THE INFLUENCE OF DRUG CORE PROPERTIES ON DRUG RELEASE FROM EXTENDED RELEASE RESERVOIR PELLETS

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To my family,

in love and gratitude

Imagination is more important than knowledge,

for knowledge is limited.

(Albert Einstein)

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List of abbreviations

ACN	Acetonitrile
A/m ratio	Surface area/weight ratio
CA	Celluloseacetate
c.l.	Coating level
CME	Cellulose Mixed Esters (filter material)
D50	Median diameter of particles
DI water	Deionized water
EC	Ethylcellulose
ELSD	Evaporative Light Scattering Detector
ESD	External Standard
HILIC	Hydrophilic Interaction Liquid Chromatography
HPLC	High Pressure Liquid Chromatography
HPMC	Hydroxypropylmethylcellulose
HPC	Hydroxypropylcellulose
IQR	Interquartile-Range (dispersion parameter of median)
LOD	Limit of detection
LOQ	Limit of quantification
MCC	Microcrystalline cellulose
MCC cores / pellets	Drug cores / coated pellets based on MCC starter cores
n.d.	Not determined
NH_4Ac	Ammoniumacetate
NP	Nonpareils (sucrose starter cores)
NP cores / pellets	Drug cores / coated pellets based on sucrose nonpareils
PEG	Polyethylene glycol
PSD	Particle size distribution
PVA	Polyvinylalcohol
PVP	Polyvinylpyrrolidone
RID	Refractive Index Detector
RL	Eudragit® RL
RP	Reversed Phase Liquid Chromatography
RS	Eudragit® RS

RSD	Relative Standard Deviation (= SD/mean·100%)
SD	Standard Deviation
SEM	Scanning electron microscopy
SLM	Standard Litre per Minute
S/N	Signal to noise ratio in chromatograms
SST	System Suitability Test
T50	Time point of 50% drug released
T5	Time point of 5% drug released (defined as lag time in the present work)

Introduction

1 Introduction

1.1 Controlled Release Dosage Forms

A successful pharmacotherapy is the combination of optimized drug delivery to the body, minimized adverse effects and good patient compliance. To achieve this, drugs need to be administered to the human body at a specific delivery rate, time point and / or site of the body.

The oral route is generally preferred due to the obvious advantage of easy administration and excellent acceptance among patients. However, depending on the pharmacological effect and the properties of the drug administered, immediate release in the stomach of a drug is not always desirable. Gastric resistant dosage forms allow the administration of drugs which are known to be either acid-labile (e.g. didanosine), to irritate the gut wall (e.g. iron, acetylsalicylic acid) or to be transferred to a poorly absorbable form in the acidic gastric medium (e.g. omeprazole, pantoprazole). Extended / prolonged release dosage forms yield stable, dependable plasma concentrations within the therapeutic range. They are thus advantageous for drugs used in the treatment of e.g. hypertension or chronic pains or for drugs with a narrow therapeutic window. In contrast, diseases with a circadian rhythm like asthma bronchiale or angina pectoris call for a pulsatile release of the drug after a given lag time (Roy and Shahiwala 2009).

Although in few cases the desired drug delivery can be achieved by manipulations of the drug itself (e.g. choice of a less soluble salt form of the drug to prolong its effect), the majority of drugs require an appropriate dosage form to control their release. This is usually achieved by polymeric drug delivery systems in which the functionality of the system is predominantly determined by the polymer properties.

These systems can be differentiated into a) matrix systems where the drug is embedded within the polymer or b) reservoir systems where a drug core is surrounded by a polymeric film. A further differentiation can be made into a) single unit dosage forms or b) multiple unit dosage forms (Figure 1).

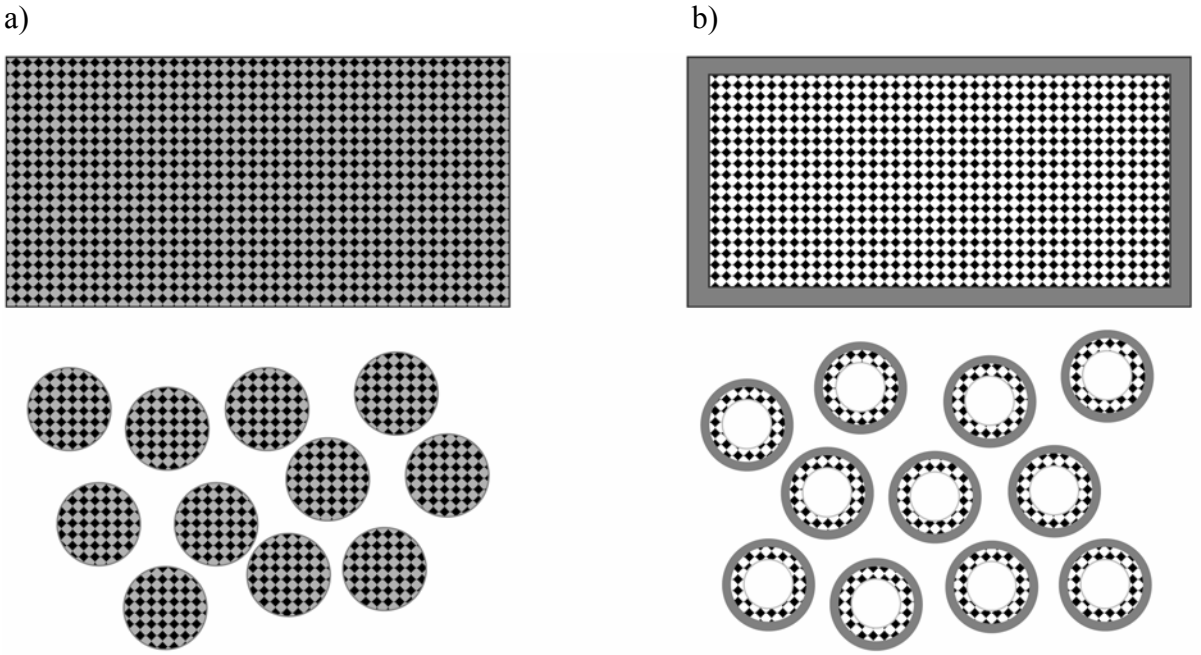


Figure 1. Schematic presentation of: a) matrix systems and b) reservoir systems; both depicted as single and multiple unit systems (size not up to scale) (black: drug; grey: release controlling polymer; white: other excipients)

1.2 Multiple unit dosage forms

In the past three decades, multiple unit drug delivery systems like e.g. pellets have gained increasing attention due to numerous advantages (Bechgaard and Nielsen 1978; Ghebre-Sellassie 1989; Roy and Shahiwala 2009). One reason may be commercial benefits like extended patent protection and market expansion. However, more important are their formulation advantages and therapeutical benefits.

Due to their multitude, pellets of different, potentially incompatible drugs or pellets with different release profiles can be combined in just one final dosage form, thus allowing a greater flexibility during formulation development (Ghebre-Sellassie 1989; Anschütz 2009). The spherical shape, narrow size distribution and excellent flow properties of pellets result in uniform and reproducible application of drug and polymer layers as well as accurate volumetric dosing on tablet presses or capsule filling machines (Ghebre-Sellassie 1989; Gryczova, Rabiskova et al. 2008).

Drug release from pellets is controlled by a multitude of particles rather than just one device as in case of single units, e.g. coated tablets. This reduces the variability in release profiles and prevents the risk of dose dumping. The gastric residence time of pellets is shorter and more predictable compared to single units. And pellets spread more homogeneously throughout the GI-tract, thus causing less local irritations of the mucosa and potentially leading to higher bioavailability.

In order to keep the easy administration of oral single unit systems, coated pellets can be either filled into hard gelatine capsules or compressed into tablets (Lehmann, Petereit et al. 1993; Bodmeier 1997; Dashevsky, Kolter et al. 2004). However, in contrast to coated single units, which must not be divided by any means, the pellets can be re-obtained easily by opening the capsule or dispersing the tablet in water. This allows easier swallowing for children and elders or even administration via naso-gastric feeding tubes.

1.2.1 Different designs of coated multiple units

The term ‘pelletization’ originally described the agglomeration of fine powders of drugs and excipients into small, free-flowing and more or less spherical beads which were referred to as pellets. However, the potential of sugar seeds (so called nonpareils) as starter cores for the formulation of layered / coated pellet dosage forms has been recognized as early as 1949 (Ghebre-Sellassie 1989). Various designs have since been developed for coated pellets (Figure 2).

High dose drugs are often incorporated in matrix pellets via extrusion and spheronization with microcrystalline cellulose (MCC), lactose or blends of the two (Wesseling and Bodmeier 2001). This technique allows sufficiently high drug loading levels. However, these matrix pellets alone would disintegrate quickly in contact with medium (Chambin, Champion et al. 2004) and thus require an outer polymer film coating in order to obtain controlled release (Figure 2a).

Potent low dose drugs, on the other hand, can be formulated easier by spraying them onto inert starter cores in a fluidized bed coater. The release-controlling polymer can be co-applied with the drug from the same solution or dispersion, yielding so called matrix-coated pellets (Figure 2b). However, this approach has several disadvantages like higher risk of drug-

polymer interactions, fast initial release and incomplete release (Mota 2010). Therefore a separate polymer coating step, subsequent to the drug layering, is more common (Figure 2c). The term ‘reservoir pellets’ typically refers to the latter system.

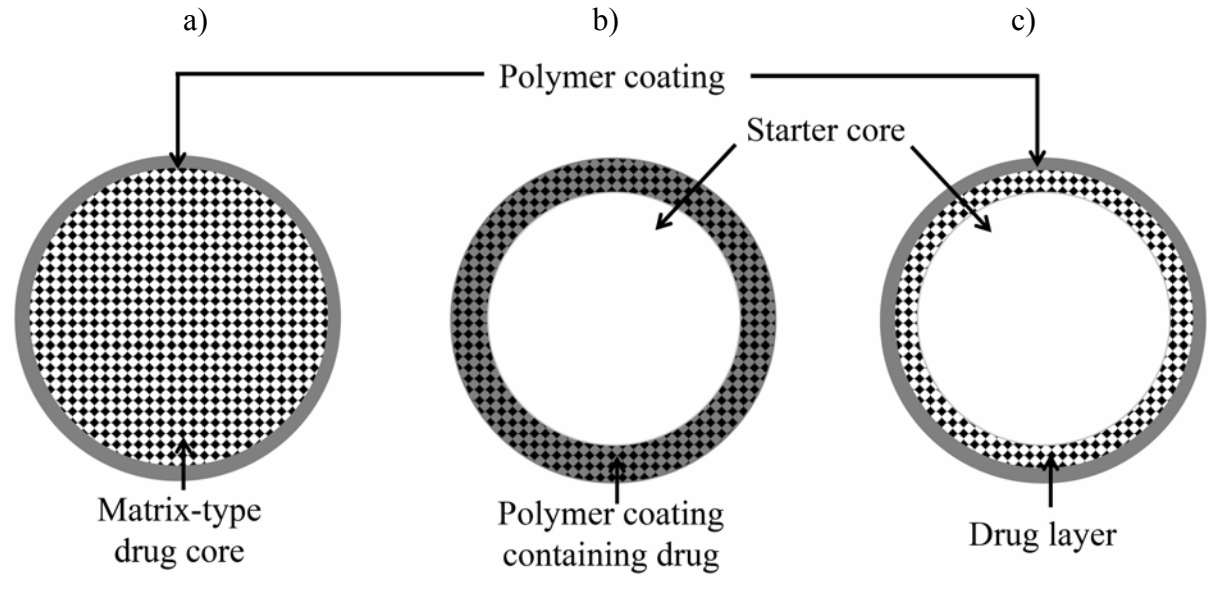


Figure 2. Schematic presentation of: a) coated matrix pellets, b) matrix-coated pellets and c) reservoir pellets (black: drug; grey: release-controlling polymer; white: other excipients)

1.3 Release from reservoir pellets

In contact with aqueous medium, release from reservoir pellets follows a typical sequence of events. First media is taken up into the pellet; soluble components (mainly drug, binder and sucrose starter cores) are dissolved and then released from the pellet across the barrier of the polymer coating. However, the precise mechanism of this release is highly complex and determined by a variety of pellet properties (Wesselingh 1993).

For pellets coated with an insoluble film, different ‘passage ways’ have been described (Ozturk, Ozturk et al. 1990). Following concentration gradients, the drug diffuses either through a) the intact coating, b) through channels made by plasticizers or pore formers or c) through medium filled channels / pores (Figure 3a-c). A further mechanism described by Ozturk et al. is d) osmotically driven release (Figure 3d).

