1 Introduction

1.1 Multiple unit dosage forms

Peroral dosage forms for modified drug release are classified into single or multiple unit dosage forms. Pellets, powders and granules are considered to be multiple unit dosage forms (MUDFs). Compared to single unit dosage forms (SUDF, e.g. enteric-coated tablets), they consist of multiple particles or they disintegrate rapidly into particles after intake [Kleinebudde, 1997].

MUDFs have many advantages: 1. Due to the small size (< 2 mm) they are able to pass the pylorus continuously even under closed conditions of the sphincter and therefore, distribute evenly in the entire gastrointestinal tract (GIT) and show a gradual decrease in the amount present in the stomach. As a result, local irritation and side-effects are reduced and more consistent plasma levels are achieved [Bechgaard and Nielsen, 1978; Davis et al., 1986; Voigt, 2006b]. 2. Modified drug release is often achieved by coating. The risk of defects in coatings of SUDFs such as cracking causes intoxication due to 'dose dumping'. Coated MUDFs prevents the risk of 'dose dumping' due to the use of multiple particles. 3. MUDFs can be variously designed: One dosage form can be composed of pellets containing different (incompatible) active pharmaceutical ingredients (APIs) or particles with different dissolution behavior. Therefore the combination of different multiple particles may reduce the daily required number of drugs, which can improve patient compliance. Finally, pellets offer technological advantages such as good flowability, low friability, narrow particle size distribution and uniform packing [Reynolds, 1970; Rowe et al., 2005]. Therefore, MUDFs are the preferred dosage forms.

MUDFs also have disadvantages. The main disadvantage is the complex production process. Furthermore, MUDFs can be bigger in volume than tablets, which can affect patient compliance. However, overall MUDFs have increasingly gained importance over the years due to their distinctive advantages in both technological and pharmacological aspects.

1.2 Micropellets

1.2.1 Definition

Pharmaceutical pellets are isometric aggregates with smooth surfaces and narrow particle size distribution [Knop, 1991]. Nowadays, the mean pellet size ranges from 300 µm to 3 mm. According to Kleinebudde, microparticles are defined as aggregates < 500 µm [Kleinebudde, 1997]. However, there is no commonly accepted definition for micropellets in the literature. Due to the production technique the diameter of the orifices for wet extrusion/ spheronization was limited to ensure a reproducible and robust process. Therefore, in this thesis pellets up to 700 µm were considered as micropellets, whereby the closer to 500 µm the better.

Micropellets have the same advantages as regular pellets (~1 mm). Besides the shape, they also have low porosity and high mechanical stability. Due to the roundness and closed shape of the particles, the flowability of pellets is excellent. Micropellets show a number of additional favorable properties. The most important of which is the larger specific surface area, which results in faster dissolution rates.

Micropellets can be used in a number of dosage forms that may be beneficial for certain patient groups. Micropellets and regular pellets are usually processed into tablets or filled into capsules. Further investigations are underway to use micropellets as solid drops in a 'sprinkle capsule' [Kjellman et al., 1988; Carrigan et al., 1990] or in a 'dose sipping technology' (DST) [Tuleu, 2005; Breitkreutz and Boos, 2007; Krause and Breitkreutz, 2008]. These application forms are especially suitable for patients who have problems swallowing drug products and therefore refuse to take medicine at all (e.g. pediatric or elderly patients). Difficulties with administering drugs to children are a widespread problem, which needs improvement with regard to off-label use for example [Schirm et al., 2003; Kearns et al., 2003; Standing and Tuleu, 2005].

1.2.2 Sprinkle capsule

A sprinkle capsule is a hard gelatin, pull-apart capsule containing drug loaded pellets, which is designed to be administered either intact or opened to sprinkle on soft food. However, the co-administration of a solid meal must be handled with care [Pedersen and Mollerpetersen, 1984]. The presence of food can be beneficial in terms of patient compliance, especially in children, and those concerned by bad taste, nausea or vomiting.

1.2.3 Dose sipping technology

With dose sipping technology, the micropellets are filled into a plastic drinking straw. The straw consists of four components (Fig. 1): the drinking straw, the micropellets, the controller and the cap. The controller is located at the bottom of the system and acts like a filter. Therefore, it will transport the micropellets to the top with sipping. The cap on top of the straw, for hygienic safeguards and to keep the micropellets inside the straw, has to be removed before use.

