
d_{10} [μm]	69	68	83
d_{50} [μm]	351	355	392
d_{90} [μm]	775	734	755
σ [%]	201	187	171

Table 9.1.27: Particle Size Distribution Formulation GDB75, a) Powder Blend, b) Granulate

a)

Mesh Size [μm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	44.1	23.4	25.5
75	45.9	51.1	53.3
125	4.4	12.3	13.8
180	2.0	2.9	2.5
250	1.9	7.1	2.1
355	1.0	1.9	1.3
500	0.7	1.2	1.5
	Blend 1	**Blend 2**	**Blend 3**
d_{10} [μm]	17	32	29
d_{50} [μm]	81	101	98
d_{90} [μm]	125	254	170
σ [%]	133	220	143

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	11.1	16.5	16.3
180	5.4	6.8	7.1
250	8.3	9.3	10.1
355	12.9	14.1	15.6
500	25.7	25.3	25.9
710	35.3	26.5	24.0
1000	1.3	1.5	1.0
	Granulate 1	**Granulate 2**	**Granulate 3**
d_{10} [μm]	162	109	110
d_{50} [μm]	600	527	507
d_{90} [μm]	928	907	891
σ [%]	128	151	154

Table 9.1.28: Particle Size Distribution Formulation GPS25, a) Powder Blend, b) Granulate

a)

Mesh Size [µm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	17.5	18.6	10.9
75	58.5	58.7	68.5
125	7.3	15.2	11.0
180	2.2	3.6	3.0
250	3.1	1.2	1.1
355	3.0	1.6	2.4
500	8.5	1.1	3.1

	Blend 1	Blend 2	Blend 3
d_{10} [µm]	43	40	69
d_{50} [µm]	103	102	104
d_{90} [µm]	424	171	178
σ [%]	371	128	106

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	12.8	10.9	7.6
180	7.8	22.6	18.5
250	12.3	13.9	15.0
355	18.4	17.6	18.5
500	26.8	18.3	22.9
710	18.3	11.8	15.4
1000	3.6	5.0	2.2

	Granulate 1	Granulate 2	Granulate 3
d_{10} [µm]	141	165	189
d_{50} [µm]	490	377	425
d_{90} [µm]	899	877	852
σ [%]	155	189	156

Table 9.1.29: Particle Size Distribution Formulation GPS50, a) Powder Blend, b) Granulate

a)

Mesh Size [µm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	22.5	16.2	14.8
75	62.8	71.1	69.1
125	3.5	6.0	7.5
180	1.6	1.8	2.4
250	2.4	2.1	2.0
355	2.2	1.5	2.0
500	4.9	1.4	2.2

	Blend 1	Blend 2	Blend 3
d_{10} [µm]	33	46	51
d_{50} [µm]	97	99	100
d_{90} [µm]	229	150	169
σ [%]	202	105	118

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	6.7	18.3	10.4
180	3.8	27.0	19.5
250	7.1	12.1	13.6
355	13.0	15.7	18.5
500	26.3	16.2	22.4
710	39.2	9.5	13.9
1000	3.9	1.2	1.6

	Granulate 1	Granulate 2	Granulate 3
d_{10} [µm]	240	99	173
d_{50} [µm]	655	291	406
d_{90} [µm]	955	730	825
σ [%]	109	217	161

Table 9.1.30: Particle Size Distribution Formulation GPS75, a) Powder Blend, b) Granulate

a)

Mesh Size [µm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	32.4	10.9	21.9
75	51.6	68.5	58.4
125	4.7	11.0	11.6
180	1.9	3.0	1.7
250	2.8	1.1	3.0
355	2.1	2.4	1.6
500	4.5	3.1	1.8

	Blend 1	Blend 2	Blend 3
d_{10} [µm]	23	69	34
d_{50} [µm]	92	104	99
d_{90} [µm]	227	178	171
σ [%]	222	106	138

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	16.0	10.7	15.8
180	7.3	16.1	5.8
250	10.1	10.6	9.5
355	13.5	13.4	13.0
500	21.7	19.1	21.0
710	27.8	25.8	30.7
1000	3.7	4.2	4.2

	Granulate 1	Granulate 2	Granulate 3
d_{10} [µm]	113	168	114
d_{50} [µm]	531	491	559
d_{90} [µm]	934	935	945
σ [%]	155	156	149

Table 9.1.31: Particle Size Distribution Formulation SUS25, a) Powder Blend, b) Granulate

a)

Mesh Size [µm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	2.8	3.8	2.0
75	19.5	21.4	17.7
125	40.2	35.9	38.2
180	31.7	28.5	32.5
250	3.8	6.0	6.8
355	1.0	2.6	1.6
500	1.0	1.9	1.3
	Blend 1	**Blend 2**	**Blend 3**
d_{10} [µm]	94	90	98
d_{50} [µm]	163	163	169
d_{90} [µm]	241	259	249
σ [%]	90	104	90

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	11.2	20.0	20.9
180	3.4	6.8	7.7
250	6.1	10.4	11.4
355	9.8	15.4	17.6
500	24.7	24.3	25.8
710	42.9	22.3	16.3
1000	1.8	0.7	0.3
	Granulate 1	**Granulate 2**	**Granulate 3**
d_{10} [µm]	161	90	86
d_{50} [µm]	665	475	437
d_{90} [µm]	945	880	827
σ [%]	118	161	169

Table 9.1.32: Particle Size Distribution Formulation SUS50, a) Powder Blend, b) Granulate

a)

Mesh Size [µm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	5.5	2.2	2.8
75	44.2	16.4	26.3
125	37.9	54.6	50.1
180	7.5	20.2	14.7
250	2.4	3.5	3.5
355	0.9	1.6	1.5
500	1.5	1.4	1.1
	Blend 1	**Blend 2**	**Blend 3**
d_{10} [µm]	80	99	89
d_{50} [µm]	125	157	148
d_{90} [µm]	202	238	231
σ [%]	97	89	96

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	10.7	16.5	17.1
180	4.5	4.9	5.1
250	6.4	7.2	8.3
355	9.6	10.7	13.5
500	19.0	22.5	26.1
710	45.0	36.0	28.4
1000	4.9	2.3	1.5
	Granulate 1	**Granulate 2**	**Granulate 3**
d_{10} [µm]	168	109	105
d_{50} [µm]	709	601	549
d_{90} [µm]	967	938	914
σ [%]	113	138	147

Table 9.1.33: Particle Size Distribution Formulation SUS75 a) Powder Blend, b) Granulate

a)

Mesh Size [µm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	30.8	18.9	14.2
75	47.6	61.3	68.6
125	14.7	12.0	10.6
180	2.4	3.6	2.5
250	2.3	2.2	2.0
355	1.0	1.1	1.2
500	1.1	0.9	0.9
	Blend 1	**Blend 2**	**Blend 3**
d_{10} [µm]	24	40	53
d_{50} [µm]	95	100	101
d_{90} [µm]	168	170	162
σ [%]	151	130	108

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	14.6	19.6	18.6
180	4.2	6.6	6.0
250	5.8	10.1	8.2
355	7.9	13.0	10.6
500	18.8	25.2	23.6
710	42.9	24.4	32.1
1000	5.8	1.0	1.0
	Granulate 1	**Granulate 2**	**Granulate 3**
d_{10} [µm]	124	92	97
d_{50} [µm]	695	505	559
d_{90} [µm]	972	893	919
σ [%]	122	159	147

Table 9.1.34: Particle Size Distribution Formulation HPC25, a) Powder Blend, b) Granulate

a)

Mesh Size [µm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	15.0	14.9	14.6
75	10.2	12.0	12.1
125	14.0	15.4	16.2
180	15.5	14.6	13.0
250	25.5	25.5	25.1
355	15.2	13.9	14.7
500	4.5	3.8	4.3
	Blend 1	**Blend 2**	**Blend 3**
d_{10} [µm]	50	50	51
d_{50} [µm]	228	217	218
d_{90} [µm]	448	435	444
σ [%]	174	177	180

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	14.9	12.4	10.7
180	4.5	3.9	5.3
250	7.1	7.5	9.8
355	8.8	8.5	10.7
500	14.0	12.9	18.2
710	29.1	24.8	28.9
1000	21.7	30.0	16.3
	Granulate 1	**Granulate 2**	**Granulate 3**
d_{10} [µm]	121	145	169
d_{50} [µm]	718	766	655
d_{90} [µm]	1150	1286	1077
σ [%]	143	149	139

Table 9.1.35: Particle Size Distribution Formulation HPC50, a) Powder Blend, b) Granulate

a)

Mesh Size [µm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	24.1	22.0	22.0
75	14.1	14.3	17.8
125	15.9	14.9	15.5
180	11.0	14.2	13.3
250	20.2	17.8	18.7
355	11.4	12.8	10.0
500	3.3	4.1	2.8
	Blend 1	**Blend 2**	**Blend 3**
d_{10} [µm]	31	34	34
d_{50} [µm]	166	176	161
d_{90} [µm]	415	433	394
σ [%]	231	227	223

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	10.6	8.2	10.5
180	4.5	4.6	4.7
250	8.2	8.5	8.7
355	9.9	9.7	9.5
500	18.9	27.1	26.3
710	36.9	28.2	31.5
1000	10.8	13.6	8.7
	Granulate 1	**Granulate 2**	**Granulate 3**
d_{10} [µm]	169	207	171
d_{50} [µm]	685	647	632
d_{90} [µm]	1010	1042	988
σ [%]	123	129	129

Table 9.1.36: Particle Size Distribution Formulation HPC75, a) Powder Blend, b) Granulate

a)

Mesh Size [µm]	Fraction [%] Blend 1	Fraction [%] Blend 2	Fraction [%] Blend 3
0	42.7	40.7	39.9
75	20.8	21.8	24.0
125	11.8	11.0	11.6
180	6.5	6.4	6.2
250	10.0	11.0	10.2
355	5.7	6.6	6.1
500	2.5	2.3	2.1
	Blend 1	**Blend 2**	**Blend 3**
d_{10} [µm]	18	18	19
d_{50} [µm]	93	96	96
d_{90} [µm]	336	345	337
σ [%]	344	339	331

b)

Mesh Size [microns]	Fraction [%] Granulate 1	Fraction [%] Granulate 2	Fraction [%] Granulate 3
0	10.0	11.6	12.9
180	4.8	5.3	6.0
250	9.1	10.2	11.6
355	10.2	12.2	15.0
500	27.0	26.4	28.8
710	34.1	27.4	22.6
1000	4.7	6.8	3.0
	Granulate 1	**Granulate 2**	**Granulate 3**
d_{10} [µm]	179	155	139
d_{50} [µm]	623	584	533
d_{90} [µm]	955	967	911
σ [%]	124	139	145

Table 9.1.37: True Densities of Bulk Materials (Powder Blend, Granulates)

	True Density [g/cm^3]									
Formulation	**GDB25**	**GDB50**	**GDB75**	**GPS25**	**GPS75**	**SUS25**	**SUS50**	**SUS75**	**HPC25**	**HPC75**
Blend	1.0978	1.1894	1.3426	1.0927	1.2941	1.2532	1.3321	1.3939	1.2475	1.4001
Granulate	1.0959	1.1933	1.3306	1.0873	1.2926	1.2236	1.2547	1.3451	1.2721	1.4219

Table 9.1.38: Compression Properties Formulation GDB25, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**
9.9	6.4	0.966	0.980	2.408	2.393	2.62	2.55	0.18	0.53
6.5	5.5	0.989	0.990	2.396	2.380	2.63	2.53	0.18	0.50
7.1	4.6	0.996	0.979	2.396	2.404	2.61	2.56	0.18	0.53
8.4	5.3	0.956	0.982	2.388	2.413	2.60	2.60	0.18	0.52

Table 9.1.39: Compression Properties Formulation GDB50, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**
9.6	5.6	0.995	0.981	2.385	2.392	2.56	2.51	0.44	0.95
9.1	6.8	0.983	0.985	2.415	2.407	2.58	2.51	0.49	0.89
11.1	6.6	0.985	0.987	2.415	2.401	2.57	2.50	0.43	0.92
10.6	6.5	0.994	0.988	2.400	2.401	2.58	2.50	0.43	0.95

Table 9.1.40: Compression Properties Formulation GDB75, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**
44.3	11.5	0.996	0.997	2.395	2.383	2.55	2.44	1.06	1.50
42.8	14.0	0.997	0.992	2.393	2.430	2.58	2.52	1.02	1.55
45.7	13.3	0.992	0.993	2.399	2.415	2.58	2.47	1.02	1.51
45.6	12.0	0.998	0.992	2.387	2.374	2.59	2.46	1.08	1.49
48.3	-	0.995	-	2.372	-	2.54	-	1.07	-