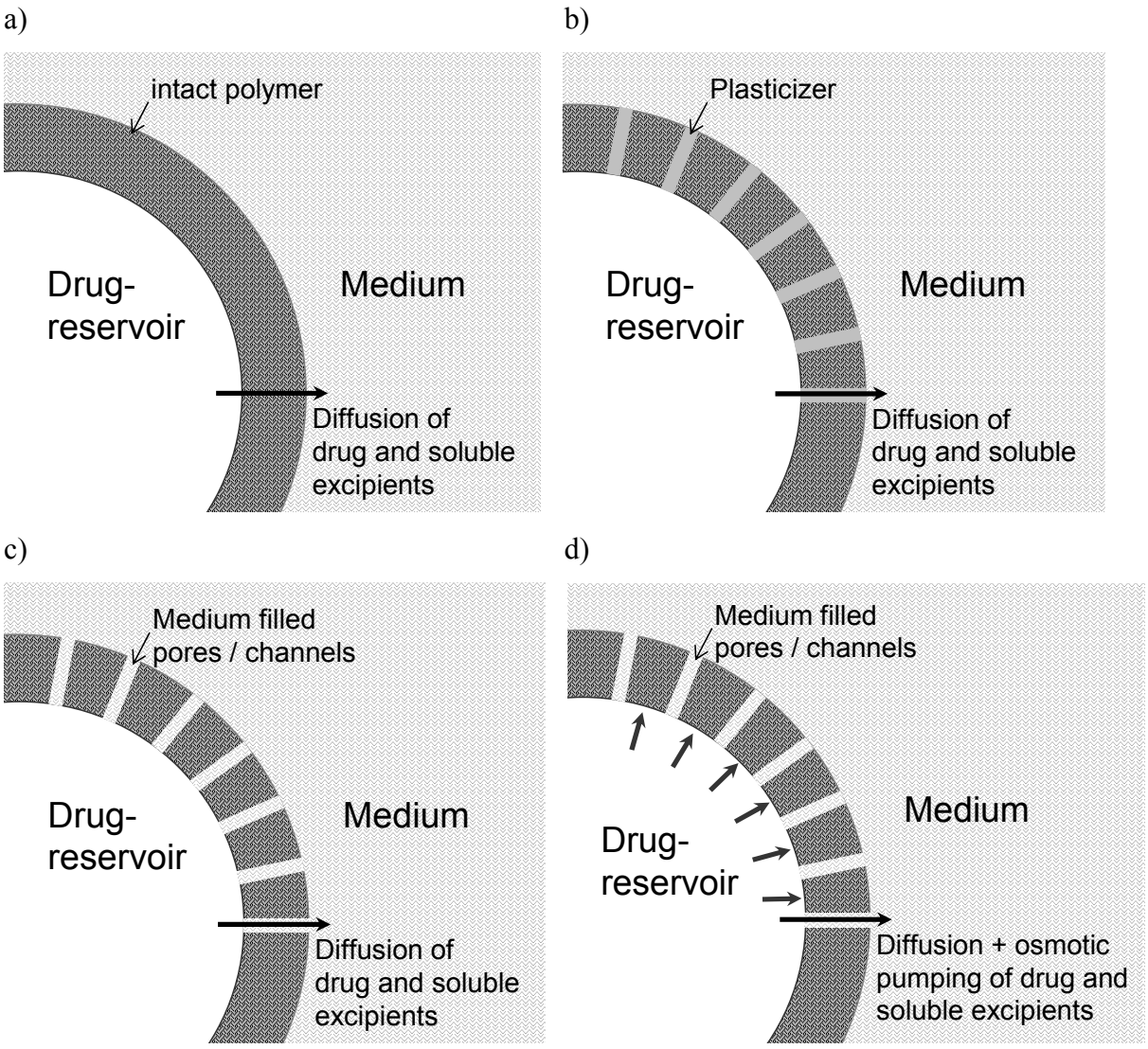


Figure 3. Schematic representation of typical release mechanisms of coated pellets (for reasons of simplicity, channels / pores / cracks are depicted interconnected and without any tortuosity)

Diffusion through intact polymer is often described quantitatively by applying Fick's Law to coated systems:

$$\frac{dm}{dt} = \frac{D \cdot A \cdot c_S}{h}$$

Assuming perfect sink conditions (conc. in medium ≈ 0) and steady state, the amount of drug dm released in time period dt is directly proportional to the apparent diffusivity D, the surface area A available for diffusion and the saturation concentration c_S inside the pellet; and inversely correlated to the diffusional path length / coating thickness h.

In contrast to matrix systems (where the length of diffusional pathways increases during drug release unless the matrix erodes) this diffusional path length is assumed to be rather constant for reservoir systems: the coating thickness. Hence zero-order release is possible for coated systems in steady state, as long as there is still undissolved drug left inside the reservoir to allow for saturation. Once all drug is dissolved, the concentration gradient and in consequence the driving force of diffusional release decrease. The fraction of drug which is potentially released in zero-order can be estimated from its solubility and its volume fraction inside the core (Theeuwes 1975; Zentner, Rork et al. 1985).

Unfortunately, Fick´s Law (which was only ever intended to describe diffusion in binary mixtures) can not be extended to drug release from reservoir pellets that easily (Wesselingh 1993). The diffusivity for example is assumed to be constant in homogeneous, intact polymer films. However, in reality many polymers swell upon contact with medium which is known to gradually increase the diffusivity over time. In addition most polymers contain crystalline regions in which drug diffusion is negligible.

Drug diffusion in the amorphous regions of polymers has been described by the so-called 'jump-and-run'-model (Pace and Datyner 1979). It was proposed that the amorphous segments in polymers contain homogeneous, semi-crystalline structures of polymer molecules which are aligned in parallel. Permeants like the diffusing drug 'run' along the tube between parallel polymer chains until reaching a 'dead-end' (a crystalline region or a point of high chain entanglement). There they are forced to 'jump' from one tube to the next, pushing and bending the polymer chains apart (Figure 4).

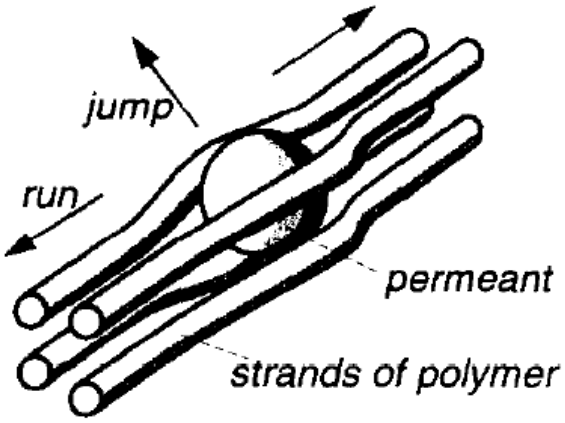


Figure 4. The jump-and-run model of permeant diffusion through intact polymer (Wesselingh 1993)

Naturally, this requires energy and thus determines the frequency of such ‘jumps’ and in consequence the apparent diffusivity. Even if the proposed parallel alignment of polymer chains in the amorphous segments seems somewhat unlikely and a more random structure is assumed; these ‘jumps’ between the chains will nonetheless be necessary for diffusion. Increased chain mobility, e.g. due to hydration of the polymer, use of plasticizers or elevated temperatures, will facilitate ‘jumps’ by increasing the free volume within dense polymer films and thus increase diffusivity (Turnbull and Cohen 1961; Guo 1993; Siepmann, Lecomte et al. 1999).

Fick’s Law further does not consider potential swelling of pellets (which changes surface area A and coating thickness h) or interactions between medium, drug and polymer during diffusion (e.g. ionic interactions between charged drugs and polymers (Sun, Hsu et al. 2001)) or counter-diffusive processes: ‘medium in’ versus ‘drug out’. Especially cores containing osmotically active substances induce a pronounced medium influx which could result in swelling of pellets as well as counter-act the outwards diffusion of the drug (Narisawa, Nagata et al. 1997; Schultz and Kleinebudde 1997; Marucci, Ragnarsson et al. 2008; Muschert, Siepmann et al. 2009 b).

Diffusion through plasticizer channels (Figure 3b), although theoretically possible, was not reported in the literature to the best of our knowledge. This could be due to the fact that most drugs exhibit a higher solubility in aqueous media than in plasticizer. In addition, plasticizers are often used in amounts which are not expected to form a continuous, interconnected plasticizer phase (Ozturk, Ozturk et al. 1990).

However, diffusion through medium filled pores / cracks (Figure 3c) is a rather common release mechanism. Such pores are either the product of the coating process or they form in situ during release. Factors which potentially cause formation of porous membranes during the application of the coating are e.g. poor film formation or spray drying of the polymer, the use of non-solvents in the applied polymer solution as well as the evaporation of plasticizers (Reuvers and Smolders 1987; Lippold and Pages 2001; Meier, Kanis et al. 2004).

In contact with medium, pores can be formed in situ by either leaching and / or cracking. Pore formers like water-soluble sorbitol or urea are easily dissolved and leached from the film. But also water-soluble polymers like polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), hydroxypropyl-methylcellulose (HPMC), hydroxypropylcellulose (HPC) are commonly applied as pore formers (Zentner, Rork et al. 1985; Appel, Clair et al. 1992; Rekhi and Jambhekar 1995; Sakellariou and Rowe 1995; Sotthivirat, Haslam et al. 2007; Muschert, Siepmann et al. 2009 c). Naturally, water-soluble plasticizers like triethylcitrate (TEC) can also act like a pore former when they are leached from the coating (Bodmeier and Paeratakul 1993).

The interconnectivity of the resulting pores – and hence the extent of the diffusivity increase - depends on the volume fraction of the pore former within the insoluble coating. However, even unconnected medium filled pores will facilitate the ‘jumps’ of a dissolved molecule by increasing the free volume in the coating (Turnbull and Cohen 1961; Pace and Datyner 1979).

Another important case is the formation of pores by swelling-induced cracking. The osmotic pressure of the soluble substances inside the reservoir pellets induces a pronounced medium uptake. Depending on the (semi)permeability of the coating and the porosity of the drug core, this medium uptake can lead to the build-up of hydrostatic pressure inside the reservoir. Unless the rigidity of the coating is considerably high, this hydrostatic pressure will expand the coating; thereby reducing the thickness of the film. Once a critical strain is reached, the coating starts to crack.

The size and number of such cracks is of course dependent on the applied stress (Figure 5). It can range from minute micro-voids, cracks or fissures (Hjärtstam, Borg et al. 1990; Schultz and Kleinebudde 1997; Hjartstam and Hjertberg 1998), which are visible only in SEM-pictures to pronounced rupturing as observed in pulsatile drug delivery systems (Ueda, Yamaguchi et al. 1994; Heng, Chan et al. 1999; Roy and Shahiwala 2009). Hence there is a gradual transition from predominantly diffusional release through very small medium filled cracks → osmotic pumping through medium filled cracks → convective release (when the size of the cracks gets large enough to allow the efflux of fluids) → pulsatile release in case of rather complete membrane destruction.

This highlights the vital importance of the mechanical properties of film coatings. Naturally, brittle polymers will crack easily whereas flexible polymers or sufficiently plasticized polymers can exhibit pronounced expansion before cracking or rupturing (Ueda, Hata et al. 1994).

a) thin fissures in an SEM-picture b) macroscopically visible coating ruptures

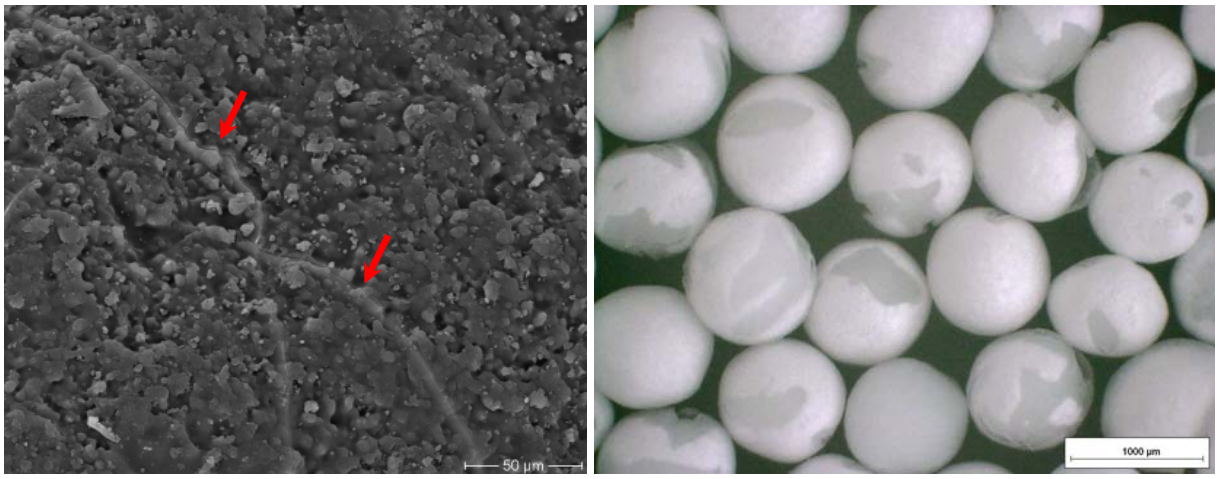


Figure 5. Examples of swelling induced damages in the polymer coating

Osmotic pumping is a common release mechanism which combines diffusional release through medium filled openings with osmotic release components (Ozturk, Ozturk et al. 1990). It can be seen as the intermediate mechanism between pure diffusion and convection and has been described for a variety of coated dosage forms containing osmotically active core excipients (Theeuwes 1975; Zentner, Rork et al. 1985; Lindstedt, Ragnarsson et al. 1989;

Hjärtstam, Borg et al. 1990; Sotthivirat, Haslam et al. 2007). The coating can have either one opening (e.g. a laser-drilled orifice) or numerous pores usually created by leaching or cracking. Drug is released by diffusion through these medium filled channels. However, this process is increased by the hydrostatic pressure inside the coating which results from the osmotic activity of core components like sucrose, sodium chloride or highly soluble drugs.

The osmotic contribution to the overall release rate is often evaluated by increasing the osmolarity of the release medium (Zentner, Rork et al. 1985; Ozturk, Ozturk et al. 1990; Ragnarsson, Sandberg et al. 1992; Schultz and Kleinebudde 1997; Zhang, Zhang et al. 2003; Sotthivirat, Haslam et al. 2007). In order to reduce the osmotic pressure difference across the coating, substances like sodium chloride, urea, sucrose or glucose are added to the medium.