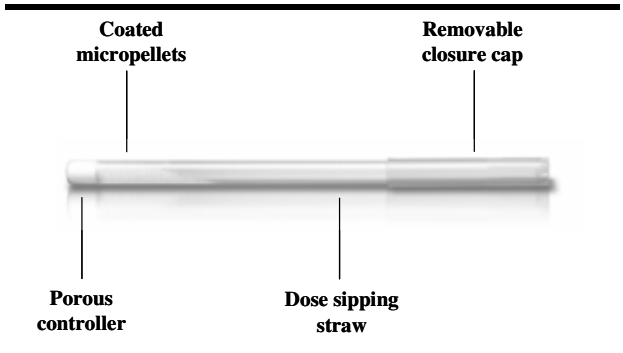

Fig. 1: Dose sipping technology

The DST is a flow-through system, which is dependent on the entering liquid. Therefore, carbonated drinks, teas and liquids with low viscosity are suitable, while juice with pulp and viscose liquids like milk shakes might block the system.

The advantages of DST and sprinkle capsules are basically related to patient psychology. Patients may be reluctant to take their medication due to the size of a tablet; especially children who often refuse to take drugs and can spit them out easily. However, a straw is associated with drinking and therefore, related to a natural habit. They can be carried in the bag without peculiarities and used for almost every drink. During sipping, micropellets disperse in the liquid and enter the mouth easily. The small pellet size of the micropellets (combined with the concomitant intake of liquid) helps to pass the mouth almost unnoticed. Therefore, the drug is given to the patient without difficulties.
For example, Clarosip® (Grünenthal GmbH) was an antibiotic in a drinking straw. It contained clarithromycin as API and was available in 3 different dosages: 125 mg, 187.5 mg and 250 mg. The micropellets were enteric coated with a copolymer of methacrylic acid-ethyl acrylate (1:1).

1.3 Pelletization aids

1.3.1 Definition

To produce pellets by wet extrusion/ spheronization the formulation must contain a pelletization aid and meet specific rheological requirements for the process. During extrusion the wetted mass must show i) suitable flow characteristics, which allows a mass transport during the process; ii) self-lubricating properties without sticking to each other and; iii) sufficient rigidity to keep the shape of the extrudate.

For the spheronization process the moistened extrudates must show i) sufficient firmness; ii) enough brittleness to break into smaller pieces (cylinders) at the beginning of the spheronization process; iii) plasticity to convert the cylinders into pellets and; iv) that it is non-adhesive to remain in shape [Fielden et al., 1992].
Due to the various required properties, the range of materials suitable to act as pelletization aid in the extrusion/ spheronization process is limited.

1.3.2 Microcrystalline Cellulose

Microcrystalline cellulose (MCC) was the first excipient used as pelletization aid to produce pharmaceutical pellets successfully with a relatively low amount in the formulation. After its discovery for pharmaceutical pelletization by Reynolds [1970] and Conine and Hadley [1970], numerous investigations followed in which MCC showed its special role as a pelletization aid - during wet extrusion, MCC binds the moisture and therefore, the wetted mass becomes rigid to be extruded. At the same time in the spheronization process, the extrudates are still brittle to break into small cylinders and simultaneously plastic enough to convert into pellets. However the drawbacks of MCC, such as matrix dissolution and prolonged drug release [O'Connor and Schwartz, 1993; Zimm et al., 1995] led to further investigations. To try to overcome its drawbacks, MCC was combined with different excipients to improve the drug

release [Mesiha and Valles, 1993; Gazzaniga et al., 1998; Souto et al., 2005] or wetted with different extrusion liquids than pure water [Millili and Schwartz, 1990; Schroder and Kleinebudde, 1995; Boutell et al., 2002]. Alternative pelletization aids were also sought [Liew et al., 2005; Sergio et al., 2007; Charoenthai et al., 2007]. Bornhoft et al. [2005] introduced κ-carrageenan, which showed special capacities for pellet production and became a suitable pelletization aid, which was confirmed by subsequent investigations [Thommes and Kleinebudde, 2006a; b].

1.3.3 κ-Carrageenan

κ-Carrageenan belongs to a group of acid polysaccharides taken from the cell walls of red seaweeds, in particular of the *Gigartinales spp*. [Dawes et al., 1977; Amimi et al., 2001]. It is a natural ingredient and generally recognized as safe (GRAS-status). Some physiological effects of carrageenan have been reported. Wagner [1999] observed that it had effects on blood coagulation and defecation and Hänsel et al. [1999] suspected low-molecular carrageenan as a cause for ulceration in the GIT. Therefore, Rochas and Heyraud [1981] emphasized the avoidance of acid and enzymatic hydrolysis in the production.
As carrageenans are not absorbed after oral intake [Fiedler, 1996], they are mainly used in food applications (also known as E407, a food additive) [Bundesministerium für Gesundheit, 2006]. Thus, they serve as thickening, suspending or gelling agents [Voragen, 2001].