Table 9.1.41: Compression Properties Formulation GPS25, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**	**Blend**	**Granulate**
5.6	5.6	0.992	0.981	2.405	2.371	2.52	2.45	0.54	0.81
6.2	6.5	0.992	0.985	2.416	2.382	2.53	2.45	0.60	0.88
6.3	6.2	0.990	0.993	2.418	2.375	2.55	2.41	0.56	0.89
5.8	6.6	0.988	0.969	2.403	2.380	2.53	2.45	0.47	0.81

Table 9.1.42: Compression Properties Formulation GPS75, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate
22.6	6.7	0.998	0.992	2.429	2.396	2.52	2.42	1.04	1.35
25.5	7.0	0.994	0.985	2.411	2.384	2.52	2.39	1.07	1.45
20.4	7.4	0.994	0.978	2.415	2.415	2.50	2.42	1.08	1.38
21.6	6.8	0.992	0.980	2.406	2.404	2.54	2.40	1.00	1.37
21.7	-	0.997	-	2.404	-	2.46	-	1.13	-

Table 9.1.43: Compression Properties Formulation SUS25, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate
33.6	22.6	0.997	0.987	2.407	2.397	2.62	2.48	0.76	0.83
31.3	21.9	0.997	0.990	2.435	2.429	2.62	2.52	0.85	0.69
31.8	22.0	0.996	0.991	2.362	2.419	2.56	2.52	0.71	0.63
32.8	20.8	0.996	0.997	2.384	2.413	2.55	2.50	0.84	0.76

Table 9.1.44: Compression Properties Formulation SUS50, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate
38.9	21.3	0.996	0.996	2.404	2.415	2.65	2.42	1.14	1.48
41.7	22.6	0.999	0.994	2.403	2.416	2.65	2.45	1.20	1.33
39.9	23.7	0.999	0.998	2.397	2.389	2.63	2.41	1.12	1.52
40.9	20.0	0.997	0.993	2.396	2.394	2.57	2.41	1.11	1.55

Table 9.1.45: Compression Properties Formulation SUS75, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate
44.6	21.7	0.997	0.995	2.421	2.412	2.57	2.41	2.07	2.64
39.3	22.8	0.995	0.990	2.399	2.421	2.52	2.42	1.89	2.16
46.0	21.7	0.997	0.986	2.374	2.414	2.50	2.44	1.88	2.61
45.4	21.0	0.999	0.992	2.374	2.420	2.51	2.42	1.84	2.42

Table 9.1.46: Compression Properties Formulation HPC25, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate
29.7	35.9	0.995	0.997	2.427	2.552	2.74	3.00	1.71	1.33
31.5	36.2	0.996	0.997	2.378	2.571	2.71	3.04	1.70	1.28
31.9	34.5	0.997	0.998	2.365	2.548	2.70	2.98	1.77	1.34
26.9	35.3	0.994	0.999	2.395	2.530	2.74	3.00	1.60	1.25

Table 9.1.47: Compression Properties Formulation HPC75, (Powder) Blend vs. Granulate

Yield Pressure [MPa]		Correlation Coefficient		d_0 [mm]		d_1 [mm]		RTS [MPa]	
Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate	Blend	Granulate
57.0	56.5	0.998	0.998	2.391	2.380	2.68	2.59	1.81	2.43
59.2	52.1	0.996	0.994	2.401	2.391	2.61	2.56	1.86	2.49
61.7	57.5	0.992	0.997	2.379	2.407	2.61	2.61	1.89	2.38
62.4	49.9	0.998	0.995	2.391	2.405	2.64	2.61	1.93	2.23

Table 9.1.48: Compression Force-Tablet Hardness Relation Formulation GDB25

Mean Compression Force [kN]	Count	Mean Tablet Hardness [N]	Median Tablet Hardness [N]	SD Tablet Hardness	Tablet Hardness [N]	
					Minimum	Maximum
0.5	20	14	14	2.4	11	18
0.6	10	18	17	2.7	12	22
1.7	10	31	31	1.5	29	33
5.3	10	38	38	1.4	36	41
5.9	10	34	33	1.8	32	37
7.8	10	32	32	1.9	30	36
9.0	10	34	34	1.8	32	39
11.3	10	33	33	1.8	30	36
11.9	10	37	37	1.7	34	39
14.2	10	35	35	2.0	31	37
15.5	10	37	37	1.6	35	40
17.8	10	33	33	2.3	29	36
20.8	10	34	34	2.2	31	39
21.9	10	37	37	1.9	34	41

Table 9.1.49: Compression Force-Tablet Hardness Relation Formulation GPS25

Mean Compression Force [kN]	Count	Mean Tablet Hardness [N]	Median Tablet Hardness [N]	SD Tablet Hardness	Tablet Hardness [N]	
					Minimum	Maximum
0.6	10	28	28	1.1	27	31
0.6	10	27	26	3.2	21	33
1.0	10	33	33	1.9	29	36
1.2	10	38	38	2.1	34	40
1.4	10	33	33	1.8	30	36
1.5	10	33	33	1.8	31	36
2.0	6	38	38	3.9	33	45
2.6	6	33	34	1.3	31	34
5.1	10	36	36	4.2	28	41
5.9	10	35	35	3.2	30	41
6.2	10	40	40	3.4	34	46
7.1	10	36	36	2.4	32	40
10.3	10	35	35	2.8	29	39
10.7	6	38	38	3.9	33	45
13.0	10	35	35	2.4	30	40

Table 9.1.50: Compression Force-Tablet Hardness Relation Formulation SUS50

Mean Compression Force [kN]	Count	Mean Tablet Hardness [N]	Median Tablet Hardness [N]	SD Tablet Hardness	Tablet Hardness [N] Minimum	Tablet Hardness [N] Maximum
3.5	10	12	11	3.7	9	17
4.0	10	15	15	2.4	9	17
4.1	10	14	13	4.4	9	25
4.2	10	18	17	6.6	12	35
5.4	10	24	22	7.6	17	42
6.0	10	35	40	11	21	47
7.5	10	46	46	3.4	37	50
7.6	10	37	40	11	21	49
9.9	10	52	52	1.9	47	55
10.1	10	47	47	2.1	43	51
11.2	10	45	45	5.5	30	51
13.3	10	42	44	8.1	21	50
14.6	10	41	45	9.0	27	51
15.3	10	46	50	13	20	60
16.7	10	35	42	12	15	47
21.2	10	40	45	11	23	49
23.8	10	33	34	12	12	50

Table 9.1.51: Tablet Hardness of CR Matrix Tablets, Interbatch Comparison

Formulation	Mean Tablet Hardness 1 (±SD) [N]	Mean Tablet Hardness 2 (±SD) [N]	Mean Tablet Hardness 3 (±SD) [N]
GDB25	30.6 (±1.71)	34.3 (±1.83)	30.8 (±1.87)
GDB50	35.2 (±1.23)	30.4 (1.51)	28.6 (±0.70)
GDB75	29.2 (±7.55)	29.5 (±1.90)	29.3 (±4.74)
GPS25	29.3 (±7.24)	34.4 (±1.90)	32.6 (±2.80)
GPS50	36.7 (±4.14)	36.5 (±1.72)	33.4 (±3.24)
GPS75	24.7 (±7.70)	26.2 (±6.56)	22.6 (±2.63)
SUS25	22.8 (±5.87)	22.1 (±6.77)	22.8 (±1.40)
SUS50	41.8 (±2.86)	46.7 (±6.45)	51.4 (±3.72)
SUS75	26.0 (±6.72)	27.0 (±4.50)	28.2 (±5.41)
HPC25	81.5 (±7.71)	83.0 (±11.2)	77.5 (±4.45)
HPC50	57.6 (±4.55)	61.6 (±6.43)	57.3 (±12.4)
HPC75	35.7 (±3.74)	30.7 (±1.83)	31.0 (±1.90)

Table 9.1.52: Friability of Tablets manufactured from Granulates processed by Melt-Extrusion

Formulation	Weight Loss 1 [g]	Friability 1 [%]	Weight Loss 2 [g]	Friability 2 [%]	Weight Loss 3 [g]	Friability 3 [%]
GDB25	0.00567	0.071	0.00711	0.088	0.00637	0.079
GDB50	0.00237	0.058	0.00163	0.040	0.00080	0.020
GDB75	0.00476	0.178	0.00263	0.099	0.00448	0.167
GPS25	0.02562	0.317	Fail/ Capping		0.01870	0.234
GPS50	0.00416	0.104	0.00528	0.130	0.00356	0.087
GPS75	0.00527	0.205	0.00598	0.228	0.00438	0.163
SUS25	0.09547	1.178	0.0888	1.099	0.11583	1.441
SUS50	0.01447	0.353	0.01424	0.354	0.01255	0.308
SUS75	0.00513	0.192	0.00552	0.207	0.00582	0.220
HPC25	0.00229	0.028	0.00293	0.037	0.00283	0.036
HPC50	0.00822	0.200	0.00806	0.196	0.01793	0.432
HPC75	0.00258	0.095	0.00219	0.081	0.00195	0.076

Table 9.1.53: Uniformity of Mass of Tablets manufactured from Granulates processed by Melt-Extrusion

Formulation	Mean Weight [mg] (±SD)	Maximum Weight [mg]		Minimum Weight [mg]		Pass/ Fail
		Range	Found	Range	Found	
GDB25	400.62 (±4.0689)	420.65	407.80	380.59	391.09	Pass
	403.50 (±2.7191)	423.68	410.19	383.33	390.66	Pass
	404.11 (±3.3575)	424.32	411.09	393.90	397.97	Pass
GDB50	204.81 (±4.6167)	220.17	208.18	189.45	198.93	Pass
	203.86 (±5.3240)	219.15	209.40	188.57	197.82	Pass
	200.65 (±3.5814)	215.70	205.56	185.60	188.18	Pass
GDB75	133.56 (±1.6957)	143.58	136.73	123.54	130.07	Pass
	132.08 (±2.1775)	141.99	135.93	122.17	127.73	Pass
	134.29 (±1.6482)	144.36	136.59	124.22	129.91	Pass
GPS25	403.96 (±3.8688)	424.16	409.01	383.76	393.69	Pass
	392.41 (±9.8018)	412.03	410.74	372.79	380.99	Pass
	399.74 (±4.4712)	419.73	409.17	379.75	390.52	Pass
GPS50	200.72 (±3.3407)	215.77	207.88	185.67	195.65	Pass
	203.37 (±2.6872)	218.63	207.77	188.12	194.26	Pass
	205.52 (±1.9316)	220.93	208.97	190.11	201.67	Pass
GPS75	128.71 (±2.0035)	138.36	133.47	119.06	125.27	Pass
	132.13 (±3.3556)	142.04	142.46	122.22	125.33	Pass
	133.98 (±1.6950)	144.03	137.02	123.93	131.31	Pass
SUS25	404.88 (±7.3657)	425.12	413.39	384.64	388.32	Pass
	403.54 (±5.2634)	423.71	409.41	383.36	389.93	Pass
	401.66 (±6.8468)	421.74	409.05	381.58	381.45	Pass
SUS50	204.63 (±5.4021)	219.98	213.06	189.28	193.24	Pass
	201.25 (±2.3813)	216.35	205.09	186.16	196.26	Pass
	203.63 (±2.0928)	218.90	206.26	188.36	199.47	Pass
SUS75	133.60 (±3.3606)	143.62	138.19	123.58	126.65	Pass
	133.19 (±3.1581)	143.17	137.89	123.20	126.69	Pass
	132.10 (±2.1082)	142.01	137.31	122.19	129.28	Pass
HPC25	402.36 (±7.8569)	422.48	417.89	382.24	384.59	Pass
	393.32 (±5.7876)	412.99	406.56	373.65	387.12	Pass
	393.68 (±6.8784)	413.36	407.75	374.00	378.46	Pass
HPC50	204.72 (±4.6986)	220.07	212.58	189.37	192.58	Pass
	204.67 (±6.6908)	220.02	215.23	189.32	193.30	Pass
	206.44 (±8.9596)	221.92	221.59	190.96	180.58	Pass
HPC75	135.44 (±3.6474)	145.60	140.43	125.28	126.71	Pass
	134.74 (±3.1100)	144.85	138.99	124.63	128.67	Pass
	134.76 (±3.1532)	144.87	139.98	124.65	129.62	Pass

Validation HPLC Assay Theophylline

Column: LiChrospher 100RP18, 125 x 4, 5microns (Merck KgAa, Darmstadt, Germany)
Mobile Phase: Methanol: Water (20:80)
Flow Rate: 1.2ml/min
Temperature: 25 degrees centigrade
Detection: UV 272nm

Samples prepared from stock solution (250mg/100ml)   (n=4)
Samples were diluted with Acetate Buffer pH5.0 (blank FeSSIF)

Conc. Sample [mg/ 50ml]	Mean Area [AU]
125.12	8286576
120.12	7908410
115.11	7555957
110.11	7221532
105.09	6930367
100.10	6571154
95.09	6244318
90.09	5890046
85.08	5605772
80.08	5273113
75.07	4939489