If the release rates decrease, the release mechanism is assumed to be governed by osmotic phenomena. Plotting release rates as a function of the osmotic pressure difference and extrapolating the data to zero osmotic pressure difference (y-intercept) allows an estimation of the diffusional contribution (Figure 6). However, the addition of soluble substances to the medium does not only affect the osmotic pressure difference but can also influence the hydration of the coating, the solubility of the drug and the viscosity of the medium (Sotthivirat, Haslam et al. 2007; Kallai, Luhn et al. 2010). Hence, decreasing release rates in high osmolarity media are not always caused by reduced osmotic pumping.

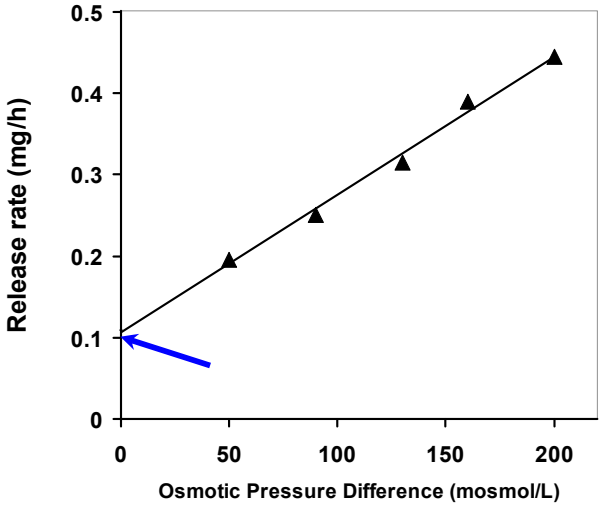


Figure 6. Release rate as a function of the osmotic pressure difference (example)

1.3.1 Determination of sucrose release from reservoir pellets

The majority of drugs can be detected by its UV-absorption. However, sucrose, the soluble and hence osmotically active core component in nonpareil-based pellets, lacks a UV-absorbing chromophore. It is thus commonly detected by either refractive index detectors (RIDs), post-column derivatization or by evaporative light scattering detectors (ELSDs) (Coquet A. 1992; Yuan and Chen 1999; Steinike 2003; Chavez-Servin, Castellote et al. 2004; Li, Chen et al. 2007). Usually samples are separated in an HPLC step first, in order to allow the assignment of a detector signal to the respective single substance.

The principle of ELS-detection is that the liquid HPLC-sample is nebulised into fine droplets by pressurized air (Figure 7a). The resulting mist is then passed with an inert gas (nitrogen or filtered air) through the heated drift tube of the detector where the eluent evaporates (Figure 7b) and particles of all non-volatile materials remain behind. The scattering of an LED light beam (480 nm) caused by these particles is recorded with a photomultiplier tube (Figure 7c).

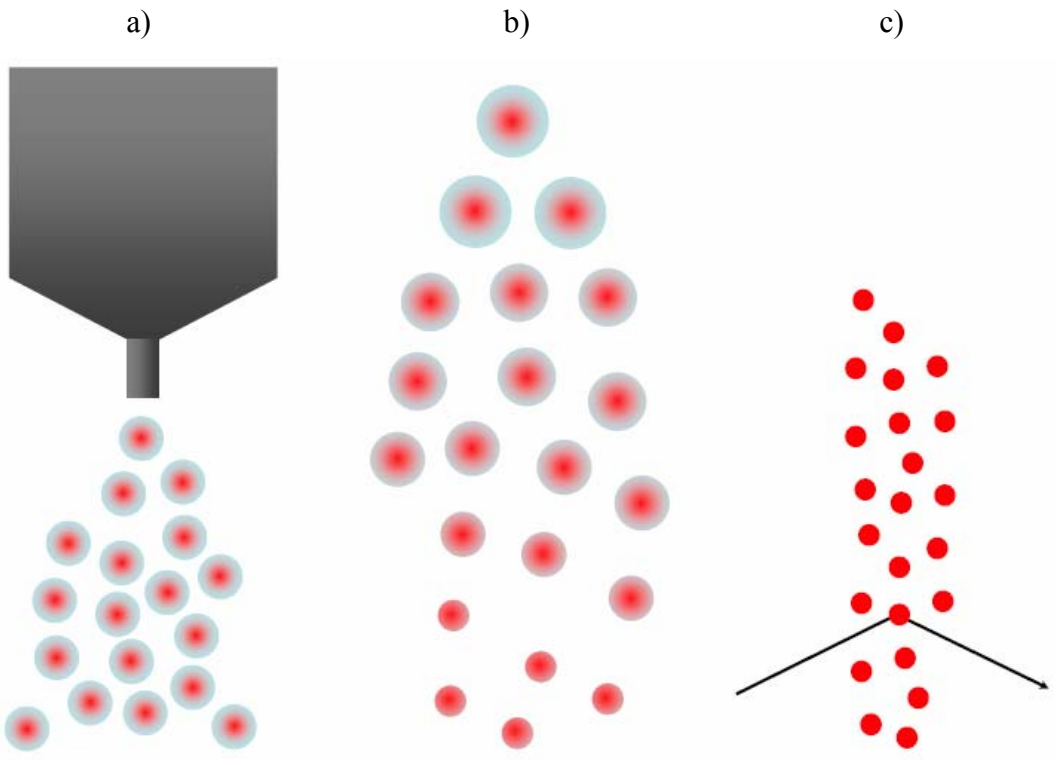


Figure 7. Schematic presentation of the processes inside an ELS-detector; a) nebulization of the liquid sample, b) evaporation of the volatile eluent and c) light scattering of solid, non-volatile analyte particles

Naturally, all eluents have to be volatile in order to avoid interferences with the analytes detection. Acetonitrile (ACN), methanol (MeOH), water and ammonium-acetate-buffers (NH_4Ac) are commonly recommended by the suppliers of ELSDs.

The major advantage of ELSDs over RIDs is their compatibility with eluent gradients and a higher baseline stability (Steinike 2003). Refractive index detectors require isocratic conditions (constant eluent composition), stable flow and sufficient equilibration times. Fluctuations of the pump or air bubbles affect the signal of RIDs. In contrast, the signal in ELSDs is neither affected by air nor the composition of the eluent because the eluent is completely evaporated before the actual detection step.

The light scattering step is a function of the particle size in relation to the wavelength; reflection, refraction and so-called Mie scattering were identified as the main mechanisms in ELSD (Charlesworth 1978). Thus, the signal intensity depends on the size, shape and surface of the dried analyte particles, not their precise chemical composition (Charlesworth 1978; Cardenas, Gallego et al. 1999). However, the size of droplets (and hence the size of the resulting dried particle) is a function of operation parameters. Increased detector response and minimized baseline noise were achieved by higher nebulizer and evaporator temperatures as well as lower gas flow rates through the drift tube (Rashan and Chen 2007).

Unlike UV-detectors, ELSDs exhibit a double-logarithmic correlation between concentration and signal peak area (Liu, Zhou et al. 2007; Rashan and Chen 2007).

For the separation of highly polar substances like carbohydrates or peptides so-called HILIC-methods (hydrophilic interaction chromatography) have become increasingly important. They combine the normal phase (NP) retention of hydrophilic substances with the semi-aqueous mobile phases of reverse phase (RP) methods (SeQuant AB 2006). Typical HILIC-eluents consist of 40%-97% acetonitrile (ACN) in either water or aqueous buffers like ammonium-acetate (NH_4Ac). Due to their volatility they are all suitable for ELS-detection. Since the retention is inverted to RP-methods, higher amounts of organic solvent will lead to longer retention times.

The stationary phase of HILIC-columns is usually based on porous silica particles and is thus hydrophilic. It forms a water-enriched layer in which analytes are retained mainly by hydrogen bonding as well as dipole-dipole interactions. Charged HILIC-columns can additionally retain the analyte by electrostatic interactions. However, to disrupt these interactions and finally elute the analyte, (buffer) salts are required in the eluent. This could

be detrimental for mass detection because many buffer salts are non-volatile and thus produce a signal in ELSDs. This problem is partly outbalanced in zwitterionic HILIC-columns like e.g. ZIC®-HILIC which carry sulfobetaine structures covalently bound to the silica particles (SeQuant AB 2006). These sulfobetaine strucutures have a positive and a negative charge. Due to the proximity of a counter-ion within the water layer of the stationary phase, the electrostatic interactions with charged analytes become weaker. This allows elution in appropriate retention times.

1.4 Formulation of reservoir pellets

1.4.1 Coating equipment

Due to their small size, pellets are commonly coated in fluidized bed coaters in order to achieve homogeneous distribution of the coating formulation and avoid formation of agglomerates. The fluidizing air serves several functions: movement of the pellets, separating them from each other and adjusting the required product temperature. However, the drawback of this large airflow is a higher risk of spray drying during drug layering or polymer coating processes. In fluidized-bed-coating, different processing modes are differentiated by the spraying direction and the principle of air distribution in the processing chamber: top spray, bottom spray, Wurster or rotor coating (Behzadi 2008). Due to the shorter distance between spray nozzle and product, polymer losses due to spray drying are less pronounced in bottom spray coaters compared to top spray coaters (Wheatley 1997). Bottom spray coaters equipped with Wurster inserts, which concentrate the particle flow close to the nozzle, can reduce spray drying further. Rotogranulators are also used for pellet coating and yield comparable coating efficiencies to Wurster-coating when the nozzle position is tangential to the particle flow (Iyer, Augsburger et al. 1993). Since fluidized bed coaters are equipped with pneumatic binary nozzles, both solutions and suspensions of drugs / polymers can be sprayed with a low risk of nozzle clogging. Still, the viscosity of solutions or the solids content of suspensions should be adjusted to the nozzle diameter, in order to further reduce clogging.

1.4.2 Drug layering

Layering is a term commonly describing the application of active pharmaceutical ingredients to multiparticulate starter cores. This can be done from either drug solution or drug suspension. A drawback of aqueous drug solutions is the partial dissolution of soluble starter cores like sucrose nonpareils during the layering process. This can reduce the yield of properly layered pellets by increased agglomerates formation (‘doubles’, ‘triples’) or by increased attrition or breakage of the drug cores (Gryczova, Rabiskova et al. 2008; McConnell, Macfarlane et al. 2009). Pure organic drug solutions on the other hand may evaporate rapidly. In one report this led to very uneven, pockmarked core surfaces which rendered the subsequent extended release coating impossible (McConnell, Macfarlane et al. 2009). Another limiting factor for drug solutions is usually their viscosity which can cause stickiness (Opota, Joachim et al. 1999). The resulting agglomeration of pellets (or sticking to the walls of the coating chamber) can be partially circumvented by dilution or lower spray rates. However, if drug contents of only 10% in solution lead to high viscosities already, suspension layering is usually the more economic technique (Jones 1989). For suspension layering the use of low-viscosity binders like hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC) or polyvinylpyrrolidone (PVP) is highly recommended in order to improve drug adherence to the starter cores and to prevent sedimentation of drug powder in the tubing (Iyer, Augsburger et al. 1993; Sinchaipanid, Chitropas et al. 2004). However, binders can also be necessary for solution layering to prevent cracking, attrition and delaminating of recrystallized and brittle drug layers (Jones 1989).

1.4.3 Polymer coating

Since many polymers used for controlled drug release are water-insoluble, they were traditionally applied from organic solutions. The disadvantages of this process are explosion / flammability hazards, environmental considerations, risk of residual solvents in the polymer film and the higher viscosity of polymer solutions. As an alternative aqueous dispersions of the polymers have been developed, offering low viscosities even at higher molecular weight or solids content (Vanderhoff 1970; Wheatley 1997).

However, the mechanism of film formation on the substrate differs strongly between organic and aqueous coating (Vanderhoff 1970; Bindschaedler, Gurny et al. 1986; Iyer 1990; Lippold and Pages 2001; Lecomte, Siepmann et al. 2004).

Film formation from organic solution is a simple consequence of solvent evaporation: the solution droplets containing discrete polymer molecules coalesce to a fluid-layer on the substrate surface and gradually solidify to a dense, closed film due to the transition solution → sol → gel → film (Figure 8a). Naturally, the same sequence occurs for water-soluble polymers when applied from aqueous solutions. Plasticizers are not a requirement when applying polymer solutions but they can be added to reduce the brittleness of the final film on the dosage form.