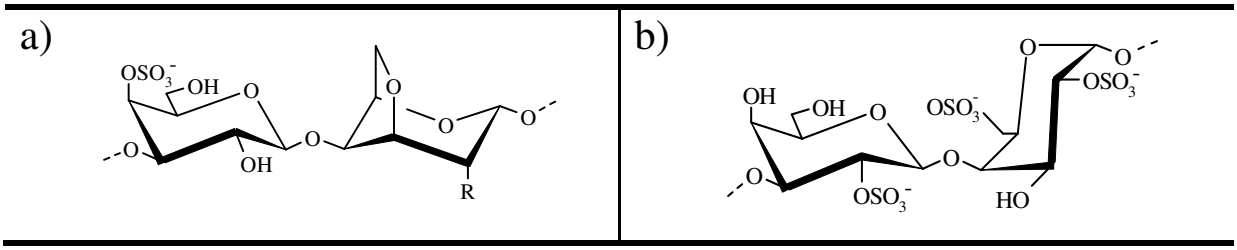

Fig. 2: Ideal repeating dimer unit of different types of carrageenan a) κ-carrageenan or ι-carrageenan, b) λ-carrageenan

The production of carrageenan involves several steps: hot extraction, clarification, evaporation, precipitation and drying. Through these processes, the commercially available types, ι-, κ- and λ-carrageenan, are obtained [FMC, 1993]. Due to the production process, the obtained carrageenans are not pure. They show impurities from one another [Rochas et al., 1989; Ridout et al., 1996]. The linear backbone of κ-carrageenan bases on the repetition of disaccharide sequences of sulfate esters of β-1,3-linked galactose and α-1,4-linked 3,6-anhydrogalactose, which are mainly charged with potassium, sodium, calcium, magnesium and ammonium as counter-ions. κ-Carrageenan differs from ι- and λ-carrageenan in the amount and location of the sulfate ester groups and the presence (or absence) of the 3,6-anhydrogalactose residue [Voragen, 2001; Stortz and Cerezo, 2003]. Fig. 2 contains the different structures of the carrageenans, where κ-carrageenan showed $R = OH$ and ι-carrageenan had $R = OSO_3^-$.

After the inclusion of carrageenan in the US Pharmacopoeia [USP 31 NF26, 2008] with its own monograph, it was used in numerous investigations in pharmaceutical technology. In particular κ-carrageenan was investigated in i) gels [Hoffman, 2002; Mangione et al., 2007]; ii) films [Park et al., 2001]; iii) tablets [Picker, 1999; Gupta et al., 2001; Rosario and Ghaly, 2002]; iv) capsules [Scherer RP, 2003; Tuleu et al., 2007]; v) inhalants [Yamada et al., 2005]; vi) pellets [Garcia and Ghaly, 2001; Sipahigil and Dortunc, 2001; Bornhoft et al., 2005]. It was also investigated with regard to the pronounced effects of ions and its interactions with APIs [Hugerth, 2001; Sipahigil and Dortunc, 2001; Naim et al., 2004].

2 Micropellets production techniques

2.1 Introduction

Several methods to produce micropellets are well-known such as extrusion/ spheronization; direct pelletization [Kristensen et al., 2000]; spray-drying [Eldem et al., 1991; Giunchedi and Conte, 1995]; spray-layering of solutions, suspensions or powders [Jones, 1989; Goodhart and Jan, 1989]; spray-congealing [Akiyama et al., 1993; Maschke et al., 2007] or different emulsification-solvent evaporation/ extraction or emulsion-congealing techniques [Kim et al., 1994; Hassan et al., 1995; Berchane et al., 2007]. Extrusion processes are classified into solvent-free extrusion (melt extrusion, solid-lipid extrusion) and wet extrusion. The latter is the commonly used technique in the pharmaceutical industry to produce pellets since the pioneering work of Reynolds [1970] and Conine and Hadley [1970]. The methods of extrusion have a number of advantages: i) the processes are robust; ii) they have good reproducibility; and iii) they enable the production of pellets with often high loading, high density and narrow size distribution. Thus, the methods are used for manufacturing multiple unit dosage forms by coating, tableting or encapsulation [Ghebre-Sellassie, 1989a].