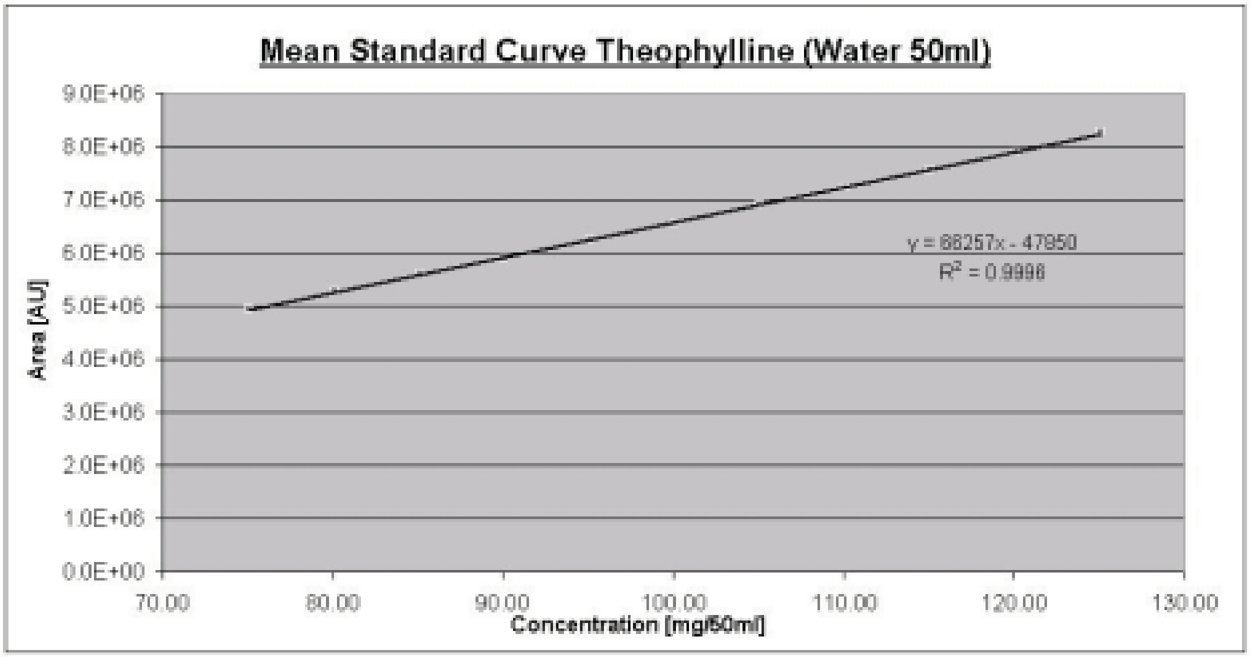

Fig. 9.1.1: Mean Standard Curves for Validation of Theophylline HPLC Assay

Table 9.1.54: Uniformity of Content of Tablets manufactured from Granulates processed by Melt-Extrusion

Formulation	Mean Content [mg] (±SD)	Maximum Content [mg]		Minimum Content [mg]		Pass/ Fail
		Range	Found	Range	Found	
GDB25	100.27 (±1.7059)	115.31	101.81	85.23	96.48	Pass
	101.21 (±1.9635)	116.39	102.56	86.03	95.87	Pass
	98.35 (±3.725)	113.10	101.38	83.60	91.37	Pass
GDB50	102.07 (±1.3528)	117.38	103.63	86.76	99.29	Pass
	100.96 (±2.4751)	116.10	103.78	85.82	96.33	Pass
	101.78 (±4.0516)	117.05	112.89	86.51	98.14	Pass
GDB75	99.54 (±1.495)	114.47	101.70	84.61	97.51	Pass
	98.97 (±1.517)	113.82	101.02	84.12	96.56	Pass
	99.29 (±1.470)	114.18	101.11	84.40	96.77	Pass
GPS25	100.34 (±1.3154)	115.39	102.30	85.29	98.20	Pass
	96.89 (±1.771)	111.42	100.20	82.36	95.08	Pass
	98.34 (±2.149)	113.09	102.44	83.59	95.83	Pass
GPS50	99.30 (±1.996)	114.20	103.39	84.41	96.94	Pass
	100.15 (±1.7354)	115.17	101.77	85.13	95.62	Pass
	100.93 (±1.5317)	116.07	103.06	85.79	98.29	Pass
GPS75	95.19 (±1.401)	109.47	97.42	80.91	93.29	Pass
	95.81 (±2.916)	110.18	99.84	81.44	90.04	Pass
	97.02 (±1.536)	111.57	99.34	82.47	94.18	Pass
SUS25	97.83 (±1.952)	112.50	100.84	83.16	94.05	Pass
	98.05 (±2.554)	112.76	103.81	83.34	94.41	Pass
	96.64 (±2.032)	111.14	98.70	82.14	93.71	Pass
SUS50	99.26 (±3.258)	114.15	105.17	84.37	94.04	Pass
	97.83 (±2.335)	112.50	101.00	83.16	94.26	Pass
	99.00 (±1.432)	113.85	101.06	84.15	96.65	Pass
SUS75	97.21 (±3.375)	111.79	101.00	82.63	91.06	Pass
	95.67 (±2.573)	110.02	98.84	81.32	91.40	Pass
	95.26 (1.917)	109.55	99.64	80.97	93.53	Pass
HPC25	94.18 (±2.906)	108.31	99.15	80.05	88.74	Pass
	95.49 (±3.482)	109.81	101.27	81.17	91.33	Pass
	98.60 (±3.397)	113.39	102.19	83.81	89.85	Pass
HPC50	106.03 (±4.7893)	121.93	114.33	90.13	97.18	Pass
	101.21 (±3.8571)	116.39	107.22	86.03	96.53	Pass
	103.44 (±3.6062)	118.96	109.76	87.92	97.80	Pass
HPC75	101.90 (±1.4996)	117.19	103.56	86.62	99.35	Pass
	98.61 (±2.848)	113.40	101.82	83.82	94.47	Pass
	99.08 (±3.199)	113.94	103.37	84.22	93.70	Pass

Table 9.1.55: **Dissolution Formulation GDB25 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus**

Time [min]	GDB25 Batch 1 Release [%]	GDB25 Batch 1 SD Release	GDB25 Batch 2 Release [%]	GDB25 Batch 2 SD Release	GDB25 Batch 3 Release [%]	GDB25 Batch 3 SD Release
0	0.0	0.00	0.0	0.00	0.0	0.00
15	1.3	0.18	1.8	0.06	1.5	0.33
30	2.0	0.14	2.6	0.03	2.1	0.44
75	3.1	0.06	4.0	0.06	3.2	0.47
105	3.8	0.10	4.6	0.07	4.2	0.48
180	5.1	0.22	6.0	0.10	5.4	0.47
240	5.9	0.22	6.8	0.10	6.2	0.47
300	6.7	0.22	7.6	0.11	7.0	0.51
360	7.3	0.24	8.3	0.15	7.7	0.49
420	7.9	0.25	9.0	0.13	8.3	0.50
480	8.5	0.29	9.6	0.14	8.8	0.48
540	9.1	0.31	10.1	0.14	9.4	0.52
600	9.6	0.35	10.6	0.15	9.9	0.52
660	10.2	0.38	11.1	0.12	10.3	0.49
720	10.8	0.42	11.6	0.12	10.8	0.48

Table 9.1.56: Dissolution Formulation GDB50 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GDB50 Batch 1 Release [%]	GDB50 Batch 1 SD Release	GDB50 Batch 2 Release [%]	GDB50 Batch 2 SD Release	GDB50 Batch 3 Release [%]	GDB50 Batch 3 SD Release
0	0.0	0.00	0.0	0.00	0.0	0.00
15	3.8	0.14	3.6	0.25	2.4	0.69
30	5.4	0.17	5.2	0.29	4.3	0.64
45	6.6	0.24	6.3	0.28	5.3	0.66
75	8.4	0.26	8.0	0.29	6.7	0.63
105	9.8	0.30	9.3	0.27	7.8	0.65
135	11.0	0.31	10.3	0.27	8.7	0.66
180	12.5	0.26	11.6	0.28	9.9	0.67
240	14.3	0.34	13.2	0.30	11.3	0.69
300	15.9	0.42	14.7	0.34	12.6	0.71
360	17.3	0.38	16.1	0.35	13.8	0.74
420	18.5	0.45	17.3	0.38	14.9	0.76
480	19.6	0.50	18.5	0.39	16.0	0.77
540	20.7	0.53	19.7	0.38	17.1	0.79
600	21.7	0.62	20.8	0.41	18.0	0.81
660	22.7	0.63	21.9	0.43	19.0	0.78
720	23.6	0.70	23.0	0.44	19.9	0.81

Table 9.1.57: Dissolution Formulation GDB75 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GDB75 Batch 1 Release [%]	GDB75 Batch 1 SD Release	GDB75 Batch 2 Release [%]	GDB75 Batch 2 SD Release	GDB75 Batch 3 Release [%]	GDB75 Batch 3 SD Release
0	0.0	0.00	0.0	0.00	0.0	0.00
15	7.0	0.27	7.2	0.12	7.5	0.69
30	10.5	0.41	10.9	0.16	11.2	0.64
75	16.2	0.61	17.9	0.34	18.4	0.62
105	18.8	0.72	21.3	0.43	22.0	0.57
180	24.3	0.94	27.9	0.60	28.9	0.56
240	28.0	1.09	32.0	0.70	33.3	0.56
300	31.4	1.24	35.3	0.76	37.0	0.61
360	34.5	1.39	38.2	0.92	40.2	0.71
420	37.4	1.54	40.7	1.0	43.0	0.81
480	40.1	1.70	43.0	1.1	45.5	0.89
540	42.7	1.92	45.2	1.1	47.8	0.93
600	45.1	2.15	47.4	1.1	49.8	1.0
660	47.5	2.44	49.6	1.2	51.9	1.1
720	49.8	2.75	52.0	1.3	54.0	1.2

Table 9.1.58: Dissolution Formulation GPS25 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GPS25 Batch 1 Release [%]	GPS25 Batch 1 SD Release	GPS25 Batch 2 Release [%]	GPS25 Batch 2 SD Release	GPS25 Batch 3 Release [%]	GPS25 Batch 3 SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	1.6	0.1	1.7	0.2	1.7	0.4
30	2.3	0.1	2.6	0.2	2.6	0.2
75	3.8	0.7	4.2	0.4	4.3	0.1
105	4.6	0.9	5.1	0.4	5.1	0.2
180	6.5	1.4	7.1	0.9	7.0	0.3
240	7.7	1.7	8.7	1.4	8.3	0.5
300	8.9	1.9	10.2	2.0	9.5	0.6
360	10.0	2.2	11.7	2.5	10.7	0.8
420	11.0	2.5	13.1	3.2	11.9	1.0
480	11.9	2.6	14.6	3.8	13.1	1.1
540	13.0	3.0	16.1	4.4	14.3	1.3
600	14.0	3.2	17.6	5.0	15.5	1.4
660	14.9	3.5	19.2	5.7	16.8	1.5
720	15.9	3.7	20.8	6.4	18.0	1.7

Table 9.1.59: Dissolution Formulation GPS50 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GPS50 Batch 1 Release [%]	GPS50 Batch 1 SD Release	GPS50 Batch 2 Release [%]	GPS50 Batch 2 SD Release	GPS50 Batch 3 Release [%]	GPS50 Batch 3 SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	2.3	0.3	2.7	0.3	2.4	0.3
30	3.5	0.4	3.9	0.3	3.6	0.5
45	4.4	0.5	4.7	0.3	4.6	0.4
75	5.7	0.7	6.1	0.3	5.9	0.3
105	6.9	0.7	7.2	0.4	7.0	0.4
135	8.0	0.7	8.3	0.4	8.2	0.3
180	9.3	0.9	9.7	0.4	9.6	0.2
240	11.0	1.2	11.5	0.5	11.5	0.3
300	12.7	1.4	13.2	0.5	13.2	0.2
360	14.3	1.6	14.8	0.6	14.9	0.2
420	15.9	1.7	16.5	0.6	16.6	0.3
480	17.5	1.8	18.0	0.6	18.2	0.3
540	19.0	1.9	19.7	0.7	19.6	0.3
600	20.6	2.0	21.2	0.8	21.2	0.5
660	22.1	2.1	22.7	0.8	22.5	0.4
720	23.7	2.2	24.3	0.8	23.8	0.2