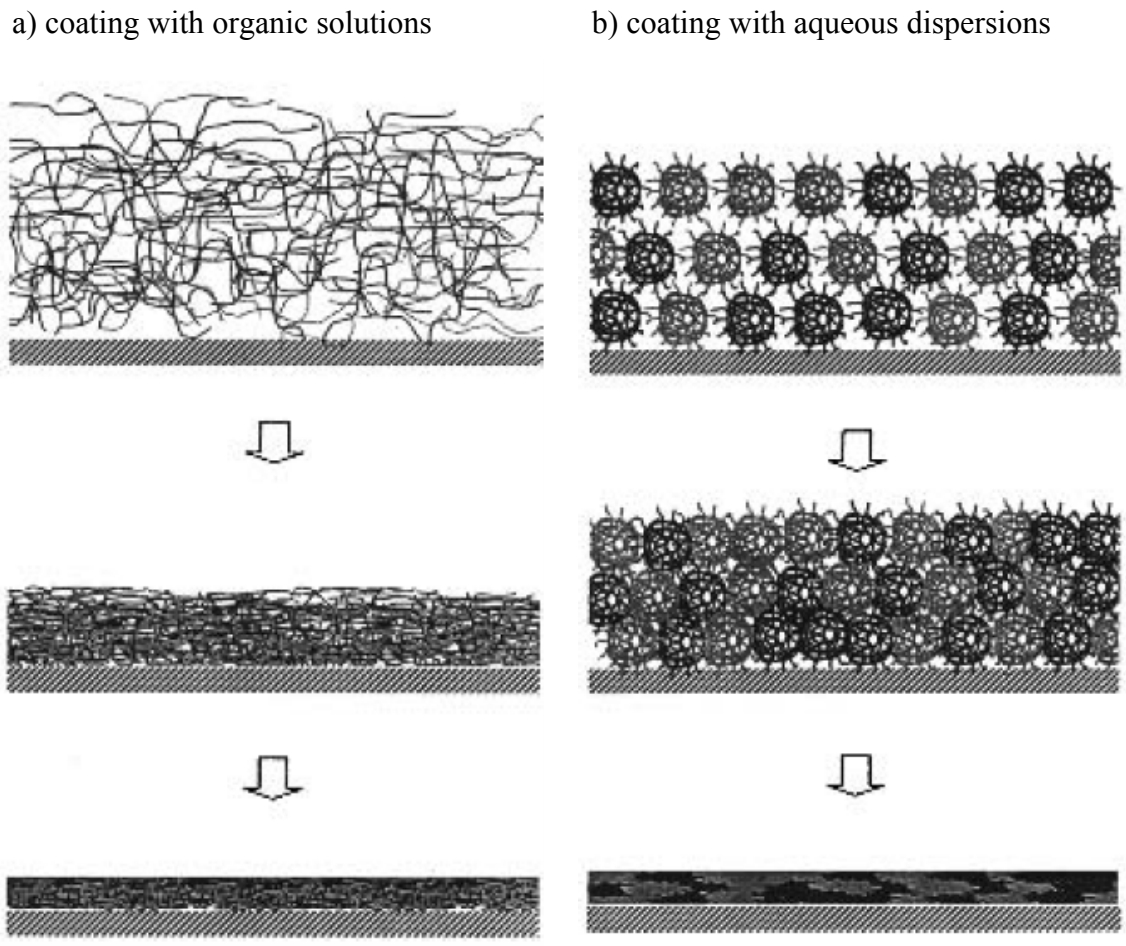


Figure 8. Schematic presentation of the film formation from: a) organic polymer solutions and b) aqueous polymer dispersion (size of polymer molecules and particles not up to scale; grey and black colour represent blends of polymer, like EC/HPC or RS/RL) (Lecomte, Siepmann et al. 2004)

With aqueous dispersions (so called latices), polymer is not applied in the form of molecules but as colloidal particles, each containing hundreds of polymer molecules (Wheatley 1997). During the evaporation of the aqueous continuous phase, the dispersed particles are gradually concentrated and ordered into a close packed, rhombohedral lattice on the substrate surface (Figure 8b).

Once in contact with each other, the particles are immobilized and the remaining water (~26% of the packing volume for monodisperse, spherical particles (Gryczova, Rabiskova et al. 2008)) evaporates from the interstices between them. This results in the deformation and coalescence of the polymer particles due to capillary forces (Brown theory) and polymer-water interfacial tension (Dillon-Matheson-Bradford theory). This process is complemented by inter-diffusion of free polymer chain ends across the particle boundaries (Voyutskii theory) (Vanderhoff 1970). To ensure sufficient coalescence, the solid polymer particles often need to be softened by use of plasticizers in the dispersion and by elevated temperatures during the coating process. Plasticizers reduce the intermolecular forces and thus cohesion inside polymer particles which makes them softer and lowers the minimum film forming temperature (MFT) as well as the glass transition temperature (T_g) of the polymer (Wheatley 1997).

However, even optimized coalescence of the particles during the coating process does not allow polymer-chain-interpenetration to the same extent as with organic solutions since the chain mobility is lower in solid particles. Hence, films applied from aqueous dispersions are usually more porous and exhibit lower tensile strength (Lecomte, Siepmann et al. 2004). In addition, migration of freely water-soluble drugs into the polymer film may occur during aqueous coating processes, thus causing a further increase in porosity once this drug is leached from the coating (Rekhi, Porter et al. 1995). Interactions between ionisable drugs with the anionic surfactants in latices can also lead to higher porosity of the film (Nesbitt, Mahjour et al. 1994). This explains why usually higher amounts of polymer are required for aqueous dispersions in order to achieve comparable coating performance (Bindschaedler, Gurny et al. 1986; Thoma and Bechtold 1999).

1.4.3.1 Storage stability of coated pellets

Another drawback of aqueous coatings is the further gradual coalescence of the polymer particles during storage which leads to denser films and potentially decreasing release rates over time (Wheatley 1997; Lippold and Pages 2001). Storage stable systems coated from aqueous dispersions are mainly obtained by curing steps at elevated temperature and / or humidity subsequent to the coating (Lippold and Pages 2001; Korber, Hoffart et al. 2010) or by incorporating small amounts of soluble or enteric polymers in the water-insoluble coat (Lecomte, Siepmann et al. 2004; Kranz and Gutsche 2009; Muschert, Siepmann et al. 2009 a).

In contrast, organically coated drug delivery systems are mostly considered storage stable (Kranz and Gutsche 2009; Korber, Hoffart et al. 2010). Since the polymer is applied in its molecularly dispersed form, very dense films can be obtained without the risk of further gradual coalescence. However, storage effects can not be ruled out totally for organic coatings (Lippold and Pages 2001). The rather dense structure of organic films can trap volatile solvents easily which then cause changes in the mechanical properties of the films upon gradual solvent evaporation during storage (Gutierrez-Rocca 1993). Pellets coated organically with pure Eudragit® RS show hardened and brittle surfaces upon visual inspection after 1 month storage at room temperature, and thus require a plasticizer in order to improve stability (Chetty and Dangor 1994). Organic solvents are also more prone to spray-drying during the coating process due to their high volatility. This can create porous, organic coatings which are likely subjected to the same storage effects as aqueous coatings (Arwidsson 1991).

1.4.3.2 Thoughts on the coating thickness

In the majority of studies, the coating is applied on a weight base. Thus coating levels are expressed as percent weight gain based on the initial weight of drug cores. This is an easy approach which does not require any characterization of the cores before the coating. However, it may yield coatings of different thickness for different pellets since it does not consider the surface area of a batch. As soon as size and / or density of the drug cores change, the thickness of a weight-based coating will change, too (Heinicke, Matthews et al. 2005).

The reason is simply that any amount of polymer is always applied to a surface area not a weight. With regard to pellets it is vital to keep in mind that the batch surface area is

depending on the surface area of a single pellet and the number of pellets in a given batch weight. Therefore not only the size but also the density (hence the weight) of a single pellet are important.

The density differences of pharmaceutical multiparticulates may appear negligible. However, the practical relevance has been reported before (Heinicke, Matthews et al. 2005). Despite compensating increasing drug loadings with decreasing sizes of starter cores, in order to get drug cores of the exact same size, the authors obtained different coating thicknesses when all batches were coated with the same amount of polymer. The reason was the lower density of the drug layer compared to the starter core; a finding which was confirmed by other authors (Gryczova, Rabiskova et al. 2008).

Thus, differences in batch surface area can be expected for different drugs, different drug loading levels, different layering techniques (e.g. solution vs. suspension) or different starter cores. The density of sugar nonpareils e.g. has been measured as 1.444 ± 0.071 mg/cm^3; the densities of starter cores made of microcrystalline cellulose from two suppliers as 1.513 ± 0.001 mg/cm^3 and 1.363 ± 0.001 mg/cm^3 for Celphere® and Cellets®, respectively (Gryczova, Rabiskova et al. 2008). Hence, whenever comparing pellets which are based on different drug cores, the coating should be applied based on the batch surface area (e.g. estimated from single pellet weight and size) rather than its weight.

1.5 Excipients for extended release reservoir pellets

1.5.1 Polymers

1.5.1.1 Ethylcellulose (EC)

Ethylcellulose is a semi-synthetic, water-insoluble, pH-independent polymer derived from the polymeric backbone of cellulose, a natural polymer of ~1000 β-anhydroglucose units. Each of these glucose units contains three replaceable hydroxyl groups which are etherified with ethyl groups in a synthetic step. In commercially available EC grades, the degree of substitution ranges from 2.2 to 2.6 (of max. 3) which explains the water-insolubility and pH-independency of this polymer (Rekhi and Jambhekar 1995).

The viscosity of EC solutions and the mechanical properties of the resulting coating, on the other hand, depend on the molecular weight (chain length) of the polymer. Viscosity and tensile strength increased at higher molecular weights, thus reducing the incidence of film cracking and decreasing drug release (Rowe 1986; Rowe 1992). However, with a glass transition temperature of ~133 °C (EC 10cP) films made from the pure polymer are very brittle and thus commonly require plasticizers (Terebesi and Bodmeier 2010).

Ethylcellulose is generally considered non-toxic, non-allergenic and stable under physiological conditions. Its water-insoluble and pH-independent properties have made ethylcellulose one of the most important polymers for controlled-release applications, moisture protection or taste masking purposes (Marucci, Hjärtstam et al. 2009). Pure EC exhibits a very low water permeability; only ~1/10 of celluloseacetate (Lindstedt, Ragnarsson et al. 1989). Therefore it is often combined with other more permeable polymers, like the enteric Eudragit® L or the water-soluble Kollicoat® IR (Lecomte, Siepmann et al. 2005; Muschert, Siepmann et al. 2009 c). Most common, however, are blends of EC with other, water-soluble cellulose derivatives like HPMC or HPC. Both blends, EC/HPMC and EC/HPC, were shown to phase-separate into EC and HPMC / HPC rich domains (Sakellariou, Rowe et al. 1986; Sakellariou and Rowe 1995). This phase-separation was less pronounced for HPC; due to its lower substitution, more stabilizing interactions with EC were possible.

1.5.1.2 Eudragit® RL and Eudragit® RS (RL and RS)

Eudragit® RL and RS (ammonio methacrylate copolymer type A und B) are methacrylate copolymers with cationic quaternary trimethylammonio groups which determine their hydrophilicity. Next to ethylcellulose, RS and RL are the most common polymers for extended release applications.

They are water-insoluble over the physiological pH-range but swell upon contact with aqueous media (Bodmeier, Guo et al. 1996). The extent of this swelling is controlled by the content of quaternary ammonio groups in the polymer. RL has a higher ratio of 1:20 (ammonio groups to neutral esters), while in RS it is only 1:40. Hence RL swells easier and becomes more permeable than RS. This is also indicated in their abbreviations. RL and RS stand for the german words ‘Retard Leicht’ and ‘Retard Schwer’, so ‘highly permeable’ and ‘poorly permeable’. The different permeabilities are shown quite impressively with the model substance urea which has 500 times higher permeability in RL than in RS (Okor 1982).

The major benefit of RS/RL, compared to EC/HPC or EC/HPMC blends, is their miscibility which allows easy adjustment of a desired coating permeability without the risk of incompatibilities (AlKhatib and Sakr 2003; Kramar, Turk et al. 2003). In addition, RS and RL have low glass transition temperatures of ~58-62 °C (Wagner, Maus et al. 2005; Terebesi and Bodmeier 2010). Hence they are comparably flexible polymers which require less plasticizer and lower product temperatures during coating.

Due to the quaternary ammonio groups, the ionization of RS/RL (and in consequence the hydration of the polymer) is not expected to be affected by pH within the physiological range. However, pseudo-pH-dependent release profiles have been observed due to ion-exchange processes with the counter ions of the release medium (Okor 1990; Bodmeier, Guo et al. 1996; Knop 1996; Wagner and McGinity 2002; Grützmann 2005). During release the chloride counter ions of the ammonio groups are exchanged with anions of the release medium. These can affect the hydration behaviour: anions with a small hydrodynamic radius like chloride or nitrate as well as bivalent anions like sulfate or disuccinate have a high affinity to the ammonio groups of RS/RL and reduce hydration. In contrast, ions with a large hydrodynamic radius like acetate, formate or phosphate have a low affinity and foster hydration and swelling of the polymer. The concept of pH-independency was always re-confirmed by addition of sodium chloride to buffers of different pH; hydration and hence release were markedly reduced (Bodmeier, Guo et al. 1996; Knop 1996; Wagner and McGinity 2002).

This phenomenon should also be considered before adjusting the osmolarity of the medium with sodium chloride. In order to evaluate the osmotic component of a release mechanism, uncharged glucose would be more suitable (Kallai, Luhn et al. 2010).

Naturally, interactions between cationic RS/RL and ionic substances are also feasible for drugs and core excipients or their counter ions. Narisawa et al. reported an increased permeability of thick RS coatings when incorporating succinic acid into the drug core (Narisawa, Nagata et al. 1996; Narisawa, Nagata et al. 1997). However, the sigmoidal profiles which were thus obtained were also found without the addition of acid by other authors (Bodmeier, Guo et al. 1996; Wagner and McGinity 2002; Kramar, Turk et al. 2003; Zhang, Zhang et al. 2003; Heinicke and Schwartz 2007). Hence sigmoidal release appears to be a typical feature of RS/RL films, unless the films are very thick.

Narisawa also showed that undissociated succinic acid lowers the glass transition temperature of RS. The associated increase in polymer chain mobility and hydration is an additional reason for the faster release in presence of the acid.

For diltiazem hydrochloride microspheres and solvent-cast diclofenac sodium films no drug-retaining, ionic interactions with Eudragit RS were observed (Sipos, Szucs et al. 2008; Turk, Hascicek et al. 2009). However, ionic interactions influenced the release of anionic aspirin and cationic ambroxol from RS/RL-coated pellets (Sun, Hsu et al. 2001).