2.2 Extrusion

Extrusion is a process of applying pressure to a mass until it flows through an orifice or a defined opening [Hicks and Freese, 1989]. There are several techniques for extrusion on the market, but screw extrusion is most commonly used in the pharmaceutical industry [Hicks and Freese, 1989; Baert et al., 1993a; Vervaet et al., 1995]. The screw extruder exists as a single or twin-screw extruder. The spinning direction of the twin-screw extruder can either be a ‘co-rotate’ or ‘counter-rotate’ [Mollan, 2003]. Co-rotation of the twin-screw is generally used for pharmaceutical production, due to the low energy input. Furthermore, a twin-screw extruder shows the advantage of a one-step extrusion combining blending, wetting, wet massing and extrusion in one apparatus. With one-step extrusion, several variables affect the pellet properties, which can be categorized into three groups: i) the equipment effects, e.g. type of extruder; ii) the process effects, settings of the process and; iii) the material effects, e.g. physical properties of the formulation [Erkoboni, 2003]. The interactions can be evaluated by measuring the power consumption or the torque during the process [Kleinebudde et al., 1994; Soh et al., 2006].

The production of micropellets using wet extrusion/ spheronization is challenging and scarcely reported in the literature. Previous studies with (axial) extrusion showed difficulties due to the effects of the moisture content on pellet properties, as well as the effects of the orifice size and formulation. With micropellets, the pressure on the screen increases due to the decrease in orifice size [Kanbe et al., 2007]. Micropellets have been successfully produced using L-HPC or glycerides with the addition of a surfactant [Dupont et al., 2002; Kanbe et al., 2007].

2.3 Spheronization

Compared to the extrusion process, spheronization is a discontinuous process in which the wetted extrudates are converted into spherical micropellets. Hence, spheronization is the essential step in the production, where collision of particles occurs due to the generated force of the spinning friction plate. Therefore, the extrudates must show a combination of cohesiveness, firmness and plasticity to go through the various states of forming [Erkoboni, 2003].

A spheronizer consists of a vertical hollow cylinder with an inner horizontal rotating disc (friction plate) [Hicks and Freese, 1989]. Spheronizers may vary in the friction plate diameter and its features as well as additional process variables. The surface texture of the friction plate can be designed with different grooves from which the 'cross-hatched' pattern is commonly used. Furthermore, differences in additional spheronizer process variables such as a double jacket wall or an inlet air pressure can also exist.

The mechanism of spheronization is complex and the process is affected by mechanical stress and by the temperature. Besides the requirements of the extrudates, the spheronization process is mainly dependent on three different factors: spheronization speed, residence time and loading [Hellen and Yliruusi, 1993; Wan et al., 1993; Hellen et al., 1993a; b]. Therefore, the mutual effects between the extrusion and spheronization process, especially with regard to the moisture content of the extrudates, have been investigated [Woodruff and Nuessle, 1972; Bains et al., 1991; Baert et al., 1993b].

2.4 Drying

The final step of the production is the drying process of the micropellets to remove the extrusion liquid in which the micropellets lose their plasticity. Although several methods exist, in general the fluidized bed method is preferred and commonly used [Erkoboni, 2003; Thommes et al., 2007]. In this work, no further investigations on drying were performed.

3 Dissolution behavior

3.1 Introduction

The dissolution rate of an API is often the rate-limiting step of the drug absorption. Therefore, dissolution tests provide important information about the biopharmaceutical quality of a dosage form to determine the release profiles. Several 'in-vitro' tests are described in the pharmacopoeias [Ph.Eur. 6, 2008; USP 31 NF26, 2008] containing different apparatus and various requirements for different dosage forms. Depending on the dosage form, the dissolution shows fast or modified drug release, whereby the latter is usually achieved through coating of the dosage form or embedment of the API in a matrix.

3.2 Matrix dissolution

3.2.1 Definition

There are a number of principles of classifying drug release from matrices: i) matrix is not degradable, while the API is fully dissolved; ii) matrix is not degradable, while the API is mostly suspended; iii) matrix is poreless or gets pores during dissolution; iv) matrix is gelling or v) matrix is eroding [Leuenberger, 2001]. The dissolution kinetic varies depending on the system. Different models are used and well known to describe the drug release with regard to defined conditions such as sink-conditions.