Table 9.1.60: Dissolution Formulation GPS75 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GPS75 Batch 1 Release [%]	GPS75 Batch 1 SD Release	GPS75 Batch 2 Release [%]	GPS75 Batch 2 SD Release	GPS75 Batch 3 Release [%]	GPS75 Batch 3 SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	3.1	0.2	4.4	0.3	3.9	0.1
30	4.5	0.2	6.4	0.3	5.9	0.1
75	7.5	0.1	10.4	0.6	9.9	0.1
105	9.2	0.1	12.6	0.7	11.9	0.2
180	13.4	0.2	17.6	0.8	16.3	0.2
240	16.7	0.3	21.3	0.9	19.7	0.3
300	19.8	0.4	24.7	0.9	23.1	0.4
360	22.8	0.5	27.8	1.0	26.3	0.5
420	25.5	0.6	30.9	1.0	29.5	0.5
480	28.1	0.6	33.8	1.1	32.5	0.6
540	30.6	0.7	36.7	1.2	35.4	0.6
600	32.9	0.7	39.6	1.4	38.2	0.7
660	35.2	0.8	42.4	1.5	41.0	0.7
720	37.4	0.9	45.2	1.8	43.7	0.7

Table 9.1.61: Dissolution Formulation SUS25 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	SUS25 Batch 1 Release [%]	SUS25 Batch 1 SD Release	SUS25 Batch 2 Release [%]	SUS25 Batch 2 SD Release	SUS25 Batch 3 Release [%]	SUS25 Batch 3 SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	4.7	0.2	4.6	0.1	4.4	0.1
30	7.2	0.3	6.9	0.1	6.5	0.2
75	12.3	0.6	11.4	0.2	10.7	0.2
105	14.8	0.7	13.5	0.2	12.8	0.2
180	19.6	1.1	17.8	0.2	17.1	0.2
240	22.7	1.3	20.6	0.3	19.9	0.2
300	25.4	1.5	23.1	0.4	22.4	0.2
360	27.9	1.7	25.0	0.9	24.8	0.2
421	30.2	1.8	27.2	0.9	26.9	0.2
480	32.3	2.0	29.3	0.8	28.9	0.2
540	34.3	2.1	31.2	0.9	30.9	0.2
600	36.2	2.2	33.1	0.9	32.8	0.3
660	38.0	2.4	35.0	0.9	34.5	0.2
720	39.7	2.5	36.7	0.9	36.3	0.2

Table 9.1.62: Dissolution Formulation SUS50 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	SUS50 Batch 1 Release [%]	SUS50 Batch 1 SD Release	SUS50 Batch 2 Release [%]	SUS50 Batch 2 SD Release	SUS50 Batch 3 Release [%]	SUS50 Batch 3 SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	5.1	0.4	5.4	0.2	4.8	0.2
30	7.5	0.5	7.6	0.4	7.1	0.3
75	12.3	0.6	12.2	0.4	11.8	0.9
105	14.8	0.7	14.5	0.5	14.3	0.6
180	19.5	0.8	19.0	0.6	19.0	0.6
240	22.6	0.9	20.4	0.6	21.9	0.9
300	25.2	1.0	23.1	0.6	24.2	1.2
360	27.5	1.1	25.5	0.7	26.9	1.1
420	29.5	1.1	27.8	0.7	29.3	1.1
480	31.5	1.2	29.7	0.7	31.4	1.1
540	33.5	1.2	31.7	0.7	33.4	1.3
600	35.4	1.3	33.5	0.7	35.2	1.4
660	37.2	1.3	35.3	0.8	37.0	1.5
720	38.8	1.4	36.9	0.8	38.7	1.6

Table 9.1.63: Dissolution Formulation SUS75 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	SUS75 Batch 1 Release [%]	SUS75 Batch 1 SD Release	SUS75 Batch 2 Release [%]	SUS75 Batch 2 SD Release	SUS75 Batch 3 Release [%]	SUS75 Batch 3 SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	7.6	0.6	7.3	0.7	6.6	0.4
30	10.7	0.7	10.4	0.7	9.6	0.6
75	16.5	0.9	15.9	1.0	15.4	0.9
105	19.3	1.0	18.5	1.1	18.3	1.0
180	24.7	1.1	23.7	1.2	23.8	1.4
240	28.1	1.2	26.9	1.3	27.2	1.6
300	31.0	1.3	29.6	1.4	30.1	1.9
360	33.5	1.3	32.0	1.5	32.6	2.1
420	35.8	1.4	34.2	1.6	34.8	2.4
480	37.8	1.4	36.0	1.7	36.8	2.7
540	39.6	1.5	37.8	1.8	38.6	3.0
600	41.4	1.5	39.4	1.9	40.3	3.4
660	43.0	1.5	41.0	2.0	41.9	3.6
720	44.5	1.6	42.4	2.1	43.5	3.8

Table 9.1.64: Dissolution Formulation HPC25 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	HPC25 Batch 1 Release [%]	HPC25 Batch 1 SD Release	HPC25 Batch 2 Release [%]	HPC25 Batch 2 SD Release	HPC25 Batch 3 Release [%]	HPC25 Batch 3 SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	6.1	0.7	5.7	0.6	5.9	0.3
30	9.6	1.0	9.2	0.7	9.5	0.3
45	11.8	1.6	12.1	0.8	12.4	0.3
75	16.6	2.3	17.0	1.2	17.4	0.6
105	21.2	3.2	21.6	1.5	22.0	0.9
135	25.5	3.7	25.9	1.8	26.4	1.3
180	31.5	4.8	32.1	2.2	32.7	1.6
240	39.1	6.2	39.6	2.9	40.6	2.2
300	46.0	7.6	46.8	3.4	47.9	2.8
360	52.7	8.4	53.6	4.0	55.0	3.3
420	58.9	9.0	60.2	4.4	61.6	3.9
480	64.6	9.5	66.2	4.9	67.7	4.3
540			71.9	5.4	73.4	4.6
600			77.1	5.8	78.7	4.9
660			81.9	6.0	83.5	4.9
720			86.3	6.2	87.8	4.6

Table 9.1.65: Dissolution Formulation HPC50 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	HPC50 Batch 1 Release [%]	HPC50 Batch 1 SD Release	HPC50 Batch 2 Release [%]	HPC50 Batch 2 SD Release	HPC50 Batch 3 Release [%]	HPC50 Batch 3 SD Release
0	0.0	0.0	0.0	0.0	0	0.0
15	6.9	0.3	7.5	0.5	15	6.9
30	11.8	0.5	13.1	1.0	30	11.8
45	16.1	0.7	18.3	1.5	45	16.1
75	24.4	1.0	28.4	2.7	75	24.4
105	32.3	1.4	37.6	3.6	105	32.3
135	39.4	1.5	46.1	4.3	135	39.4
180	49.7	1.6	57.7	5.3	180	49.7
240	61.7	1.4	71.3	6.2	240	61.7
300	72.4	1.2	82.3	6.3	300	72.4
360	81.3	1.0	90.7	5.6	360	81.3
420	88.7	0.7	96.1	3.6	420	88.7
480	94.6	0.6	99.3	1.4	480	94.6
540	98.9	0.5	100.4	1.0	540	98.9
600	101.3	0.7	100.8	0.9	600	101.3
660	101.7	0.9	101.0	1.0	660	101.7
720	102.0	0.8	101.3	1.0	720	102.0

Table 9.1.66: Dissolution Formulation HPC75 (% Release), Reproducibility of Drug Release, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	HPC75 Batch 1 Release [%]	HPC75 Batch 1 SD Release	HPC75 Batch 2 Release [%]	HPC75 Batch 2 SD Release	HPC75 Batch 3 Release [%]	HPC75 Batch 3 SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	10.8	1.8	11.4	1.5	9.9	2.5
30	20.4	3.7	21.4	3.2	20.2	3.6
75	43.7	7.7	47.7	7.0	45.0	8.2
105	55.8	9.2	61.5	8.3	59.3	9.6
180	77.2	9.5	85.5	7.9	83.0	9.3
240	86.8	6.0	95.1	4.4	92.7	5.4
300	91.9	3.2	98.9	1.2	97.8	1.9
360	93.7	2.2	100.0	0.2	99.8	0.3
420	93.9	2.3	100.2	0.2	100.2	0.3
480	93.9	2.3	100.4	0.2	100.3	0.3
540	94.1	2.3	100.8	0.2	100.6	0.3

Table 9.1.67: Dissolution Formulation GDB25 (% Release), Impact Medium pH° and Ionic Strength° on Drug Release, USP 2 Apparatus

Time [min]	GDB25 pH1.2 Release [%]	GDB25 pH1.2 SD Release	GDB25 pH6.8 Release [%]	GDB25 pH6.8 SD Release	GDB25 pH1.2m Release [%]	GDB25 pH1.2m SD Release
0	0.0	0.00	0.0	0.00	0.0	0.00
15	2.7	0.13	1.2	0.10	1.6	0.05
30	3.1	0.03	1.8	0.17	2.3	0.05
45	3.7	0.06	2.1	0.08	2.7	0.05
75	4.3	0.09	3.0	0.15	3.5	0.01
105	4.3	0.09	3.6	0.36	4.0	0.01
135	4.8	0.08	4.2	0.12	4.6	0.05
180	5.3	0.09	4.8	0.26	5.3	0.01
240	6.1	0.07	5.7	0.43	6.1	0.01
300	6.7	0.05	6.6	0.20	6.9	0.08
360	7.3	0.12	7.4	0.62	7.6	0.04
420	7.9	0.08	7.7	0.34	8.2	0.09
480	8.1	0.14			8.9	0.09

Table 9.1.68: Dissolution Formulation GDB75 (% Release), Impact Medium pH° and Ionic Strength° on Drug Release, USP 2 Apparatus

Time [min]	GDB75 pH1.2 Release [%]	GDB75 pH1.2 SD Release	GDB75 pH6.8 Release [%]	GDB75 pH6.8 SD Release	GDB75 pH1.2m Release [%]	GDB75 pH1.2m SD Release
0	0.0	0.00	0.0	0.00	0.0	0.00
15	8.3	0.24	6.6	0.18	7.4	0.23
30	12.2	0.12	10.0	0.11	11.3	0.17
45	15.1	0.40	12.3	0.48	14.3	0.17
75	19.5	0.28	16.1	0.35	18.9	0.12
105	22.6	0.08	18.9	0.17	22.4	0.07
135	24.9	0.55	20.9	0.19	25.3	0.11
180	28.0	0.58	23.6	0.68	28.7	0.21
240	31.5	0.76	27.1	0.51	32.5	0.24
300	34.8	0.67	29.6	0.20	35.7	0.26
360	37.4	0.87	33.1	0.61	38.7	0.19
420	40.2	0.99	35.6	0.61	41.5	0.19
480	42.6	1.4	37.5	0.40	44.2	0.19

° **pH1.2: Simulating Gastric Fluid sine pepsine USP24 pH1.2 (J=0.1mol/l)**
pH6.8: Phosphate Buffer USP 26 pH6.8
pH1.2m: Modified Simulating Gastric Fluid sine pepsine pH1.2 (J=0.36mol/l)

Table 9.1.69: Dissolution Formulation GPS25 (% Release), Impact Medium pH° and Ionic Strength° on Drug Release, USP 2 Apparatus

Time [min]	GPS25 pH1.2 Release [%]	GPS25 pH1.2 SD Release	GPS25 pH6.8 Release [%]	GPS25 pH6.8 SD Release	GPS25 pH1.2m Release [%]	GPS25 pH1.2m SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	2.7	0.2	2.2	0.0	2.2	0.0
30	3.2	0.2	3.0	0.1	3.0	0.1
45	3.6	0.3	3.6	0.1	3.6	0.1
75	4.4	0.5	4.6	0.1	4.6	0.1
105	5.0	0.6	5.5	0.1	5.5	0.1
135	5.5	0.7	6.3	0.3	6.3	0.3
180	6.3	0.8	7.5	0.5	7.5	0.5
240	7.2	1.0	9.0	1.0	9.0	1.0
300	8.0	1.3	10.7	1.7	10.7	1.7
360	8.9	1.5	12.5	2.4	12.5	2.4
420	9.8	1.7	14.1	3.0	14.1	3.0
480	10.5	2.0	16.0	3.6	16.0	3.6

Table 9.1.70: Dissolution Formulation GPS75 (% Release), Impact Medium pH° and Ionic Strength° on Drug Release, USP 2 Apparatus

Time [min]	GPS75 pH1.2 Release [%]	GPS75 pH1.2 SD Release	GPS75 pH6.8 Release [%]	GPS75 pH6.8 SD Release	GPS75 pH1.2m Release [%]	GPS75 pH1.2m SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	4.5	0.1	4.5	0.1	4.2	0.8
30	5.8	0.2	6.4	0.1	6.0	0.8
45	6.7	0.2	7.9	0.1	7.2	0.9
75	8.3	0.2	10.4	0.0	8.9	1.0
105	9.4	0.2	12.5	0.1	10.3	1.1
135	10.4	0.2	14.4	0.0	11.5	1.2
180	11.9	0.3	17.2	0.1	13.2	1.3
240	13.8	0.2	20.6	0.1	15.3	1.4
300	15.6	0.3	23.8	0.2	17.3	1.6
360	17.6	0.3	27.1	0.0	19.3	1.7
420	18.8	0.5	30.0	0.2	21.3	1.7
480	20.8	0.6	33.0	0.4	23.3	1.8