1.5.1.3 Celluloseacetate (CA)

Celluloseacetate is a semi-permeable polymer with high water permeability (~10 higher than EC (Ramakrishna and Mishra 2002)) and pronounced rigidity (T_g ~190 °C, (Guo 1993)). Thus it is predominantly used in osmotically controlled drug delivery systems (OCDD) systems but also as the release controlling membrane in reservoir type transdermal patches (Appel, Clair et al. 1992; Rao and Diwan 1997; Schultz, Tho et al. 1997).

The high rigidity of the polymer apparently stems from a high degree of chain entanglement and prevents deformation of the outer coating of OCDDs during media uptake. Typical OCDDs are composed of an osmotically active core tablet (sodium chloride, sugar and / or highly soluble drugs) and a CA-top-coating. The coating can either contain a laser-drilled orifice for the convective transport of drug solutions (Theeuwes 1975) or several pores which allow osmotic pumping (Zentner, Rork et al. 1985). These pores can be formed during the coating process by using aqueous CA-dispersions or by adding small amounts of non-solvents like water to organic CA-solutions (Meier, Kanis et al. 2004). Or they form in situ during the release by cracking or pore-former leaching (Schultz and Kleinebudde 1997; Meier, Kanis et al. 2004). Various pore-formers have been applied to create micro-porous celluloseacetate membranes with even higher water permeability and hence shorter lag times: sorbitol, polyethylene glycol, urea, sucrose, propylene glycol, castor oil (Zentner, Rork et al. 1985; Appel, Clair et al. 1992; Kelbert and Bechard 1992; Ramakrishna and Mishra 2002)

However, when working with aqueous dispersions, the high rigidity of CA can only be overcome with unusually high amounts of plasticizers (100-320% based on polymer) or high process and curing temperatures (60-80 °C) (Bindschaedler, Gurny et al. 1986; Kelbert and Bechard 1992) which may be detrimental to the stability of some drugs. Thus, cellulose acetate films are best applied from organic solutions.

1.5.2 Starter cores – Potential influences on drug release

While the influence of polymer coatings on drug release has been studied extensively, there is still only limited data available about the effect of the starter core on drug release (Muschert, Siepmann et al. 2009 c). Often sugar spheres (so called nonpareils, NP) are used as starter cores (Gryczova, Rabiskova et al. 2008; Kallai, Luhn et al. 2010). They consist of an initial sucrose crystal which is then layered to various commercially available sizes with sucrose and starch (Gryczova, Rabiskova et al. 2008).

Alternatively, water-insoluble microcrystalline cellulose (MCC) starter cores can be used. They have been reported to offer higher abrasion resistance, lower agglomeration tendencies during aqueous drug layering and less interference by mechanical stress during dissolution compared to sugar spheres (Mohamad, Dashevsky et al. 2005; Gryczova, Rabiskova et al. 2008). Just recently a third starter core made of isomalt was introduced to the market but data is still very limited (Kallai, Luhn et al. 2010).

Starter cores are usually considered inert (Ghebre-Sellassie 1989; Gryczova, Rabiskova et al. 2008; Kallai, Luhn et al. 2010). However, recent reports indicate that the starter cores could affect the release from reservoir pellets.

MCC starter cores are insoluble but adsorption of drugs to MCC (in the powder form) has been reported, which may slow down the release (Okada, Nakahara et al. 1987; Rivera and Ghodbane 1994; AlNimry, Assaf et al. 1997).

In contrast sugar nonpareils dissolve and the major constituent (~75%) sucrose can be released, thus increasing the volume inside the pellets which can be filled by medium. This could be beneficial to the dissolution of drugs with poor solubilities (Muschert, Siepmann et al. 2009 c). The strong osmotic activity of sucrose starter cores has also been suggested to cause faster and higher water uptake (Tang, Schwartz et al. 2000; Lecomte, Siepmann et al. 2005; Muschert, Siepmann et al. 2009 c). Usually this results in increased tensile stress on the membrane (Hjärtstam, Borg et al. 1990; Hjartstam and Hjertberg 1998; Heng, Chan et al. 1999), dilution of the drug concentration inside pellets and potentially the formation of a counter current to the outwards diffusion of drugs (Narisawa, Nagata et al. 1997; Marucci, Ragnarsson et al. 2008; Muschert, Siepmann et al. 2009 b). After the sugar is released, the

fluid filled spheres could show a higher sensitivity to mechanical stress (Ahmad Mohamad 2005; Heinicke and Schwartz 2007). In addition, sucrose solutions could lead to changes in drug solubility and coating hydration (Paruta 1964; Etman and Naggar 1990; Heinicke and Schwartz 2007).

Mostly, drug release from ethylcellulose-coated pellets was faster when using sugar cores. As expected, this was attributed to the higher osmotic activity of the core which presumably resulted in cracking of the film coating and osmotic pumping (Heng, Chan et al. 1999; Tang, Schwartz et al. 2000; Wesseling and Bodmeier 2001; Lecomte, Siepmann et al. 2005; Mohamad, Dashevsky et al. 2005; Heinicke and Schwartz 2007; Muschert, Siepmann et al. 2009 c).

On the other hand, slower release has also been reported for ethylcellulose-coated sugar pellets, when comparing pellets based on sugar cores (either with or without a seal-coat) with MCC starter cores (Muschert, Siepmann et al. 2009 b). This was again explained by the supposedly faster water uptake into sugar pellets which could act as a counter current to drug diffusion.

Similar but fewer results were also reported for RS/RL-coated pellets. For systems coated with aqueous dispersions (RS 30D / RL 30D) drug release was faster for sugar cores compared to MCC starter cores or seal-coated sugar cores (Heng, Chan et al. 1999; Kallai, Luhn et al. 2010). Applying the RS/RL blends from organic solution, though, led to similar release rates but increased lag times for the sugar cores (Heinicke and Schwartz 2007).

These inconsistent results indicate that the effects of starter core type and film coating properties on the drug release are interconnected. Unfortunately, most studies did not consider the size or the density of their different starter and drug cores. This may have led to films of different thickness (Heinicke and Schwartz 2004). This issue as well as other factors concerning the coating (such as aqueous vs. organic, type and amount of plasticizers or other additives, cured vs. uncured) make it nearly impossible to cross-compare the scarce data.

1.5.3 Drug and Binder - Potential influences on drug release

1.5.3.1 Modeldrugs

Diprophylline, theophylline and carbamazepine were chosen as model drugs for the present study due to their different and pH-independent aqueous solubilities. Since they are non-ionisable in the physiological pH-range (Figure 9), ionic drug-polymer-interactions as described above for cationic Eudragit RS/RL are unlikely.

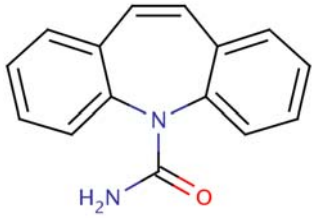
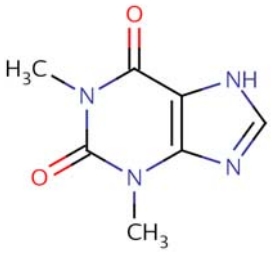
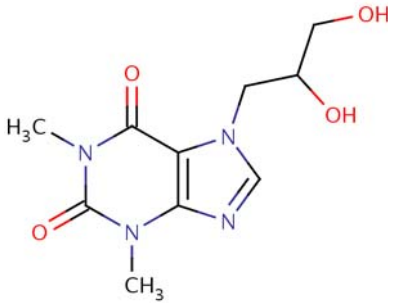
a) carbamazepine (CBZ)	b) theophylline (THP)	c) diprophylline (DPP)
		
M_R = 236.27 g / mol	M_R = 180.06 g / mol	M_R = 254.24 g / mol
c_S = 0.274 mg/mL	c_S = 11.2 mg/mL	c_S = 212 mg/mL
pKa ≈ 13.4	pKa ≈ 8.8	neutral

Figure 9. Structures and useful parameters of the model drugs

Carbamazepine (CBZ) is a widely prescribed anticonvulsant drug with a narrow therapeutic range. It is used predominantly in the treatment of epilepsy but also in the prophylactic therapy of psychiatric disorders. The drug is poorly water-soluble with values of 0.240 to 0.274 mg/mL in water at 37 °C reported in the literature (Murphy, Rodriguez-Cintron et al. 2002; Sehic, Betz et al. 2010).

At a pKa value of 13.4 CBZ is considered non-ionisable in the physiologic pH-range (Queiroza, Bertucci et al. 2008). Nonetheless, solubility at pH 1.2 and 37 °C was slightly higher with 0.311 mg/mL (Kobayashi, Ito et al. 2000).

However, CBZ is known to exist in at least 4 anhydrous polymorphic forms as well as a dihydrate (Murphy, Rodriguez-Cintron et al. 2002; Strachan, Howell et al. 2004; Sehic, Betz et al. 2010). The polymorphic forms have different crystal structures and hence different physicochemical properties, like melting point, compressibility, dissolution rate, solubility and bioavailability (Kobayashi, Ito et al. 2000). The P-monoclinic anhydrous form of CBZ is thermodynamically more stable at room temperature than the triclinic form and is thus used in marketed products (Sehic, Betz et al. 2010). However, in aqueous solutions the dihydrate is the most stable form. All polymorphs are converted to the dihydrate within ~20 min (Kobayashi, Ito et al. 2000; Otsuka, Ohfusa et al. 2000; Murphy, Rodriguez-Cintron et al. 2002; Sehic, Betz et al. 2010).

The dihydrate exhibits a slightly lower solubility than the anhydrous form. Values of 0.240 vs. 0.515 mg/mL, 0.283 vs. 0.491 mg/mL and 0.311 vs. 0.499 mg/mL were determined (Kobayashi, Ito et al. 2000; Murphy, Rodriguez-Cintron et al. 2002; Sehic, Betz et al. 2010). The dihydrate also has the lowest intrinsic dissolution rates: 16.6 vs. 37.6 µg/min·cm^2, 23.1 vs. 69.1 µg/min·cm^2 and 41.8 vs. 67.4 µg/min·cm^2.

Naturally, this conversion of anhydrous polymorphs to the dihydrate can also take place during formulation steps such as wet granulation or during storage at high humidities (Wang, Shiu et al. 1993; Otsuka, Hasegawa et al. 1999). However, the dihydrate formation is slowed down significantly by use of binders like HPMC and HPC (Katzhendler, Azoury et al. 1998; Otsuka, Ohfusa et al. 2000; Qu, Louhi-Kultanen et al. 2007). Grinding of CBZ samples, on the other hand, leads to a faster conversion of the anhydrous form to the dihydrate (Murphy, Rodriguez-Cintron et al. 2002).

Theophylline (THP) is an anionic methylxanthine drug with a narrow therapeutic range. However, at a pKa of 8.8 it will not be ionized within the physiological pH-range (Blanco and Valverde 2002). Commonly it is used as a bronchodilatator in the therapy of respiratory disorders such as asthma. Similar to carbamazepine it is known to exist in a crystalline monoclinic monohydrate form and four anhydrous polymorphs (Seton, Khamar et al. 2010). The stable, orthorhombic anhydrous form II can be produced from the monohydrate by dehydration. In organic theophylline slurries, a new form IV was obtained which appears to be even more stable. However, if the water content in these slurries was increased above ~70%, solution-mediated conversion of the anhydrous forms to the monohydrate occurs gradually in ~10h (Seton, Khamar et al. 2010).

Naturally, in purely aqueous media the same anhydrate-monohydrate-conversion takes place rapidly within 10min, e.g. during dissolution or release of THP (Desmidt, Fokkens et al. 1986; Rodriguezhornedo, Lechugaballesteros et al. 1992). Therefore all aqueous solubility values are typically those of the less soluble monohydrate form.

The reported solubilities range from 5.8 – 8.0 mg/mL at 25 °C (Paruta and Sheth 1966; Brossard, Ratsimbazafy et al. 1991; Desmidt, Offringa et al. 1991; Seton, Khamar et al. 2010), to 11.2 - 11.8 mg/mL at 37 °C (Freichel and Lippold 2000; Grassi, Zema et al. 2004; Sriamornsak and Kennedy 2007).

For the anhydrous form of THP significantly higher values were calculated, 12.6 mg/mL (vs. 5.6 mg/mL) at 25 °C (Desmidt, Fokkens et al. 1986) or 8.75 mg/mL (vs. 2.99 mg/mL) at 10 °C (Rodriguezhornedo, Lechugaballesteros et al. 1992).
Slightly higher values of 12.5 and 14 mg/mL were noted for THP in 0.1N HCl at 37 °C (Sriamornsak and Kennedy 2007; Muschert, Siepmann et al. 2009 a).

Diprophylline (DPP) is a neutral, highly soluble theophylline derivative, also known as dyphylline or dihydroxypropyl-theophylline. Since all protons of the xanthine structure are replaced by either methyl-groups or the dihydroxypropyl-group, DPP is non-ionisable over the physiological pH-range (Blanco and Valverde 2002). It is used alternatively to or in combination with theophylline as a bronchodilatator in the treatment of asthma or COPD. Combinations of diprophylline and theophylline were reported to provide synergistic effects on relaxation of the bronchial tissue at a larger therapeutic range (Kukovetz, Poch et al. 1983; Agbaba, Zivanovstakic et al. 1992). However, owing to its cAMP phosphodiesterase inhibiting properties, diprophylline was also considered for the local treatment of psoriasis (Touitou, Shacoezra et al. 1992). Unlike carbamazepine and theophylline, no polymorphic forms were reported for diprophylline to date. Nonetheless literature reports different solubility values, ranging from 140 mg/mL at 25 °C to 212 mg/mL and 333 mg/mL at 37 °C (Brossard, Ratsimbazafy et al. 1991; Neau, Howard et al. 1999; Grassi, Zema et al. 2004).

