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.

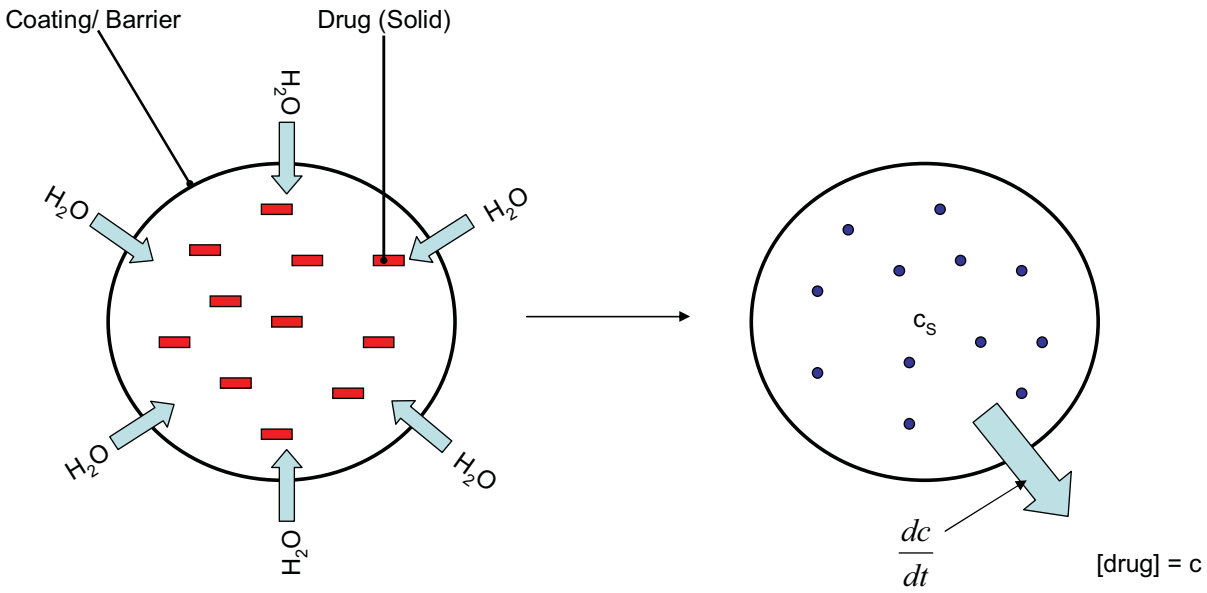

Fig. 1.2.1: Control of drug release from coated controlled release (CR) oral dosage forms

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.