° **pH1.2: Simulating Gastric Fluid sine pepsine USP24 pH1.2 (J=0.1mol/l)**
pH6.8: Phosphate Buffer USP 26 pH6.8
pH1.2m: Modified Simulating Gastric Fluid sine pepsine pH1.2 (J=0.36mol/l)

Table 9.1.71: Dissolution Formulation SUS25 (% Release), Impact Medium pH° and Ionic Strength° on Drug Release, USP 2 Apparatus

Time [min]	SUS25 pH1.2 Release [%]	SUS25 pH1.2 SD Release	SUS25 pH6.8 Release [%]	SUS25 pH6.8 SD Release	SUS25 pH1.2m Release [%]	SUS25 pH1.2m SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	6.7	0.7	5.5	0.2	3.4	1.4
30	8.6	0.7	7.7	0.2	5.8	1.4
45	10.2	0.8	9.6	0.2	7.7	1.3
75	12.6	0.4	12.5	0.3	10.6	1.4
105	14.6	0.3	14.9	0.4	12.9	1.4
135	16.5	0.4	16.7	0.5	14.8	1.3
205	19.9	0.5	20.4	0.6	17.1	1.3
240	21.4	0.5	22.0	0.7	19.8	1.3
300	23.4	0.6	24.4	0.6	22.0	1.2
360	25.3	0.5	26.8	0.7	24.0	1.2
420	26.7	0.7	28.7	0.8	25.8	1.2
480	28.1	0.5	30.3	1.1	27.5	1.3

Table 9.1.72: Dissolution Formulation SUS75 (% Release), Impact Medium pH° and Ionic Strength° on Drug Release, USP 2 Apparatus

Time [min]	SUS75 pH1.2 Release [%]	SUS75 pH1.2 SD Release	SUS75 pH6.8 Release [%]	SUS75 pH6.8 SD Release	SUS75 pH1.2m Release [%]	SUS75 pH1.2m SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	8.1	0.3	7.3	0.3	7.9	0.5
30	11.3	0.2	10.3	0.3	11.3	1.1
45	13.6	0.2	13.4	0.6	14.0	0.3
75	17.0	0.1	16.0	0.6	22.6	2.0
105	19.8	0.1	18.3	0.5	25.9	2.2
135	22.0	0.2	20.4	0.6	27.5	1.8
180	24.9	0.2	22.9	0.6	31.4	1.6
240	28.4	0.1	25.9	0.8	35.0	1.6
300	31.4	0.2	28.4	0.9	38.0	1.3
360	34.0	0.3	30.5	0.8	40.7	1.3
420	36.1	0.3	32.3	1.1	43.1	1.0
480	38.0	0.3	33.9	1.0	45.4	0.8

° **pH1.2: Simulating Gastric Fluid sine pepsine USP24 pH1.2 (J=0.1mol/l)**
pH6.8: Phosphate Buffer USP 26 pH6.8
pH1.2m: Modified Simulating Gastric Fluid sine pepsine pH1.2 (J=0.36mol/l)

Table 9.1.73: Dissolution Formulation HPC25 (% Release), Impact Medium pH° and Ionic Strength° on Drug Release, USP 2 Apparatus

Time [min]	HPC25 pH1.2 Release [%]	HPC25 pH1.2 SD Release	HPC25 pH6.8 Release [%]	HPC25 pH6.8 SD Release	HPC25 pH1.2m Release [%]	HPC25 pH1.2m SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	6.6	0.4	6.1	0.7	6.4	0.3
30	10.0	0.6	9.6	1.0	10.0	0.4
45	13.0	0.9	11.8	1.6	12.8	0.7
75	18.2	1.2	16.6	2.3	17.9	1.3
105	23.2	1.4	21.2	3.2	22.3	1.8
135	28.0	2.0	25.5	3.7	26.4	2.4
180	34.5	2.5	31.5	4.8	32.3	3.3
240	42.5	3.3	39.1	6.2	39.5	4.4
300	49.6	3.7	46.0	7.6	45.9	5.2
360	56.2	3.6	52.7	8.4	51.9	5.9
420	62.4	4.1	58.9	9.0	57.4	6.5
480	68.1	5.1	64.6	9.5	62.8	6.9

Table 9.1.74: Dissolution Formulation HPC75 (% Release), Impact Medium pH° and Ionic Strength° on Drug Release, USP 2 Apparatus

Time [min]	HPC75 pH1.2 Release [%]	HPC75 pH1.2 SD Release	HPC75 pH6.8 Release [%]	HPC75 pH6.8 SD Release	HPC75 pH1.2m Release [%]	HPC75 pH1.2m SD Release
0	0.0	0.0	0.0	0.0	0.0	0.0
15	13.2	0.8	11.0	2.1	11.6	0.9
30	23.3	2.6	21.1	3.1	21.7	1.8
75	50.0	4.1	46.8	6.9	47.8	4.5
105	64.0	4.7	60.6	8.0	61.4	5.8
180	88.3	3.5	84.4	7.6	85.2	6.4
240	96.0	1.0	94.0	4.4	96.1	4.4
300	98.4	0.7	97.9	1.8	100.4	1.5
360	96.9	0.1	99.2	1.5	101.5	0.3
420	97.5	0.2	99.5	1.4	101.7	0.2
480	98.0	0.2	99.8	1.3	101.9	0.3

° **pH1.2: Simulating Gastric Fluid sine pepsine USP24 pH1.2 (J=0.1mol/l)**
pH6.8: Phosphate Buffer USP 26 pH6.8
pH1.2m: Modified Simulating Gastric Fluid sine pepsine pH1.2 (J=0.36mol/l)

Table 9.1.75: Dissolution Formulation GDB25 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GDB25 (25°C/60%rh) Release [%]	GDB25 (25°C/60%rh) SD Release	GDB25 (40°C/30%rh) Release [%]	GDB25 (40°C/30%rh) SD Release
0	0.0	0.00	0.0	0.00
15	1.3	0.03	0.3	0.04
30	2.1	0.05	0.6	0.07
75	3.3	0.07	1.2	0.01
105	3.9	0.10	1.4	0.04
180	5.1	0.11	1.8	0.07
240	5.9	0.10	2.0	0.04
300	6.6	0.17	2.2	0.02
360	7.3	0.16	2.5	0.02
420	8.0	0.18	2.6	0.04
480	8.5	0.16	2.7	0.01
540	9.2	0.19	2.9	0.09
600	9.7	0.18	3.0	0.05
660	10.2	0.18	3.1	0.05
720	10.7	0.26	3.2	0.08

Table 9.1.76: Dissolution Formulation GDB50 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GDB50 (25°C/60%rh) Release [%]	GDB50 (25°C/60%rh) SD Release	GDB50 (40°C/30%rh) Release [%]	GDB50 (40°C/30%rh) SD Release
0	0.0	0.00	0.0	0.00
15	3.1	0.08	1.6	0.05
30	4.5	0.09	2.7	0.12
75	6.9	0.09	4.7	0.07
105	8.3	0.05	5.7	0.13
180	10.7	0.13	7.2	0.09
240	12.3	0.05	8.1	0.10
300	13.6	0.15	8.9	0.08
360	14.9	0.13	9.6	0.15
420	16.0	0.13	10.3	0.07
480	17.2	0.14	10.9	0.07
540	18.3	0.19	11.4	0.11
600	19.2	0.16	11.9	0.11
660	20.2	0.24	12.4	0.11
720	21.2	0.28		

Table 9.1.77: Dissolution Formulation GDB75 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GDB75 (25°C/60%rh) Release [%]	GDB75 (25°C/60%rh) SD Release	GDB75 (40°C/30%rh) Release [%]	GDB75 (40°C/30%rh) SD Release
0	0.0	0.00	0.0	0.00
15	6.6	0.19	6.3	0.07
30	10.1	0.25	9.7	0.09
75	16.8	0.22	15.9	0.17
105	20.1	0.23	18.7	0.20
180	26.2	0.32	24.0	0.19
240	30.1	0.40	27.4	0.31
300	33.4	0.48	30.4	0.34
360	36.2	0.57	33.0	0.41
420	38.7	0.67	35.4	0.42
480	41.1	0.68	37.6	0.43
540	43.4	0.66	39.7	0.47
600	45.5	0.68	41.7	0.56
660	47.7	0.74	43.6	0.56
720	49.9	0.74	45.4	0.57

Table 9.1.78: Dissolution Formulation GPS25 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GPS25 (25°C/60%rh) Release [%]	GPS25 (25°C/60%rh) SD Release	GPS25 (40°C/30%rh) Release [%]	GPS25 (40°C/30%rh) SD Release
0	0.0	0.0	0.0	0.0
15	1.1	0.1	0.5	0.4
30	1.8	0.1	0.6	0.4
75	3.3	0.1	0.7	0.2
105	4.1	0.1	1.0	0.3
180	5.7	0.1	1.8	0.4
240	6.7	0.2	2.5	0.5
300	7.8	0.2	3.2	0.5
360	8.8	0.3	4.0	0.5
420	9.8	0.3	4.8	0.5
480	10.8	0.3	5.6	0.6
540	11.8	0.3	6.5	0.6
600	12.8	0.5	7.5	0.6
660	13.9	0.5	8.3	0.6
720	14.9	0.6	9.2	0.7

Table 9.1.79: Dissolution Formulation GPS50 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GPS50 (25°C/60%rh) Release [%]	GPS50 (25°C/60%rh) SD Release	GPS50 (40°C/30%rh) Release [%]	GPS50 (40°C/30%rh) SD Release
0	0.0	0.0	0.0	0.0
15	1.6	0.1	0.2	0.0
30	2.7	0.1	0.4	0.0
75	4.7	0.1	1.1	0.1
105	5.7	0.1	1.8	0.2
180	7.7	0.1	3.4	0.4
240	9.0	0.1	5.0	0.7
300	10.3	0.1	6.8	0.9
360	11.5	0.1	8.8	1.1
420	12.8	0.1	11.0	1.3
480	14.0	0.1	13.2	1.6
540	15.1	0.3	15.5	1.6
600	16.3	0.2	17.7	1.9
660	17.6	0.2	20.2	1.9
720	18.9	0.3	22.7	1.8

Table 9.1.80: Dissolution Formulation GPS75 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	GPS75 (25°C/60%rh) Release [%]	GPS75 (25°C/60%rh) SD Release	GPS75 (40°C/30%rh) Release [%]	GPS75 (40°C/30%rh) SD Release
0	0.0	0.0	0.0	0.0
15	3.1	0.4	0.2	0.1
30	5.6	0.4	0.5	0.1
75	10.4	0.5	1.3	0.1
105	12.9	0.5	1.9	0.1
180	17.9	0.5	4.8	2.0
240	21.4	0.5	8.6	5.2
300	24.8	0.6	12.2	6.8
360	28.1	0.6	17.0	7.5
420	31.3	0.6	21.3	8.2
480	34.6	0.7	25.8	8.6
540	37.7	0.8	31.2	8.8
600	40.9	0.9	36.5	9.1
660	43.9	0.9	41.2	9.1
720	46.9	1.0	45.6	8.9

Table 9.1.81: Dissolution Formulation SUS25 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	SUS25 (25°C/60%rh) Release [%]	SUS25 (25°C/60%rh) SD Release	SUS25 (40°C/30%rh) Release [%]	SUS25 (40°C/30%rh) SD Release
0	0.0	0.0	0.0	0.0
15	4.8	0.0	4.5	0.0
30	7.3	0.0	7.0	0.1
75	12.3	0.2	12.2	0.2
105	14.6	0.3	14.8	0.3
180	19.3	0.4	19.8	0.3
240	22.3	0.5	23.3	0.3
300	25.0	0.6	26.4	0.4
360	27.5	0.6	29.2	0.5
421	29.7	0.7	31.8	0.5
480	31.8	0.8	34.3	0.5
540	33.8	0.8	36.6	0.6
600	35.6	1.0	38.8	0.6
660	37.4	1.0	40.9	0.6
720	39.1	1.1	42.9	0.7

Table 9.1.82: Dissolution Formulation SUS50 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	SUS50 (25°C/60%rh) Release [%]	SUS50 (25°C/60%rh) SD Release	SUS50 (40°C/30%rh) Release [%]	SUS50 (40°C/30%rh) SD Release
0	0.0	0.0	0.0	0.0
15	3.4	0.3	3.6	0.2
30	5.0	0.3	5.6	0.2
75	8.2	0.5	9.6	0.3
105	9.7	0.6	11.6	0.3
180	12.8	0.7	15.1	0.4
240	14.8	0.7	17.0	0.4
300	16.6	0.8	18.7	0.4
360	18.2	0.8	20.2	0.4
420	19.6	0.8	21.6	0.4
480	21.0	0.8	22.9	0.4
540	22.3	0.8	24.1	0.4
600	23.4	0.9	25.3	0.4
660	24.5	0.8	26.4	0.4
720	25.6	0.9	27.4	0.4