1.5.3.2 Potential influences of the drug layer on drug release

Drug and binder are applied together to the starter cores in a layering step, in order to produce drug cores. As described earlier (1.4.2) this is done either from drug solution or drug suspension. Typical binders are low-viscosity, water-soluble polymers like hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC) or polyvinylpyrrolidone (PVP). Sucrose has also been used as binder (Narisawa, Nagata et al. 1996).

However, the binder is not only 'sticking' the drug onto the starter core but forms a spray-dried layer of solid drug dispersion / solution. The binder HPMC has been shown to improve wettability, dissolution rate and solubility of poorly soluble drugs, as well as preventing recrystallization and thus prolonging supersaturation in a wide variety of formulations (Usui, Maeda et al. 1997; Raghavan, Trividic et al. 2000; Gao, Rush et al. 2003; Verreck, Six et al. 2003; Matteucci, Brettmann et al. 2007; Kennedy, Hu et al. 2008; Gao, Akrami et al. 2009). These effects were also reported for physical mixtures of crystalline drugs and HPMC obtained by simple cogrinding; proving that conversion of the drug into the amorphous state is not a general requirement for the improved dissolution behaviour (Vogt, Kunath et al. 2008). The prolongation of supersaturation correlates with the HPMC concentration and its molecular weight (Usui, Maeda et al. 1997; Raghavan, Trividic et al. 2000; Matteucci, Brettmann et al. 2007; Gao, Akrami et al. 2009). This was partially attributed to the resulting viscosity but also to drug-HPMC-interactions. In other reports, HPMC was simply described as a 'spacer' between drug molecules or drug particles or it was used as a surface coating on amorphous drug particles (Matteucci, Brettmann et al. 2007). Recrystallization was also successfully delayed or prevented when HPMC was added to supersaturated release media instead of the formulation (Matteucci, Brettmann et al. 2007; Albers, Alles et al. 2009).

Hence, increasing the HPMC contents in layered pellets could have a positive effect on the release of poorly soluble drugs. However, to date the binder content has rarely been evaluated beyond the layering efficiency. For pellets layered and coated in a rotary coater, a higher binder content did not affect the layering efficiency but led to slower release (Iyer, Augsburger et al. 1993). When using a bottom spray coater, though, increased binder contents led to slightly improved layering efficiencies but had no effect on drug release (Sinchaipanid, Chitropas et al. 2004).

Another parameter of the drug layer is the drug loading, mostly referring to percent drug based on the weight of the starter cores. Due to percolation issues, the effect of drug loading on release has been well described for matrix systems. However, for coated reservoir pellets it was investigated by very few studies.

For pellets coated with an aqueous EC-dispersion (Aquacoat® ECD-30) faster release was reported at higher drug loadings of poorly soluble indobufen (Bianchini and Vecchio 1989) or highly soluble propranolol hydrochloride, respectively (Rekhi, Porter et al. 1995). In contrast, no effect of propranolol hydrochloride loading on release was observed for pellets coated with another aqueous, pre-plasticized EC-dispersion (Surelease®) (Rekhi, Porter et al. 1995). Due to the pKa-value of this drug (~9.45), it was more soluble in the Aquacoat-dispersion (pH 7) than in the Surelease-dispersion (pH 12). Consequently, more propranolol hydrochloride migrated into Aquacoat films during the coating process.

In another study the faster release of diltiazem hydrochloride from Eudragit® RS/RL 100 coated pellets at higher loadings was attributed to longer periods of saturation of the highly soluble drug inside the reservoir (Heinicke and Schwartz 2007). This in accordance with reports for systems with an osmotic pumping release mechanism, where high drug solubility equates to shorter periods of saturation and thus lower fractions releasable in zero-order (Theeuwes 1975; Zentner, Rork et al. 1985).

However, despite the decreasing driving force for diffusion below the saturation, increased aqueous solubility usually results in enhanced diffusion through hydrated coating or aqueous channels. This is also reflected in Fick's Law where the release rate dm/dt is directly proportional to drug solubility c_S. Hence, as expected, most studies reported a faster release of drugs with a higher solubility from coated dosage forms (Ragnarsson, Sandberg et al. 1992; Kim 1999; Neau, Howard et al. 1999; Sriamornsak and Kennedy 2007).

However, drug permeability of a coating is also governed by the molecular size of the drug or its affinity to the polymer (Muschert, Siepmann et al. 2009 c). In addition, high drug solubilities do not necessarily correlate with fast dissolution rates (Grassi, Zema et al. 2004). These factors can lead to release profiles which are not in agreement with the drug solubility (Nesbitt, Mahjour et al. 1994; Sadeghi, Ford et al. 2003; Muschert, Siepmann et al. 2009 c).

1.6 Objectives

The objectives of this work were:

to clarify the impact of two common starter core types, water-soluble nonpareils and water-insoluble MCC starter cores, on the drug release from extended release reservoir pellets coated to comparable film thickness,

to identify the release mechanism of Eudragit® RS/RL 100-coated pellets based on different starter cores

and

to investigate how drug layer properties such as drug solubility, binder content and drug loading, influence the drug release from reservoir pellets coated with Eudragit® RS/RL 100 blends.

Materials and Methods

2 Materials and methods

2.1 Materials

Unless mentioned otherwise, all materials were of reagent grade and used as received.

Drugs and Pigment

carbamazepine micronized (CBZ, FIS Fabrica Italiana Sintetici, Alto de Montevecchio, Italy), anhydrous theophylline micronized and diprophylline micronized (THP and DPP, BASF, Ludwigshafen, Germany), red pigment (Sicovit® red 30, E172 , BASF, Ludwigshafen, Germany)

Binder

hydroxypropylmethylcellulose (HPMC, Methocel® E5 Premium, Colorcon, Orpington, UK)

Polymers

celluloseacetate (CA, CA-398-10, Eastman, Kingsport, TN, USA), ethylcellulose (EC, Ethocel® standard 10cP, premium grade, Dow Chemical, Midland, MI, USA), ammonio methacrylate copolymer type A and B (Eudragit® RL 100 and RS 100, Evonik Röhm GmbH, Darmstadt, Germany)

Pore formers

for EC: hydroxypropylcellulose (HPC, Klucel® EF Pharm, Hercules Incorporated, Wilmington, USA),

for CA: polyethylene glycol (PEG) 3350 (Lutrol® E 3350, BASF, Ludwigshafen, Germany)

Starter cores

sucrose nonpareils 710-850 µm (NP, Suglets®, NP Pharm S.A., Bazainville, France),

microcrystalline cellulose cores 500-710 and 710-850 µm (MCC, Celphere™ 507 and 708, Asahi Kasei, Japan), microcrystalline cellulose cores 710-850 µm (Cellets® 780, Harke Pharma, Mühlheim a.d.R., Germany)

Solvents

acetone, isopropanol, deionized water, acetonitrile (HPLC-grade)

2.2 Methods

2.2.1 Preparation of coated pellets

In order to avoid incompatibilities with the ammonio-groups of the Eudragit® RS/RL coating three non-ionisable drugs were chosen as model drugs with different solubilities: carbamazepine, theophylline and diprophylline. Suspensions of the micronized drugs (solids content 10% w/w) were prepared in an aceotropic isopropanol-water-mixture (88:12 w/w) containing 40% HPMC (based on drug) as the binder. Additional batches at 5% and 20% HPMC were prepared for the binder effect study. The suspensions were stirred overnight with a blade stirrer before layering them to drug loading levels of 2, 10 or 50% (w/w, based on starter core weight) onto either sucrose nonpareils or microcrystalline cellulose starter cores in a Glatt GPCG 1.1 fluidized bed coater. Unless mentioned otherwise, Celphere™ starter cores were used for the MCC batches. Layering conditions were: 1.0 mm nozzle diameter, 1.2 bar atomizing air pressure, spray rate 10-13 g/min and product temperature ~30 °C.

Red pigment cores with 10% weight gain were prepared likewise, replacing 25% of the carbamazepine amount by pre-sieved (125 µm) Sicovit® red pigment.

Drug cores (450 g) were then coated to coating levels of 1 – 5 mg/cm^2 from organic solution with either Eudragit RS/RL 100 blends (12.5% polymer in isopropanol / acetone / water 82:15:3 w/w) or EC/HPC blends (7% polymer in isopropanol / water 96:4 w/w). The surface area-based coating approach ensured comparable film thicknesses for all different drug cores.

In a preliminary study CA/PEG films were applied from organic solution (7% polymer in acetone / water 96:4 w/w) to coating levels 5-25% (w/w based on initial drug core weight).

Coating conditions were: 1.0 mm nozzle diameter, 2.0 bar atomizing air pressure, spray rate 5-6 g/min and product temperature 28 °C for RS/RL and CA/PEG or 45 °C for EC/HPC. Before further use, drug cores and coated pellets were stored in a hot air oven at product temperature overnight, in order to remove residual solvent.

Coated pellets based on sucrose nonpareils and microcrystalline cellulose starter cores will hereafter be referred to as NP pellets and MCC pellets. Batch names represent the drug loading in percent, the drug, the starter core type, the polymer blend and the polymer ratio; e.g. 50-CBZ-NP-RS/RL-65:35.

2.2.2 Characterization of drug cores and coated pellets

2.2.2.1 Mean weight, size distribution and aspect ratio

The mean weight of drug cores and pellets as well as their respective median diameter (D50) were determined by counting and weighing 3 x 100 cores, in order to estimate the batch surface area of 450 g drug cores prior to coating. All 300 single cores / pellets were measured manually in top view photographs using a macroscope at 55x magnification (DFK 31F03 colour camera, The Imaging Source Europe GmbH, Bremen, Germany) coupled with an image analysis software (IQ Easy measure®, INTEQ Informationstechnik GmbH, Berlin, Germany). Each single pellet diameter represents the mean of two measurements (longest and shortest diameter) to determine the aspect ratio (AR) and to account for deviations from circular shape (AR < 1.20 was considered circular).

2.2.2.2 Apparent density and surface area/weight ratio

The apparent density and the surface area/weight ratio were calculated from mean weight and D50 values (assuming perfect sphericity und non-porous surfaces for all particles) in order to estimate the batch surface area of 450 g drug cores prior to coating.

2.2.2.3 Sphericity

Sphericity of starter cores was determined by placing ~100 mg at one side of a melamine board positioned at a low angle of ~7°. Cores which were more or less spherical rolled freely, whereas non-spherical material like e.g. aggregates, egg-shaped or flattened platelet-like cores remained behind. Ten gram of each starter core type was separated like this and percentage of spherical cores determined.

2.2.2.4 Coating thickness

The coating thickness of pellets coated to 5 mg/cm^2 was calculated as half the difference between D50 values of drug cores and pellets. The highest coating level was chosen for the coating thickness study in order to increase the accuracy.

2.2.2.5 SEM pictures of RS/RL-90:10-coated pellets

Coated pellets were sputtered with gold palladium for 230 s and then observed under a scanning electron microscope (Philips SEM 515, Typ PW6703, Philips Optical Electronics, Endhoven, Netherlands).

2.2.3 Drug solubility studies

Excess amounts of drug were placed in 20 mL screw cap glass vials with 10.0 g of deionized water, 0.1N HCl, pH 6.8 phosphate buffer solution (USP), sucrose solutions (10%, 30% and 50% w/w) or HPMC solutions (0.5%, 1%, 2.5%, 5% and 10% w/w) (n=3). The slurries were stirred magnetically at ~200 rpm at 37 °C for 24 h and then allowed to sediment and equilibrate for another 48 h at 37 °C before sampling. The samples were filtered through a 0.22 µm CME-syringe-filter and analysed for drug concentration UV-spectrophotometrically (Shimadzu UV-2101PC, Shimadzu Europa GmbH, Duisburg, Germany) after appropriate dilution (λ CBZ = 285 nm; λ THP = 271 nm; λ DPP = 273 nm). Blanks of drug-free sucrose or HPMC solutions were treated and measured likewise.

2.2.4 Drug release studies

Pellet amounts equalling ~20 mg drug at coating level 3 mg/cm^2 were released in 900 mL deionized water at 37 °C in a USP II dissolution tester (VK 7000, Vankel Industries, Edison, NJ, USA) at 100 rpm paddle speed. At predetermined time intervals, 4 mL samples were withdrawn and analysed for drug concentration UV-spectrophotometrically (Shimadzu UV-2101PC, Shimadzu Europa GmbH, Duisburg, Germany). Presented data are mean values of n≥3.

2.2.4.1 Effect of buffer species

Drug release from RS/RL-coated pellets was determined as described (2.2.4), replacing deionized water with other aqueous media which were adjusted to ~330 mosmol/kg: 10% (w/w) sucrose solution, KH_2PO_4-solution and NaCl solution. Presented data are mean values of n≥3.

2.2.4.2 Effect of core type on coating integrity

Drug release from RS/RL-65:35-coated pellets containing carbamazepine and red pigment 3:1 (w/w) was determined as described (2.2.4). Every 15 min the release medium was checked visually for signs of release of red pigment (n=3). The test was repeated with a larger amount of 1600 mg pellets to improve visibility (n=3). Due to the insolubility of iron oxide pigments in water, colouring of the medium was considered an indicator for cracks in the coating.

2.2.4.3 Estimation of carbamazepine concentration inside pellets

Carbamazepine pellets (2000 mg) coated with 3 mg/cm^2 RS/RL 65:35 were released as described (2.2.4) and carefully retrieved from the vessels after 2h. After gently blotting off excess surface water by pouring the pellets onto filter paper, they were filled into 5 mL syringes and their internal fluid volume squeezed out through a 0.22 µm CME-syringe-filter. The clear solution was immediately diluted 1:25 with deionized water and analyzed UV-spectrophotometrically at 285 nm for carbamazepine content (n=3).