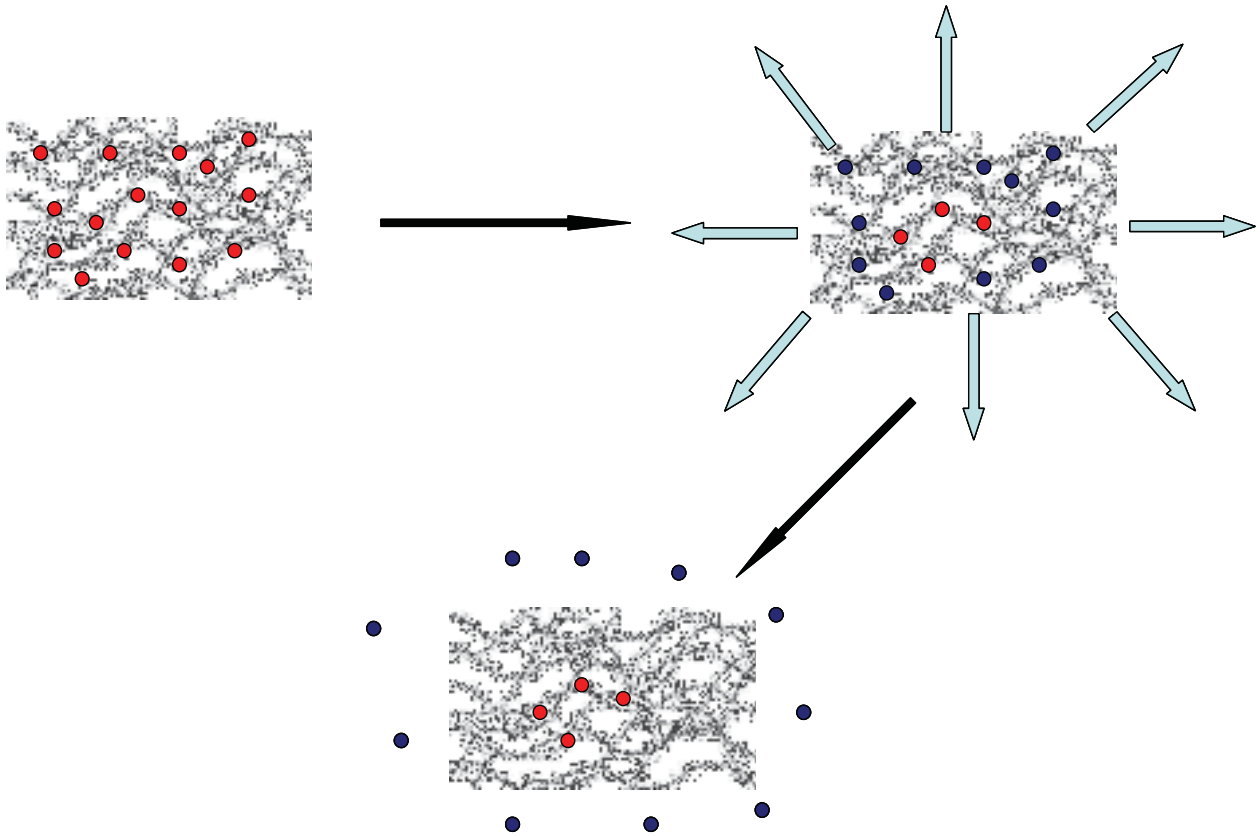

Fig. 1.2.2: Schematic description of diffusion controlled drug release from inert matrices (Case I)

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)).

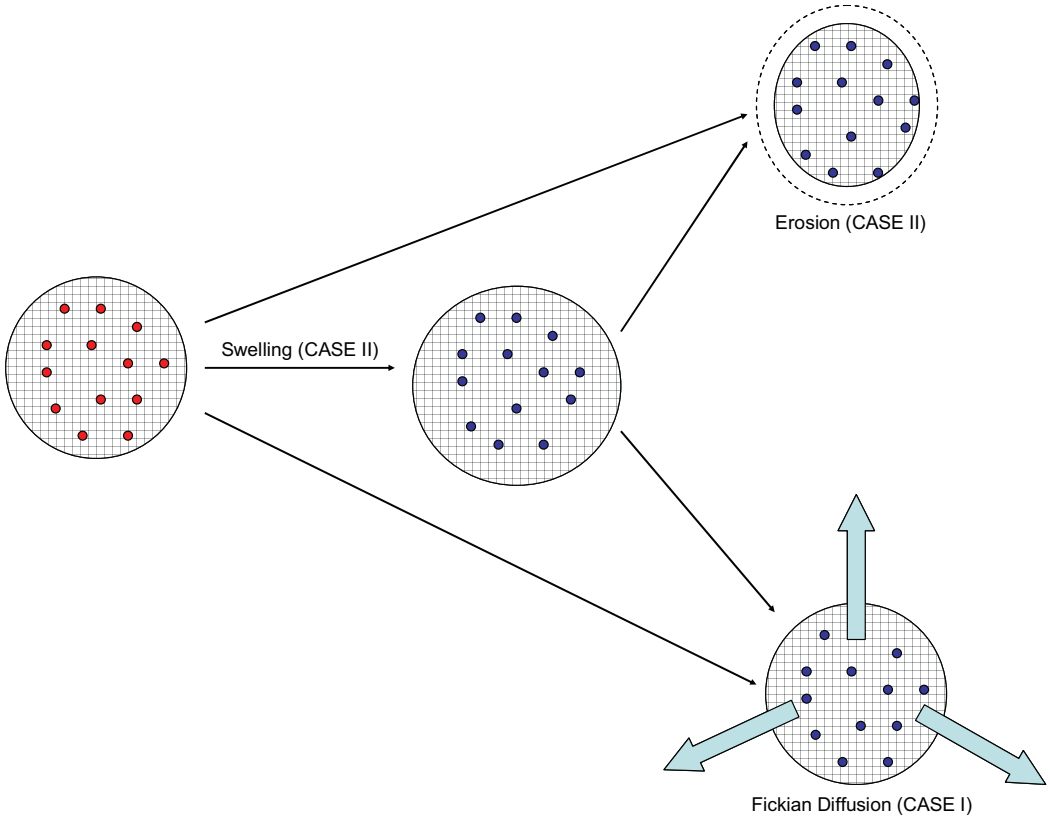

Fig. 1.2.3: Case I and Case II drug release from hydrocolloid matrices

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

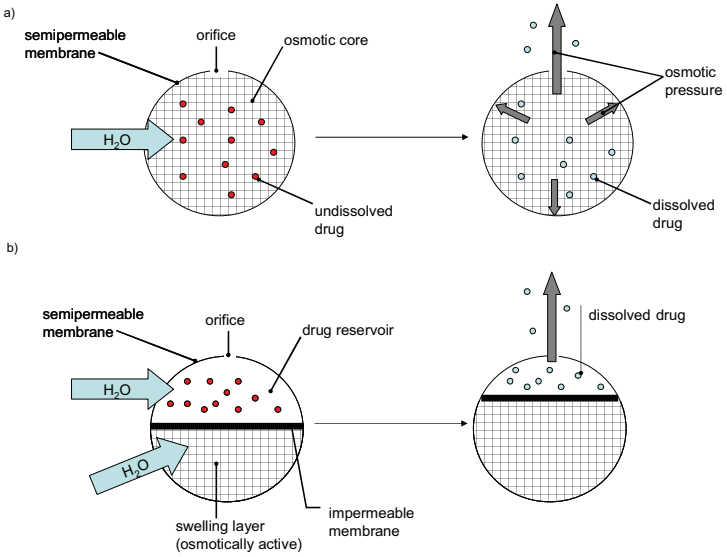

Fig. 1.2.4: Working principle of osmotic devices for oral controlled release dosage forms: a) osmotic pump, b) oral osmotic system (OROS)

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.