Table 9.1.83: Dissolution Formulation SUS75 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	SUS75 (25°C/60%rh) Release [%]	SUS75 (25°C/60%rh) SD Release	SUS75 (40°C/30%rh) Release [%]	SUS75 (40°C/30%rh) SD Release
0	0.0	0.0	0.0	0.0
15	6.2	2.8	7.9	0.3
30	11.1	1.9	12.3	0.4
75	18.4	1.0	20.2	0.5
105	21.0	1.0	23.8	0.6
180	26.0	0.9	30.4	0.7
240	29.3	0.5	34.1	0.7
300	31.9	0.6	36.6	0.8
360	34.1	0.8	38.6	0.8
420	36.2	0.7	40.4	0.8
480	38.1	0.6	42.1	0.9
540	39.8	0.6	43.6	0.9
600	41.5	0.6	45.0	1.0
660	42.9	0.7	46.3	1.0
720	44.3	0.6	47.6	1.0

Table 9.1.84: Dissolution Formulation HPC50 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	HPC50 (25°C/60%rh) Release [%]	HPC50 (25°C/60%rh) SD Release	HPC50 (40°C/30%rh) Release [%]	HPC50 (40°C/30%rh) SD Release
0	0.0	0.0	0.0	0.0
15	6.9	0.3	7.5	0.5
30	11.8	0.5	13.1	1.0
45	16.1	0.7	18.3	1.5
75	24.4	1.0	28.4	2.7
105	32.3	1.4	37.6	3.6
135	39.4	1.5	46.1	4.3
180	49.7	1.6	57.7	5.3
240	61.7	1.4	71.3	6.2
300	72.4	1.2	82.3	6.3
360	81.3	1.0	90.7	5.6
420	88.7	0.7	96.1	3.6
480	94.6	0.6	99.3	1.4
540	98.9	0.5	100.4	1.0
600	101.3	0.7	100.8	0.9
660	101.7	0.9	101.0	1.0
720	102.0	0.8	101.3	1.0

Table 9.1.85: Dissolution Formulation HPC75 (% Release), one-year Stability of Drug Release under two different storage conditions, Phosphate Buffer USP 26 pH6.8, USP 2 Apparatus

Time [min]	HPC75 (25°C/60%rh) Release [%]	HPC75 (25°C/60%rh) SD Release	HPC75 (40°C/30%rh) Release [%]	HPC75 (40°C/30%rh) SD Release
0	0.0	0.0	0.0	0.0
15	11.3	0.7	13.9	0.4
30	21.7	1.6	26.9	0.4
75	48.1	3.5	58.8	0.1
105	62.0	4.6	74.0	0.2
180	86.3	4.7	96.4	0.1
240	96.9	2.8	99.9	0.3
300	100.4	0.2	100.1	0.2
360	100.9	0.4	100.3	0.3
420	101.2	0.4	100.6	0.2
480	101.4	0.4	100.8	0.2
540	101.6	0.4	101.0	0.2

Table 9.1.86: Dissolution Formulation GDB25 [% Released], Impact of Food Components on Drug Release (Fasted State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	GDB25 CompFasted		GDB25 BioFasted	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
30	2.2	0.0	3.2	0.1
60	3.0	0.1	4.3	0.1
75	3.5	0.1	5.1	0.2
90	3.9	0.1	5.7	0.2
120	4.6	0.1	6.8	0.2
180	5.6	0.2	8.3	0.3
240	6.4	0.3	9.4	0.3
300	7.4	0.3	10.5	0.4
420	9.0	0.5	12.0	0.4
540	10.3	0.7	13.4	0.4
660	11.5	0.8	14.7	0.5
840	12.9	1.1	16.2	0.5
1020	14.3	1.2	17.7	0.6
1200	15.8	1.3	19.1	0.6

Table 9.1.87: Dissolution Formulation GDB75 [% Released], Impact of Food Components on Drug Release (Fasted State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	GDB75 CompFasted		GDB75 BioFasted	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
30	11.9	0.6	14.1	0.1
60	16.7	1.0	20.5	0.4
75	18.7	1.4	23.9	0.6
90	20.5	1.5	26.3	0.6
120	24.0	1.2	30.4	0.6
180	29.4	0.9	36.4	0.6
240	33.3	1.0	40.9	0.6
300	36.6	0.9	44.5	0.6
420	41.4	0.9	49.9	0.5
540	46.3	0.6	54.2	0.5
660	51.8	1.4	58.2	0.4
840	57.8	1.2	65.0	0.4
1020	64.6	2.0	72.0	0.4
1200	70.1	2.4	77.8	0.7

Table 9.1.88: Dissolution Formulation GPS25 [% Released], Impact of Food Components on Drug Release (Fasted State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	GPS25 CompFasted		GPS25 BioFasted	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
30	2.7	0.2	3.6	0.1
60	3.6	0.1	5.0	0.1
75	4.2	0.1	6.0	0.1
90	4.7	0.2	6.9	0.1
120	5.5	0.2	8.3	0.1
180	6.9	0.2	9.9	0.2
240	8.2	0.2	11.2	0.2
300	9.4	0.2	12.4	0.3
420	11.5	0.2	14.4	0.2
540	13.5	0.2	16.3	0.3
660	15.8	0.3	18.3	0.3
840	19.6	0.7	21.6	0.6
1020	24.1	0.8	23.3	3.2
1200	30.2	1.4	28.3	3.2

Table 9.1.89: Dissolution Formulation GPS75 [% Released], Impact of Food Components on Drug Release (Fasted State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	GPS75 CompFasted		GPS75 BioFasted	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
30	7.0	0.2	12.2	0.1
60	9.3	0.3	18.8	0.1
75	10.8	0.3	22.1	0.1
90	12.3	0.3	24.9	0.1
120	15.0	0.3	29.0	0.2
180	19.6	0.3	34.0	0.1
240	23.6	0.3	37.5	0.1
300	27.6	0.9	40.5	0.1
420	34.7	2.6	46.4	0.5
540	41.6	4.5	52.9	1.8
660	48.1	5.7	59.8	2.6
840	57.8	4.9	69.0	2.0
1020	66.9	3.3	76.4	1.6
1200	74.0	2.1	82.2	1.5

Table 9.1.90: Dissolution Formulation SUS25 [% Released], Impact of Food Components on Drug Release (Fasted State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	SUS25 CompFasted		SUS25 BioFasted	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
30	7.5	0.3	7.4	0.0
60	11.4	0.3	11.1	0.1
75	13.3	0.3	12.8	0.1
90	14.9	0.3	14.4	0.1
120	17.5	0.4	17.2	0.2
180	22.0	0.5	21.5	0.1
240	25.9	0.6	25.1	0.1
300	29.1	0.7	28.1	0.2
420	34.1	0.7	32.8	0.6
540	38.4	0.7	36.9	0.8
660	42.1	0.7	40.6	1.0
840	47.1	0.7	45.6	1.2
1020	51.8	0.8	50.5	0.8
1200	56.1	0.8	55.1	0.7

Table 9.1.91: Dissolution Formulation SUS75 [% Released], Impact of Food Components on Drug Release (Fasted State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	SUS75 CompFasted		SUS75 BioFasted	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
30	14.6	0.3	16.6	0.2
60	20.2	0.5	23.4	0.4
75	22.8	0.4	26.8	0.4
90	24.8	0.3	29.4	0.3
120	28.3	0.2	33.6	0.3
180	33.7	0.1	39.5	0.5
240	38.7	0.1	43.8	0.4
300	42.5	0.2	47.1	0.3
420	48.8	0.5	52.6	0.3
540	54.4	0.6	57.5	0.5
660	59.4	0.5	62.1	0.7
840	65.7	0.4	68.1	1.1
1020	71.9	0.6	73.9	1.6
1200	77.1	0.8	78.9	2.0

Table 9.1.92: Dissolution Formulation HPC25 [% Released], Impact of Food Components on Drug Release (Fasted State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	HPC25 CompFasted		HPC25 BioFasted	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
30	15.1	0.4	15.9	1.1
60	25.9	0.7	29.4	2.7
75	31.6	1.1	35.1	3.0
90	36.8	1.3	40.3	2.9
120	45.4	1.4	48.7	3.1
180	60.5	0.6	63.2	3.4
240	73.0	0.6	75.6	3.8
300	82.9	2.5	87.7	4.0
420	94.6	5.0	101.2	3.7
540	98.0	4.4	102.8	3.2
840	98.3	4.4	102.8	3.2
1200	98.3	4.4	102.8	3.2

Table 9.1.93: Dissolution Formulation HPC75 [% Released], Impact of Food Components on Drug Release (Fasted State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	HPC75 CompFasted		HPC75 BioFasted	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
30	57.1	2.2	55.6	0.9
60	91.0	3.4	91.7	1.3
75	100.3	1.5	100.1	2.0
90	102.9	0.4	103.2	1.8
120	103.1	0.4	103.2	1.8
180	103.4	0.3	103.2	1.8
240	103.7	0.3	103.4	1.9

Table 9.1.94: Dissolution Formulation GDB25 [% Released], Impact of Food Components on Drug Release (Fed State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	GDB25 CompFed		GDB25 BioFed	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	3.5	0.0	2.4	0.3
120	4.8	0.0	3.0	0.2
180	6.1	0.0	4.0	0.3
240	6.9	0.1	4.4	0.4
255	7.4	0.1	5.0	0.4
270	7.5	0.1	5.4	0.4
300	7.9	0.1	6.2	0.4
420	9.4	0.2	8.4	0.5
540	10.6	0.2	9.1	0.5
660	11.7	0.2	10.4	0.3
840	13.3	0.2	12.4	0.4
1020	14.7	0.3	14.2	0.5
1200	16.1	0.3	15.8	0.7

Table 9.1.95: Dissolution Formulation GDB75 [% Released], Impact of Food Components on Drug Release (Fed State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	GDB75 CompFed		GDB75 BioFed	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	16.6	0.4	10.4	0.2
120	24.7	0.6	16.9	0.1
180	30.8	0.6	21.5	0.7
240	35.2	0.8	23.7	0.8
255	36.4	0.8	25.6	0.9
270	37.7	0.8	27.5	1.0
300	39.7	0.9	30.8	1.2
420	45.5	0.7	40.8	1.7
540	50.5	0.4	47.2	2.1
660	55.9	0.5	52.4	2.6
840	64.7	2.3	60.3	3.7
1020	73.5	3.5	68.9	4.1
1200	80.7	4.0	76.6	3.9

Table 9.1.96: Dissolution Formulation GPS25 [% Released], Impact of Food Components on Drug Release (Fed State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	GPS25 CompFed		GPS25 BioFed	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	3.7	0.2	2.3	0.1
120	4.9	0.3	3.1	0.2
180	6.1	0.4	3.5	0.2
240	6.9	0.6	4.1	0.1
255	7.3	0.6	4.6	0.1
270	7.6	0.7	5.2	0.1
300	8.2	0.7	6.3	0.1
420	11.3	1.0	9.0	0.2
540	14.6	1.4	11.1	0.3
660	17.6	1.1	13.0	0.4
840	23.3	0.6	15.6	0.5
1020	30.0	2.8	18.5	0.7
1200	38.2	4.1	22.0	0.8

Table 9.1.97: Dissolution Formulation GPS75 [% Released], Impact of Food Components on Drug Release (Fed State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	GPS75 CompFed		GPS75 BioFed	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	10.3	0.3	8.8	0.3
120	14.6	0.3	12.6	0.3
180	18.3	0.4	16.0	0.2
240	21.3	0.5	18.8	0.2
255	22.4	0.6	20.6	0.1
270	23.3	0.6	22.6	0.1
300	25.1	0.6	26.2	0.1
420	32.6	0.7	35.1	0.3
540	40.0	1.5	41.9	0.8
660	47.0	3.2	49.2	2.7
840	56.8	4.1	60.3	3.2
1020	66.6	3.2	69.8	2.6
1200	74.5	2.4	77.3	2.1

Table 9.1.98: Dissolution Formulation SUS25 [% Released], Impact of Food Components on Drug Release (Fed State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	SUS25 CompFed		SUS25 BioFed	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	11.2	0.4	7.6	0.1
120	15.9	0.4	10.3	0.4
180	19.7	0.4	12.3	0.4
240	22.3	0.6	14.0	0.3
255	23.0	0.5	15.0	0.3
270	24.0	0.6	16.2	0.4
300	25.5	0.6	19.3	0.5
360	30.6	0.7	25.9	0.4
540	35.0	0.8	41.5	1.4
660	38.9	1.0	48.3	1.7
840	44.2	1.5	56.5	2.1
1020	49.0	2.1	64.7	2.3
1200	54.1	2.8	72.0	2.4

Table 9.1.99: Dissolution Formulation SUS75 [% Released], Impact of Food Components on Drug Release (Fed State), Compendial and Biorelevant Media, USP 3 Apparatus