3.2.2 Diffusion-controlled dissolution

Two different mechanisms are known for diffusion-controlled drug release. The matrix is not degradable and the API is either fully dissolved or mostly suspended. In the latter case, the matrix is a diffusion barrier in which water penetrates during the dissolution process and the API dissolves. Thus, the drug release is only diffusion-controlled.

The Higuchi equation [Higuchi, 1961; 1963] describes the kinetic of the drug release, which assumes the existence of sink conditions and a decreasing gradient of concentration. A linear relationship between drug release and the square root of time demonstrates that a diffusional process occurs (Eq. 1):

$$Q = \sqrt{\frac{D\varepsilon}{\tau} * Cs * (2A - \varepsilon Cs) * t} = k_H * \sqrt{t} \qquad \text{Eq. (1)}$$

where Q is the cumulative amount of drug released after time per unit surface area of the matrix [mg·cm^{-2}], D is the diffusion coefficient of the drug in the permeating fluid [cm^2·min^{-1}], ε is the porosity factor of the matrix, τ is the tortuosity factor of the capillary system, A is the concentration of drug in the matrix [mg·cm^{-3}], Cs is the solubility of the API in the permeating fluid [mg·cm^{-3}], t is the time [min] and k_H is the system-dependent proportionality

constant (slope). Hence, a plot of the amount of drug release (Q) versus the square root of time predicts a linear relationship.

Changes in the dissolution kinetic are obtained when the total concentration is below the saturated concentration or the diffusion coefficient is changed due to matrix changes (Eq. 2):

$$D = \frac{R * T}{6 * \pi * \eta * r * N} \qquad \text{Eq. (2)}$$

where R is the gas constant [8.314 $J \cdot K^{-1} \cdot mol^{-1}$], T the absolute temperature, η the viscosity of the solvent, r the hydrodynamic radius of the dissolved molecules and N is Avogadro's number [$6.0221 * 10^{23}$].
Although the Higuchi equation was originally derived to describe drug release from a planar surface system, it is also an accepted method for multiparticulate pellet systems [O'Connor and Schwartz, 1989]. The evaluation by Korsmeyer and Peppas [Korsmeyer et al., 1983] considered the geometry dependence of the matrix system on drug release.

3.3 Evaluation by Korsmeyer and Peppas

An empirical equation was developed to determine the mechanism of drug release by means of the effects of structural characteristics of polymeric matrices [Korsmeyer and Peppas, 1981]. In general, the dissolution behavior from polymers was strictly limited to thin films. The drug release can be described by Fickian diffusion in which the first 60 % of the fractional release is characterized by the square root of time profile at any time. However, another drug release behavior, where the release rate is independent on the time, is characterized to be a zero-order kinetic. Therefore, Korsmeyer and Peppas postulated a double logarithmic plot of drug release as a function of time combining both drug release behaviors (Eq. 3):

$$\frac{M_t}{M_\infty} = kt^n \qquad \text{Eq. (3)}$$

where M_t/M_∞ is the fraction of drug released at the time t, k is the apparent release rate constant with respect to the structural and geometric characteristics of the drug delivery system and n is the diffusional exponent which characterizes the transport mechanism of the drug.

The evaluation by Korsmeyer and Peppas considered the effects of the matrix geometry on the dissolution kinetic. It describes the intermediate range between Fickian diffusion and zero-order kinetics with respect to the shape. Thus, the exponent n and the kinetic constant k

strongly depend on the geometry of the matrix. The Fickian diffusion is generally defined by n = 0.5 and zero-order kinetic by n = 1. The release processes in between, 0.5 < n < 1, is characterized as anomalous (non-Fickian) diffusion, where swelling, diffusion and erosion play an important role.

Tab. 1: Diffusional exponent and drug release mechanism of different geometry of the matrix

Diffusional exponent (n)			Drug release mechanism
Cylindrical sample	Spherical sample	Thin film	
0.45	0.43	0.5	Fickian diffusion
0.45 < n < 0.89	0.43 < n < 0.85	0.5 < n < 1.0	Anomalous (non-Fickian) diffusion
0.89	0.85	1.0	Zero order kinetic

Due to the composition of both drug release behaviors in one equation, some agreements remained like the validity for the first 60 % of the fractional release. In addition, [Ritger and Peppas, 1987a; b] concluded that the Fickian diffusion process, described by n = 0.5, was only acceptable for thin films. For spherical particles, the gradient was about 0.43 (Tab. 1).