2.2.4.4 Single pellet release

Single pellet release of carbamazepine (n=16) was performed in 24-well cell culture plates with ~2.5 mL well volume. One pellet was placed per well, 2.0 mL pre-warmed medium added by pipette and the well plate put in a shaker at 37 °C and 80 rpm. At sample time points, 750 µL were sampled by pipette, replaced by fresh medium and 700 µL analyzed for carbamazepine content by UV in a quartz cuvette.

Single pellet release of water-insoluble red pigment was tested qualitatively in a similar procedure by visual observation of the number of pellets which had expelled red powder at sample time points (n=24).

2.2.5 Water uptake-weight loss and swelling studies

Approximately 400 mg pellets of the 3 mg/cm^2 coating level were accurately weighed (initial weight w_{ini}) and released as described under 2.2.4. At predetermined time intervals, pellets were retrieved from the vessels with a pipette. Pictures of n≥10 random pellets were taken immediately (as described under 2.2.2) before pouring them onto filter paper to strip off surface water. Then their wet weight (w_{wet}) was determined. After drying at 60 °C for 48 h and cooling in a desiccator, samples were weighed again (w_{dry}). Absolute and relative water uptake and weight loss were calculated:

absolute: $$weight\ loss = w_{ini} - w_{dry} \qquad water\ uptake = w_{wet} - w_{dry}$$

relative: $$weight\ loss = \frac{w_{ini} - w_{dry}}{w_{ini}} \cdot 100\% \qquad water\ uptake = \frac{w_{wet} - w_{dry}}{w_{dry}} \cdot 100\%$$

The pictures of pellets taken during this study were used to determine the median diameter D50 of 10 pellets at every time point. Swelling data are expressed as percent increase in median diameter and are considered a rough estimation because a different set of 10 pellets was measured at every time point. All measurements were performed n≥2.

2.2.6 Sucrose release studies

Release samples were obtained similar to 2.2.4, with the minor change that 800 mg pellets were used to obtain sufficient amounts of sucrose. HPLC analysis of the samples was performed. The HPLC apparatus (SCL-10A VP, Shimadazu, Japan) was equipped with a zwitterionic HILIC column (SeQuant® Zic-HILIC 250 x 4.6 mm; 5 µm), a diode-array UV-detector (SPD M-10A, Shimadazu, Japan) and an evaporative light scattering detector (PL-ELS 2100®, Polymer Labs / Varian, Germany). The eluent consisted of acetonitrile and ammonium acetate solution (25 mM in MilliQ-water) in the ratio of 73:27 (V/V). An isocratic method was applied with a flow rate of 1 mL/min and a temperature of 40 °C. Sample volumes of 60 µL were injected. The retention time of sucrose was about 11 min. Sucrose content in samples was quantified from ELSD-chromatograms obtained at 480 nm (LED-light) using external standards. The ELSD settings were: evaporation and nebulising temperature 90 °C and 80 °C respectively, air flow 1.0 SLM and air pressure 4.5 bar. The nebulizer gas was filtered air. Measurements were performed $n \geq 2$.

In the course of experiments, weight loss studies (2.2.5) proved to yield comparable sucrose release results and were henceforward used as the less expensive but equally precise method of choice. Sucrose release was estimated from the weight loss values by simply subtracting the amount of drug released (the small amounts of HPMC-binder potentially released were not taken into consideration).

2.2.7 Drug adsorption to MCC starter cores

Glass tubes containing 10.0 mL drug solution at different concentrations (100, 75, 50 and 25% w/w of saturation) were kept in a shaker at 80 rpm and 37 °C for 24 h. Their UV absorptions with and without addition of 1.0 g MCC starter cores were compared (n=3).

2.2.8 Estimation of diprophylline and theophylline affinity to RS/RL 90:10

Organic solutions of 12.5% Eudragit RS/RL 90:10 and 1 - 6% drug (w/w, based on dry polymer weight) were prepared in isopropanol / acetone / water 82:15:3 (w/w). Ten gram of solution were cast in plastic Sabouraud dishes (Ø ~5.5 cm; Sartorius, Göttingen, Germany) and allowed to dry at room temperature for five days under perforated lids to ensure slow, homogeneous film formation. Residual solvent was removed by overnight storage at ~60 °C. The film dishes were then examined for precipitated drug crystals under polarized light. Low polymer affinity was correlated with low amounts of drug which could be dissolved in the cast film without precipitation.

2.2.9 Drug release from RS/RL-90:10-cast films

Films containing 1% drug in form of a solid solution were prepared as described under 2.2.8. Absence of drug crystals was confirmed under polarized light. Films were released in their dishes (to avoid folding of the films and ensure same surface area) using the same procedure as for pellets (2.2.4) (n=6). The paddle speed was reduced slightly to 70 rpm to avoid floating and paddle contact of the film dishes.

2.2.10 Water uptake of cast films

Drug-free films of Eudragit RS/RL 90:10 and 65:35 were prepared in plastic Sabouraud dishes similar to 2.2.8, omitting the addition of drug to the polymer solutions.
The film dishes were then equilibrated at 37 °C for 48 h in either 100 g deionized water or 143 g 30% w/w sucrose solution (equalling 100g water) before blotting off surface water and weighing.

2.2.11 Short term single pellet swelling studies by video imaging

Approximately 30 pellets were placed in a glass dish under the macroscope at 60x magnification (pellets per picture: 8-12 at t_0 and 4-8 after 240 min swelling). Deionized water was degassed (15 min boiling, cooling to 37 °C), ~15 mL were added to the pellets and pictures during release were recorded every minute using IC Capture® software (The Imaging Source Europe GmbH, Bremen, Germany). Temperature was kept at 37 °C by means of a water bath. Video images were used to monitor swelling of single pellets for short periods up to 4 h. Longer runs were affected by evaporation; however, prevention of evaporation was impossible without condensation on the camera lens. The test was repeated until n≥12 pellets were measured.

2.2.12 Sucrose hydrolysis in 0.1N HCl

Sucrose (850 mg) was dissolved in 50.0 mL 0.1N HCl (n=3) and the solution kept in water bath at 37 °C. The osmolality of the solution was measured as a function of time (via its freezing point depression), using a semimicro-osmometer (K-7400; Knauer GmbH, Berlin, Germany). A blank of 0.1N HCl was treated and measured likewise. Hydrolysis of sucrose to its monomers fructose and glucose was detectable as the gradual increase in osmolality (from ~50 to ~100 mosmol/kg). The osmolality after 24h was considered 100%.

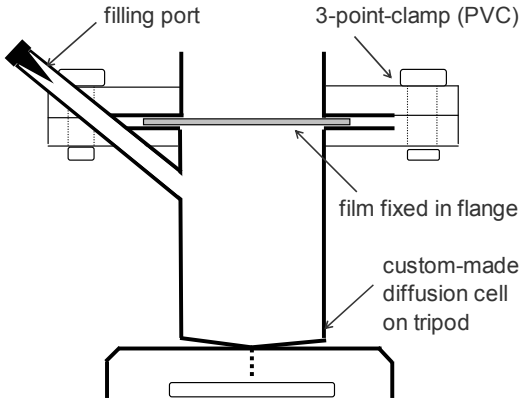
2.2.13 Preparation of thin CA and CA/PEG free films

Thin free films of CA or CA/PEG 65:35 were prepared by dissolving the polymers (see 2.2.1) and spreading the solutions on glass plates by means of a casting knife (gap 400 µm; Zehntner ZUA 2000, Zehntner Instruments, Sissach, Switzerland). Films were allowed to air-dry overnight under paper hoods before peeling them off the glass and measuring their thickness (thickness meter Minitest® 600, ElektroPhysik, Cologne, Germany). Films were kept in plastic bags, separated by sheets of paper.

2.2.14 Diffusion cell studies with thin CA and CA/PEG free films

Small amounts of excess drug were placed in custom-made glass cells which functioned as the 'donor compartment' for the diffusion experiments (Figure 10). To prevent sideways-diffusion high-vacuum-fat was applied on the flanges of the diffusion-cells (diameter flange ~2.5 cm, diameter orifice 1.8 cm) before mounting film specimens (2.1 x 2.1 cm) with a thickness of 17 ± 1 µm. The flange was additionally fastened to cell by means of PVC screw-clamps. One Litre Nalgene® boxes were used as the 'acceptor compartment'. They were filled with 900 mL pre-warmed medium and placed in a hot-air oven at 37 °C on a magnetic stirrer plate. Through the filling port, the glass cells were filled with ~10 mL saturated drug solution. Cells were held tilted to allow escape of air. The filling port was closed and the glass cell immediately placed into the Nalgene® box. The acceptor medium was stirred magnetically throughout the experiment. At predetermined time points, 3 mL samples were withdrawn using a blunt needle and a syringe and replaced by fresh medium. Samples were filtered (0.22 µm CME-syringe-filter) and analysed for drug concentration UV-spectrophotometrically (Shimadzu UV-2101PC, Shimadzu Europa GmbH, Duisburg, Germany) after appropriate dilution.

a) schematic representation of 'donor cell'



b) set-up during diffusion studies

Figure 10. Custom-made glass diffusion cells

Results and discussion

3 Results and discussion

3.1 Effect of starter core type – Nonpareils versus MCC starter cores

Two kinds of starter cores are currently commercially available to prepare drug-loaded pellets by fluidized-bed processing, water-soluble sucrose nonpareils and water-insoluble microcrystalline cellulose cores. Although often being considered inert (Ghebre-Sellassie 1989; Gryczova, Rabiskova et al. 2008; Kallai, Luhn et al. 2010), recent reports indicate that the starter cores could affect the release from reservoir pellets.

MCC beads are insoluble; however, adsorption of drugs to MCC has been reported which may reduce their release rate (Okada, Nakahara et al. 1987; Rivera and Ghodbane 1994; AlNimry, Assaf et al. 1997). In contrast, sugar nonpareils dissolve and the major constituent (~75%) sucrose could lead to changes in drug solubility and coating hydration (Paruta 1964; Etman and Naggar 1990; Heinicke and Schwartz 2007). In addition, their strong osmotic activity could result in faster and higher water uptake (Tang, Schwartz et al. 2000; Lecomte, Siepmann et al. 2005; Muschert, Siepmann et al. 2009 c). This would consequently increase the tensile stress on the membrane (Hjärtstam, Borg et al. 1990; Hjartstam and Hjertberg 1998; Heng, Chan et al. 1999), dilute the drug concentration inside the pellets and potentially form a counter current to the efflux of drugs (Narisawa, Nagata et al. 1997; Marucci, Ragnarsson et al. 2008; Muschert, Siepmann et al. 2009 b). After the sugar is released, the fluid filled spheres could also show a higher sensitivity to mechanical stress (Ahmad Mohamad 2005; Heinicke and Schwartz 2007).

3.1.1 Preliminary study with CA or CA/PEG coated pellets

The effect of osmotically active nonpareils versus inactive MCC starter cores was first tested with cellulose acetate, a rigid and highly semipermeable polymer. In diffusion cell studies with thin free films (~17 µm thickness), this reflectivity for drug molecules was shown; irrespective of the drug solubility, no drug permeated through pure CA films (Figure 11). Even for the films containing 35% PEG 3350 as a pore former only small amounts of drug passed the film, ~20% of the drug amount contained in the donor cell (Figure 11).

Poorly soluble carbamazepine (0.244 mg/mL) was unable to diffuse through the PEG-phase. Its permeation through medium filled channels started just after the pore former had been leached from the film (after ~4 h). Highly soluble diprophylline (210 mg/mL), however, seemed to diffuse through the continuous PEG-phase, as indicated by the immediate onset of drug permeation (Figure 11b).

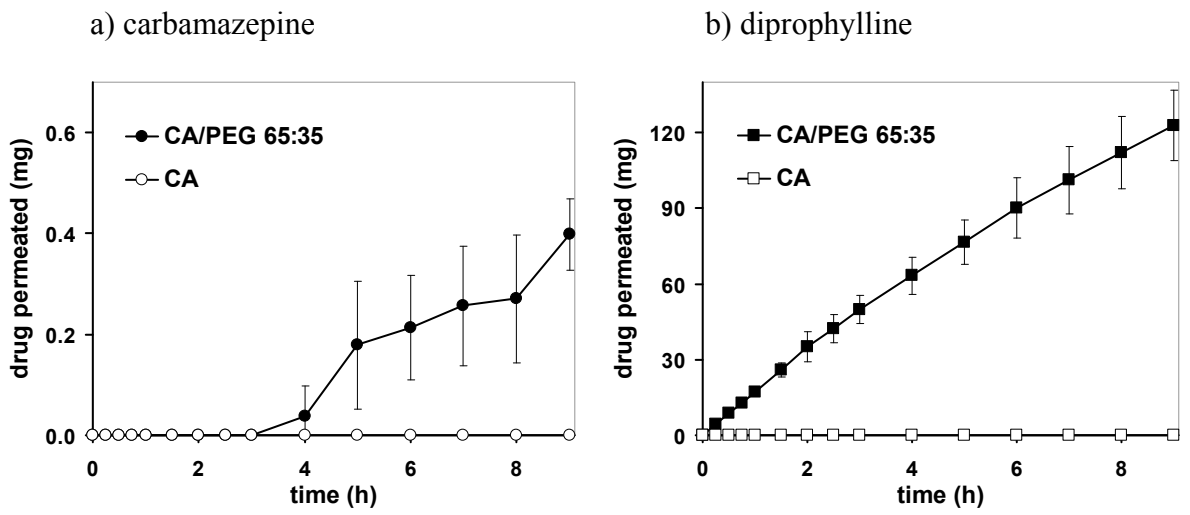


Figure 11. Diffusion cell studies of drug permeation through thin free films of pure CA or CA/PEG 65:35 (thickness ~17 µm)

Despite the free films allowing only minor drug permeation, complete release within ~18 h from CA or CA/PEG-65:35-coated pellets in 0.1N HCl was achievable for both drugs (Figure 12a-d). The release of highly soluble diprophylline could only be prolonged by using osmotically inactive MCC starter cores (Figure 12d). This was attributed to the rigidity of pure, unplasticized celluloseacetate (T_g ~190 °C, (Guo 1993)). The combined osmotic activity of the sucrose core and the highly soluble drug apparently caused a higher water uptake compared to insoluble MCC starter cores. The resulting stronger hydrostatic pressure led to more or larger cracks in the brittle celluloseacetate coating, thus increasing the release from NP pellets and levelling the effect of the coating thickness (Figure 12c, Figure 13b).