Time [min]	SUS75 CompFed		SUS75 BioFed	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0	0.0
60	22.8	1.1	60	0.0
120	31.2	2.0	120	20.5
180	38.8	2.4	180	20.6
240	44.2	2.7	240	32.0
255	45.9	2.7	255	36.1
270	47.2	2.7	270	41.2
300	49.7	2.7	300	50.8
360	54.7	2.5	360	65.0
420	60.7	1.8	420	77.5
540	68.8	1.3	540	90.9
660	75.3	2.4	660	97.9
840	84.5	5.7	840	103.1
1020	91.7	9.5	1020	103.8

Table 9.1.100: Dissolution Formulation HPC25 and HPC75 [% Released], Impact of Food Components on Drug Release (Fed State), Compendial Media, USP 3 Apparatus

Time [min]	HPC25 CompFed		HPC75 CompFed	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	20.8	1.2	81.6	2.3
120	38.6	1.6	99.2	0.7
180	53.1	2.2	100.8	0.6
240	65.4	3.1	100.5	0.6
255	68.9	3.3	100.6	0.6
270	72.5	3.5	100.6	0.6
300	80.3	4.0	100.6	0.6
420	98.2	6.0	100.6	0.6
540	100.2	5.5	100.6	0.6
660	100.8	5.4		
840	101.0	5.4		
1020	101.1	5.4		
1200	101.2	5.4		

Table 9.1.101: Dissolution Formulation GDB25 and GDB75 [% Released], Impact of Hydrodynamics on Drug Release (Fed State), Compendial Media, USP 3 Apparatus with Disc

Time [min]	GDB25 CompFed Disc		GDB75 CompFed Disc	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	3.6	0.2	22.5	4.8
120	4.9	0.2	32.2	1.8
180	6.3	0.3	43.2	3.8
240	7.3	0.3	53.2	6.7
255	7.7	0.3	56.0	7.6
270	7.9	0.3	58.9	8.4
300	8.3	0.3	64.3	10.2
420	9.8	0.3	82.9	17.6
540	11.2	0.3	97.2	12.0
660	12.4	0.4	103.5	0.6
840	14.2	0.5	103.7	0.2
1020	15.9	0.7	103.7	0.2
1200	17.5	0.8	103.7	0.2

Table 9.1.102: Dissolution Formulation GPS25 and GPS75 [% Released], Impact of Hydrodynamics on Drug Release (Fed State), Compendial Media, USP 3 Apparatus with Disc

Time [min]	GPS25 CompFed Disc		GPS75 CompFed Disc	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	3.7	0.1	12.6	0.2
120	4.8	0.1	22.4	0.5
180	6.0	0.2	33.5	0.9
240	6.9	0.2	44.7	1.2
255	7.3	0.3	48.3	1.3
270	7.6	0.3	51.6	1.5
300	8.2	0.3	58.7	1.6
420	11.1	0.6	92.1	2.5
540	14.3	0.5	93.8	2.4
660	17.2	0.7	93.8	2.4
840	21.8	1.3	93.8	2.4
1020	27.5	2.7	93.8	2.4
1200	34.2	4.9	93.8	2.4

Table 9.1.103: Dissolution Formulation SUS25 and SUS75 [% Released], Impact of Hydrodynamics on Drug Release (Fed State), Compendial Media, USP 3 Apparatus with Disc

Time [min]	SUS25 CompFed Disc		SUS75 CompFed Disc	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	16.4	1.7	39.1	3.5
120	28.4	4.8	56.5	7.1
180	39.6	6.3	69.6	8.7
240	48.6	6.9	79.2	9.1
255	51.1	7.0	82.2	9.3
270	53.9	7.0	85.0	9.3
300	59.3	7.1	90.4	9.3
360	73.4	7.5	97.8	6.7
540	81.7	8.5	101.7	1.5
660	88.3	10.8	102.6	1.3
840	93.0	10.8	103.2	2.0
1020	94.7	9.3	104.5	4.3
1200	96.0	8.0	104.6	4.3

Table 9.1.104: Dissolution Formulation HPC25 and HPC75 [% Released], Impact of Hydrodynamics on Drug Release (Fed State), Compendial Media, USP 3 Apparatus with Disc

Time [min]	HPC25 CompFed Disc		HPC75 CompFed Disc	
	Release [%]	SD Release	Release [%]	SD Release
0	0.0	0.0	0.0	0.0
60	26.4	3.8	67.2	11.9
120	44.8	5.5	90.0	7.1
180	63.2	9.2	99.5	1.9
240	80.2	13.6	101.6	0.2
255	84.3	14.5	102.0	0.1
270	87.3	14.5	102.0	0.1
300	91.9	13.2	102.0	0.1
420	98.6	6.1	102.0	0.1
540	100.8	4.4	102.0	0.1
660	101.2	4.4		
840	101.4	4.4		
1020	101.6	4.4		
1200	101.6	4.4		

Table 9.1.105: Theophylline Plasma Levels after Fasted Administration of SUS25 in four dogs

Time [h]	Theophylline Plasma Level [ng/ml] SUS25 Fasted Administration					
	Dog 1 (03AF1)	**Dog 2 (03EI3)**	**Dog 3 (03IE5)**	**Dog 4 (99DM4)**	**Mean**	**SD**
0.25	81.3	39	81.5	159	90.2	50
0.5	272	184	220	746	356	263
0.75	381	355	787	1200	681	399
1	504	586	1150	1730	993	569
1.5	641	957	1910	2840	1587	994
2	1480	1150	2620	3670	2230	1148
2.5	1550	1400	2790	4050	2448	1237
3	1560	1750	2750	4280	2585	1245
4	2230	2030	3040	5050	3088	1379
5	2680	2280	2770	5240	3243	1349
6	2050		2070		2060	14
9		1010		2140	1575	799
10	1550		3320		2435	1252
24		962		228	595	519
25	188		1150		669	680

Table 9.1.106: Theophylline Plasma Levels after Fed Administration of SUS25 in four dogs

Time [h]	Theophylline Plasma Level [ng/ml] SUS25 Fed Administration					
	Dog 1 (03AF1)	**Dog 2 (03EI3)**	**Dog 3 (03IE5)**	**Dog 4 (99DM4)**	**Mean**	**SD**
0.25	170	1220	465	95.9	488	514
0.5	495	1650	751	708	901	512
0.75	721	2560	826	896	1251	876
1	1240	4050	1180	1340	1953	1400
1.5	2080	4080	1930	2800	2723	981
2	2990	5250	2120	4010	3593	1348
2.5	4250	5200	2300	5070	4205	1338
3	4990	5750	5120	5200	5265	335
4	5570	5840	6330	4740	5620	666
5	5800	5800	4050	4170	4955	977
9.5		2750		1360	2055	983
10	2590		1360		1975	870
24	553	798	90.2	300	435	307

Table 9.1.107: Theophylline Plasma Levels after Fasted Administration of SUS75 in four dogs

Time [h]	Theophylline Plasma Level [ng/ml] SUS25 Fasted Administration					
	Dog 1 (03AF1)	Dog 2 (03EI3)	Dog 3 (03IE5)	Dog 4 (99DM4)	Mean	SD
0.25	1430	490	291	189	600	567
0.5	2290	501	506	543	960	887
0.75	3260	1250	813	1050	1593	1125
1	3220	2550	939	3090	2450	1048
1.5	3530	3940	1540	5530	3635	1642
2	3920	5730	1890	6610	4538	2090
2.5	3830	6680	2070	7370	4988	2476
3	3810	6660	3820	8650	5735	2361
4	3640	6000	4940	7250	5458	1536
5	3260	5710	5300	6080	5088	1259
6		3960		4050	4005	64
9	1730		2570		2150	594
10		1770		1480	1625	205
24	243		373		308	92
25		252		272	262	14

Table 9.1.108: Theophylline Plasma Levels after Fed Administration of SUS75 in four dogs

Time [h]	Theophylline Plasma Level [ng/ml] SUS25 Fasted Administration					
	Dog 1 (03AF1)	Dog 2 (03EI3)	Dog 3 (03IE5)	Dog 4 (99DM4)	Mean	SD
0.25	22.6	90	316	130	139.65	126
0.5	18	728	1210	773	682	493
0.75	25	1340	1390	1210	991	649
1	48.8	2160	1880	1370	1365	936
1.5	84.5	2870	2010	2400	1841	1223
2	240	3390	2480	4740	2713	1892
2.5	664	3860	2510	4960	2999	1851
3	1540	3990	3110	5120	3440	1510
4	2550	3650	4220	5950	4093	1419
5	2540	3750	4570	6040	4225	1469
9.5	3110		2910		3010	141
10		2630		1900	2265	516
24	860	721	917	417	729	224

Table 9.1.109: Theophylline Plasma Levels after i.v. Administration in four dogs and calculated pharmacokinetic parameters

Time [h]	Theophylline Plasma Level [ng/ml] i.v. Administration					
	Dog 1 (03AF1)	Dog 2 (03EI3)	Dog 3 (03IE5)	Dog 4 (99DM4)	Mean	SD
PD	BLQ	BLQ	BLQ	BLQ	BLQ	
0.08	5580	5070	4720	2540	4478	1339
0.17	4190	4080	4690	2500	3865	948
0.25	3950	3460	4640	2780	3708	785
0.33	3690	3730	4460	2460	3585	829
0.50	3800	3620	4450	2590	3615	771
0.75	3670	3490	4350	2900	3603	597
1.0	3580	3370	4290	2880	3530	585
1.5	3450	3100	4100	3240	3473	442
2.0	3090	2890	3960	3170	3278	470
3.0	2680	2870	3680	3060	3073	434
5.0	2370	2160	2980	2340	2463	357
10.0	930	920	1490	898	1060	287
24.0	80.3	156	235	165	159	63

10 Zusammenfassung

Die Schmelzextrusion bietet eine weite Spanne möglicher Anwendungen für pharmazeutische Zwecke. Bisher findet die Schmelzextrusion zur Herstellung von Arzneiformen mit kontrollierter Wirkstofffreigabe zur oralen Applikation eher mäßige Anwendung, unter anderem aufgrund des Mangels an geeigneten pharmazeutischen Hilfsstoffen. Die vorliegende Arbeit zielt daher auf die Identifizierung von Matrixhilfsstoffen, die zur Schmelzextrusion geeignet sind und Wirkstofffreigabe kontrollieren. Die Eignung der Hilfsstoffe wurde bewertet basierend auf deren Eigenschaften hinsichtlich Prozessierbarkeit und Wirkstofffreigabe.

Dabei wurden sowohl gängige als auch neuartigere pharmazeutische Hilfsstoffe auf ihre Eignung untersucht. Daher wurden zur Auswahl geeigneter pharmazeutischer Hilfsstoffe drei relevante Parameter herangezogen: (i) Eignung des Hilfsstoffs als schmelzbarer Matrixbildner, (ii) der für die Schmelzextrusion geeignete Prozesstemperaturbereich und (iii) die Wirkstofffreigabeeigenschaften des pharmazeutischen Hilfsstoffs. Basierend auf der Analyse dieser Parameter wurden vier pharmazeutische Hilfsstoffe für detaillierte Untersuchungen ausgewählt. Bei der Auswahl der zu untersuchenden Hilfsstoffe wurde auch deren Molekülstruktur berücksichtigt, um eine chemisch möglichst weite Verteilung verschiedener Hilfsstoffe zu erzielen. Folgende Matrixhilfsstoffe wurden zur detaillierten Charakterisierung ausgewählt: Glyceryldibehenate (GDB), Glycerylpalimitostearate (GPS), Sucrosestearate (SUS) und Hydrxypropylcellulose (HPC).

Die vier ausgewählten Hilfsstoffe wurden als binäre Mischungen mit einem Modellwirkstoff schmelzextrudiert. Theophylline wurde als Modellwirkstoff ausgewählt. Für die Schmelzextrusionprozesse wurde in mehreren Vorversuchen im Labormaßstab eine Reihe von Parametern vorherbestimmt, wie z.B. die Prozesstemperatur, die maximale Wirkstoffbeladung, die Notwendigkeit eines Weichmachers für den Extrusionsprozess. Die so etablierten Extrusionsprozesse waren durchweg reproduzierbar. Die Schmelzextrusionsversuche zeigten die Eignung aller vier Hilfsstoffe zur Schmelzextrusion bei den untersuchten Wirkstoffbeladungen. Für jeden Matrixhilfsstoff wurden drei Formulierungen mit steigender Wirkstoffbeladung hergestellt: 25% [w/w], 50% [w/w], 75% [w/w]. Die während des Herstellungsvorgangs gebildeten Hilfsstoffmatrices waren geeignet, um bis zu 75% [w/w] einzubetten. Die Eigenschaften von GDB, GPS und SUS erlaubten eine direkte Schmelzextrusion mit Theophyllin. Lediglich für die HPC Formulierungen wurde ein Weichmacher eingesetzt um die Prozesseigenschaften der

Mischung für die Schmelzextrusion zu verbessern. Im Allgemeinen waren für die vier Matrixbildner Prozesstemperaturen unter 130°C ausreichend. Allerdings wurden jeweils unterschiedliche Prozesstemperaturen für jeden Matrixhilfsstoff angewendet. Die im Extruder gebildeten Suspensionen zeigten entweder pseudoplastisches (GDB, GPS, HPC) oder dilatantes Fließverhalten (SUS). Die erhaltenen Extrudate wurden zu Granulaten weiterverarbeitet.

Eine röntgendiffraktometrische Untersuchung der so erhaltenen Granulate bestätigte, dass der Modellwirkstoff Theophyllin auch nach der Schmelzextrusion in kristalliner Form vorlag. Aufgrund des hohen Schmelzpunkts von Theophyllin (271°C) war eine Amorphisierung der Wirksubstanz bei den angewandten moderaten Prozesstemperaturen eher unwahrscheinlich. Zur Amorphisierung der Wirksubstanz wären deutlich höhere Prozesstemperaturen notwendig gewesen.

Die so erhaltenen Granulate wurden außerdem hinsichtlich ihrer pharmzeutisch-technologischen Qualität untersucht. Dazu wurden die Partikelgrößenverteilung, die Fließeigenschaften und die Tablettiereigenschaften der Granulate untersucht. Die Granulate von GDB, GPS und SUS Formulierungen zeigten dabei pharmazeutisch–technologisch akzeptable Fließeigenschaften und Partikelgrößenverteilungen. GDB, GPS und SUS Formulierungen zeigten ihren flexiblen Nutzen für die Herstellung von Matrixtabletten über eine breite Spanne von Wirkstoffbeladungen. Aufgrund der binären, wenig optimierten Komposition der Formulierung waren die Tablettiereigenschaften durchweg ungünstig. Daher resultierten Matrixtabletten mit niedriger Bruchfestigkeit. Dennoch erfüllten die meisten GDB, GPS und SUS Matrixtabletten die vom Arzneibuch geforderten Qualitätskriterien zur Friabilität. Die HPC Granulate lieferten Matrixtabletten mit der höchsten Bruchfestigkeit. Jedoch beeinträchtigten die Fließeigenschaften der Granulate und die Form der Partikel die Qualität der Tabletten negativ. Dabei zeigten Granulate mit hohem Wirkstoffgehalt (75%, HPC75) die günstigsten Fleißeigenschaften bei geeigneter Bruchfestigkeit der resultierenden Tabletten.

Die detaillierte Untersuchung der Tablettiereigenschaften von Pulvermischungen und Granulaten mit Hilfe einer instrumentierten Tablettenpresse lieferte eine Aussage über den Einfluss des Granulierungsprozesses auf die Tablettiereigenschaften der Formulierungen. Für die schmelzextrudierten Granulate wurde eine Erhöhung der plastischen Deformierbarkeit beobachtet. Daher lieferten Granulate Tabletten mit erhöhter Bruchfestigkeit im Vergleich zu den direkt verpressten Pulvermischungen. Dabei wurden für GDB und GPS Granulate die höchsten Anteile an plastischer Deformation während des Tablettiervorgangs beobachtet. Im Kontrast dazu, führte die Granulierung von HPC Pulvermischungen mit niedrigem Wirkstoffgehalt (25%, HPC25) zu einer deutlichen Abnahme der Plastizität und einer Erhöhung der Elastizität. Daraus resultierte eine Verschlechterung der Tablettiereigenschaften für HPC25 Granulate.

Hinsichtlich der Kontrolle der Wirkstofffreigabe decken die vier Matrixhilfsstoffe einen weiten Bereich der pharmazeutisch relevanten Freisetzungsprofile ab. Während GDB and GPS die Wirkstofffreigabe über einen Zeitraum von über 20h kontrollieren können, erlauben SUS Formulierungen eine vollständige Wirkstofffreigabe innerhalb von 10 bis 12 Stunden. HPC Matrices mit niedrigem Wirkstoffgehalt (25%, HPC25) decken den Bereich der semi-retard Formulierungen ab, für die eine vollständige Wirkstofffreisetzung innerhalb <6h gewünscht ist.

Die dominierenden Mechanismen und der Einfluss des Wirkstoffgehalts auf die Wirkstofffreisetzung wurden ebenfalls untersucht. Hieraus ergeben sich potentiell Möglichkeiten die Wirkstofffreisetzung zu verändern. Dabei zeigte sich, dass Theophyllin vor allem durch Diffusionsmechanismen aus SUS Formulierungen freigegeben wurde. Im Gegensatz zu allen anderen untersuchten Matrices war die Kinetik der Wirkstofffreigabe weitgehend unabhängig vom Wirkstoffgehalt der Formulierung. Eine Modifizierung des Freisetzungsprofils von SUS Matrixtabletten könnte daher durch den Einsatz von porenbildenen Hilfsstoffen erzielt werden. Für HPC, GDB und GPS kann das Freisetzungsprofil stark durch den eingesetzten Wirkstoffgehalt verändert werden.

Ein wesentlicher Bestandteil der vorliegenden Arbeit bestand in der Charakterisierung der Wirkstofffreisetzung. Hierbei wurden verschiedene Parameter untersucht um die Robustheit der Freisetzung zu demonstrieren: (i) Lagerstabilität, (ii) Einfluss des pH-Werts des Freisetzungsmediums, (iii) Einfluss der Ionenstärke des Freisetzungsmediums, (iv) Einfluss von Nahrung und Gallensekreten und (v) Veränderungen in der Motilität/ Hydrodynamik. Als Basis für diese Untersuchungen wurde die Reproduzierbarkeit der Wirkstofffreisetzung unter standardisierten Bedingungen untersucht.

Für Matrixsysteme auf SUS Basis konnte die Reproduzierbarkeit der Freisetzung aus verschiedenen Chargen gezeigt werden. Auch nach einem Jahr Lagerung war diese unverändert. Außerdem nahmen weder der pH-Wert noch die Ionenstärke der Dissolutionmedien Einfluss auf die Wirkstofffreisetzung.

In ähnlicher Weise waren Freisetzungsprofile aus GDB und GPS Formulierungen reproduzierbar. Zwischen den HPC Matrixtabletten dagegen wurde eine stärkere Variabilität in der Wirkstofffreisetzung gezeigt, was einen deutlichen Nachteil dieses Matrixhilfsstoffs darstellt.
Die Lagerung der Tabletten hatte unterschiedlichen Einfluss auf die Wirkstofffreisetzung. Bei GDB System mit vorwiegend diffusionkontrollierter Freisetzung wurde eine Verringerung der effektiven Oberfläche gezeigt, die zu einer Verlangsamung der Freisetzung führte. Im Gegensatz dazu wurden für GPS Systeme eine Beschleunigung der Freisetzung beobachtet. Diese wurde auf eine Veränderung der Gitterstruktur innerhalb der Matrix zurückgeführt. Die Perkolationstheorie für inerte Matrices gab hierzu einen hypothetischen Denkansatz. Die Wirkstofffreisetzung aus HPC Matrixtabletten war generell auch über einen längeren Zeitraum stabil.
Bei GDB und HPC Formulierungen war die Wirkstofffreisetzung ebenfalls pH-Wert unabhängig. Eine merkliche Abhängigkeit der Theophyllinfreisetzung vom pH-Wert des Freisetzungsmediums konnte lediglich für GPS Formulierungen beobachtet werden. Die gezeigte Verlangsamung der Freisetzung bei niedrigem pH-Wert wurde auf die Protonierung der Säurefunktion eines Bestandteils des verwendeten Hilfsstoffprodukts (Precirol Ato 5) zurückgeführt. Auch die Ionenstärke der Dissolutionmedien verursachte generell keine Änderungen im Freisetzungverhalten der Formulierungen.

Die durchgeführten Dissolutiontests weisen darauf hin, dass der Ernährungszustand die Wirkstofffreisetzung von SUS Formulierungen („Foodeffekte“) beeinflussen kann. Während Gallensalze, die im ernährten Zustand vermehrt abgegeben werden, sowie Nahrungsbestandteile nur einen geringen Effekt zeigten, beeinflusst eine verstärkte Hydrodynamik die Freisetzungsgeschwindigkeit, den dominierenden Freisetzungsmechanismus sowie das Freisetzungsprofil. In ähnlicher Weise wie für GDB und GPS gezeigt, wird ein Einfluss der Mediumviskosität auf die Wirkstofffreisetzung erwartet. Jedoch kann dieser Einfluss derzeit nicht quantifiziert werden. Eine Erhöhung der Viskosität des Dissolutionmediums resultiert in einer verlangsamten oder verzögerten Wirkstofffreisetzung.

Auch für die drei anderen untersuchten Matrixsysteme wurde die Möglichkeit eines Foodeffekts gezeigt. Als auslösende Faktoren wurden (i) verstärkte Anwesenheit von Nahrungs- und Gallenbestandteilen, (ii) verstärkte Magen-/ Darmmotilität und (iii) erhöhte Viskosität von Magen- und Darminhalt identifiziert.

Für GDB Matrixsysteme wurde *in vitro* eine Veränderung der Anfälligkeit für Foodeffekte in Abhängigkeit vom Wirkstoffgehalt gezeigt. Bei höherem Wirkstoffgehalt wurde eine verstärkte Neigung zu Foodeffekten vorhergesagt, insbesondere bei verstärkter Hydrodynamik. Dagegen zeigte sich bei niedrigerem Wirkstoffgehalt (≤25% [w/W]) eine verbesserte Robustheit der Wirkstofffreisetzung gegenüber Einflüssen von Hydrodynamik und Gallensekreten. Für GPS Formulierungen wurde eine beschleunigte Wirkstofffreisetzung sowohl bei niedrigerem als auch höherem Wirkstoffgehalt (25% [w/w] ≤ Wirkstoffgehalt ≤ 75% [w/w]) beobachtet. Insgesamt wurde ein untergeordneter Einfluss der Gallensekretion auf die *in vivo* Wirkstofffreisetzung vorhergesagt. Für GPS Matrixsysteme mit hohem Wirkstoffgehalt (>>25% [w/w]) wurde eine beschleunigte Wirkstofffreigabe bei verstärkter Motilität vorhergesagt. Wie schon bei SUS Matrixsystemen werden Effekte durch eine veränderte Viskosität des Magen-/ Darminhalts vorhergesagt. Bei HPC Formulierungen werden ebenfalls Foodeffekte vorhergesagt, die im wesentlichen durch eine verstärkte Motilität verursacht werden. Dagegen ist die Wirkstofffreisetzung aus HPC Matrixsysteme robust gegenüber erhöhter Gallensekretion und Nahrungsbestandteilen. Dies entspricht auch dem weitgehend erosionsgetriebenen Freisetzungsmechanismus.

Um die Vorhersagen aus *in vitro* Versuchen zu bestätigen, wurde die *in vivo* Wirkstofffreisetzung aus SUS25 (Wirkstoffgehalt 25% [w/w]) und SUS75 (Wirkstoffgehalt 75% [w/w]) in Hunden untersucht. Die *in vitro* Experimente lieferten ordentliche Vorhersagen des *in vivo* Verhaltens. Es ergaben sich bessere Korrelationen für den nüchternen als für den ernährten Zustand. Die aus *in vitro* Tests vorhergesagten Foodeffekte für SUS25 wurden *in vivo* bestätigt. Eine Abnahme der Wirkstofffreisetzung im ernährten Zustand konnte jedoch nicht anhand der in vitro Daten vorhergesagt werden. Es konnten Veränderungen der Motilität als wesentliche Ursache für Foodeffekte bei SUS25 bestätigt werden. Auch bei der *in vivo* Wirkstofffreisetzung aus SUS75 könnte die Motilität eine Rolle spielen, jedoch dürften andere Parameter dominieren.

Die beschriebene „disc method“ könnte ein hilfreiches Werkzeug bei der Charakterisierung der Wirkstofffreisetzung sein. So wurde sie genutzt um Formulierungen mit Tendenzen zu motilitätsgetriebenen Foodeffekten zu identifizieren. Außerdem war die Methode geeignet die *in vivo* Freisetzung im nüchternen Hund quantitativ vorherzusagen. Zur Verbesserung der *in vitro* Simulation des ernährten Zustands ist jedoch eine weitere Erhöhung der Hydrodynamik notwendig. Daher könnte die „disc method“ eine nützliche Ergänzung zu USP 3

Dissolutionexperimenten darstellen und zur Verbesserung der *in vitro* Charakterisierung von CR Matrixdarreichungsformen beitragen.

Es konnten drei zur Schmelzextrusion geeignete Matrixhilfsstoffe für feste orale Arzneiformen mit kontrollierter Wirkstofffreigabe identifiziert werden. Außerdem wurde ein weiterer Matrixhilfsstoff für semi-retard Arzneiformen gefunden. Dieser kann außerdem genutzt werden um die Wirkstofffreigabe aus Matrixsystem zu modifizieren.

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