Faster release from NP pellets was also observed for poorly soluble carbamazepine (Figure 13a). Apparently, similar film cracking occurred despite the poor solubility of the drug because the osmotic pressure (and in consequence water uptake and hydrostatic

pressure) was predominantly generated by the sucrose starter core. However, this cracking was less pronounced compared to diprophylline pellets, as indicated by a better differentiation between the CA/PEG coating levels (Figure 12a). This was ascribed to the 35% PEG 3350 which was used as a pore fomer for the carbamazepine pellets and had a plasticizing effect on celluloseacetate (Guo 1993).

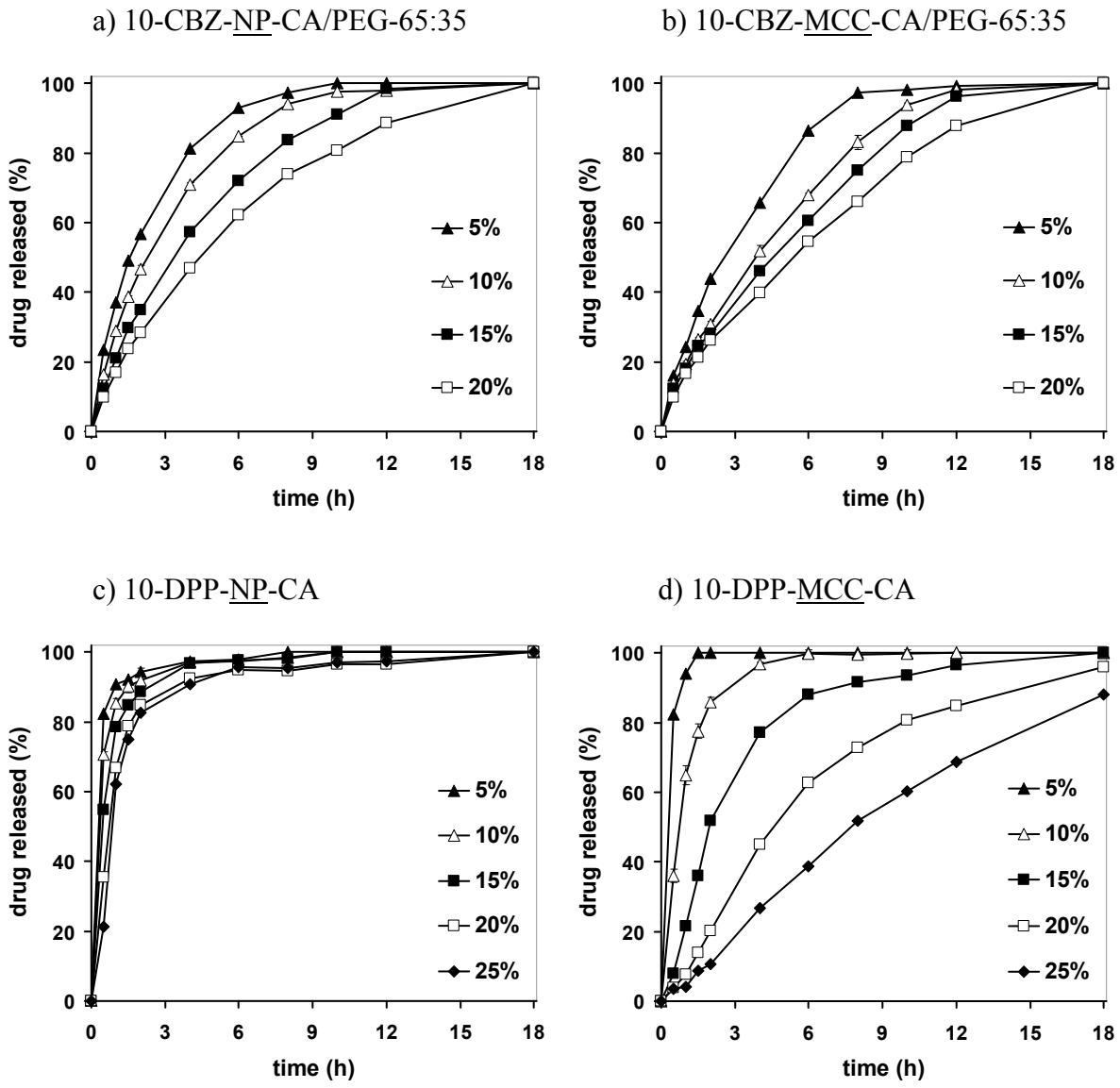


Figure 12. Drug release in 0.1N HCl as a function of coating level and starter core type
a) and b) carbamazepine pellets coated with CA/PEG 65:35;
c) and d) diprophylline pellets coated with pure CA

a) 10-CBZ-CA/PEG-65:35 b) 10-DPP-CA

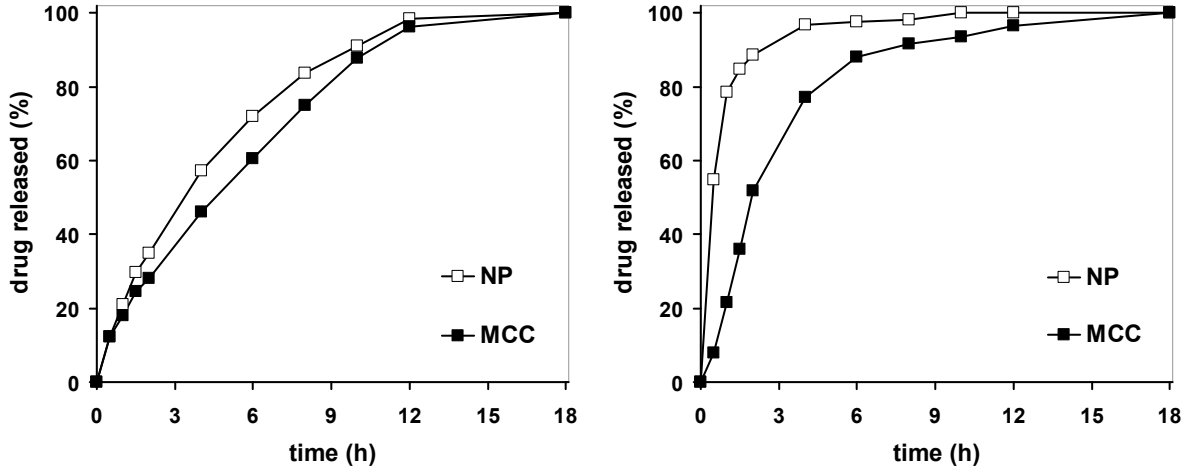


Figure 13. Drug release in 0.1N HCl as a function of the starter core type (c.l. 15%)

The ester functions in celluloseacetate could be cleaved by acidic hydrolysis; hence release was faster in 0.1N HCl than in pH 6.8 phosphate buffer solution (PBS). However, comparing the influence of the two media on diprophylline release revealed no effect for NP pellets but a pronounced effect for MCC pellets (Figure 14).

a) 10-DPP-NP-CA b) 10-DPP-MCC-CA

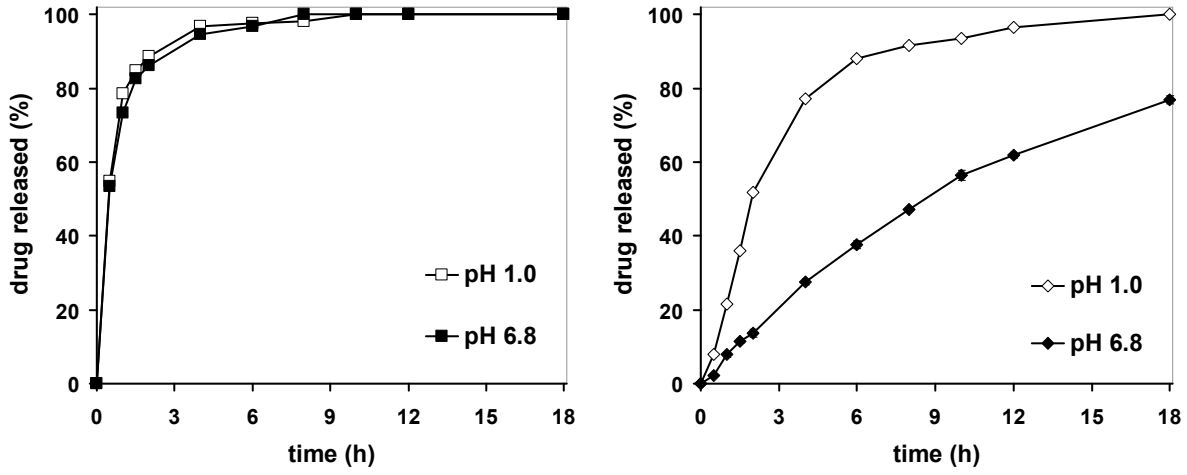


Figure 14. Effect of media (0.1N HCl vs. pH 6.8) on diprophylline release from 15%-CA-coated pellets based on different starter cores

In agreement with the minor impact of the coating thickness for diprophylline loaded NP pellets (Figure 12c), this indifference towards the media was also attributed to the cracking of the rigid CA coating under osmotic pressure. This cracking was expected to happen quicker than the cleavage of ester functions in acidic media, due to the high water permeability of CA (Ramakrishna and Mishra 2002). Once cracking was initiated, diprophylline was released quickly through medium filled cracks rather than through the polymer phase. Hence the pH-effect on the CA-coating did not have much impact anymore.

In contrast, diprophylline loaded MCC pellets generated less osmotic pressure since the drug contributes merely ~9% of the drug core. The coating stayed predominantly intact and its permeability was therefore depending stronger on the acidity of the medium.

The comparability of the NP and MCC release data was slightly hampered, though, by applying polymer based on the batch weight, not the surface area. However, the MCC cores used in this preliminary study were smaller than the sucrose starter cores (500-710µm vs. 710-850µm) and thus had a ~10% larger batch surface area (considering their respective densities). This led to different coating thicknesses for the two drug core types and slightly biased results.

The physicochemical properties of the starter cores like size or density were also not adequately considered in the majority of the aforementioned publications which compare drug release for different drug cores. This could be the reason why the reported observations appeared inconsistent in some cases, e.g. both faster and slower releases for NP pellets compared to MCC pellets.

In order to obtain comparable data for different drug cores coated with Eudragit RS/RL or EC/HPC blends, MCC starter cores of similar size were henceforward chosen (Celphere® 708, unless mentioned otherwise). In addition, all drug cores were characterized regarding their size and weight before coating.

3.1.2 Characterization of drug cores

Despite representing similar sieve fractions, the starter cores (710-850 µm) as well as the respective drug cores (850-1000 µm) differed with regard to their median size (D50), size distribution (interquartile range), density and shape (circularity vs. sphericity) (Table 1).

		starter cores			**10% drug-layered cores**					
		NP (Suglets®)	**MCC** (Celphere™)	**MCC** (Cellets®)	**DPP-NP**	**DPP-MCC**	**THP-NP**	**THP-MCC**	**CBZ-NP**	**CBZ-MCC**
median diameter D50 [µm]		**845**	**798**	**774**	**875**	**844**	**877**	**843**	**899**	**848**
interquartile range IQR [µm]		47	41	47	62	59	59	52	61	49
density [g/cm^3]		**1.31**	**1.42**	**1.32**	**1.30**	**1.37**	**1.30**	**1.38**	**1.25**	**1.35**
circularity	mean aspect ratio (AR)	1.10	1.09	1.08	1.12	1.09	1.10	1.09	1.11	1.08
	cores with AR < 1.2 [%]	94	91	95	83	92	89	94	89	94
sphericity	spherical fraction [%]	88-90	63-65	88-90	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

Table 1. Characterization of starter cores and drug-layered cores based on NP or Celphere™-MCC

The measurements of 300 single particles at 55x magnification (2.2.2.1) yielded detailed profiles of the particle size distribution (PSD) which reflected the diameter increases during drug layering (10% w/w) and polymer coating (c.l. 3 mg/cm^2 ≈ 15.7%) (Figure 15). Such precise information could not be obtained from sieve analysis.

The increasing IQR-values indicated a slight broadening of the PSD during application of drug or polymer layers which was in accordance with other reports (Heinicke and Schwartz 2004). (The IQR is a dispersion parameter of the median; 50% of the particles fall within the size range D50 ± (IQR/2).) The authors also reported similar D50-values for the starter cores; e.g. the D50-value of nonpareils often ranging at the upper limit of the specified sieve fraction.

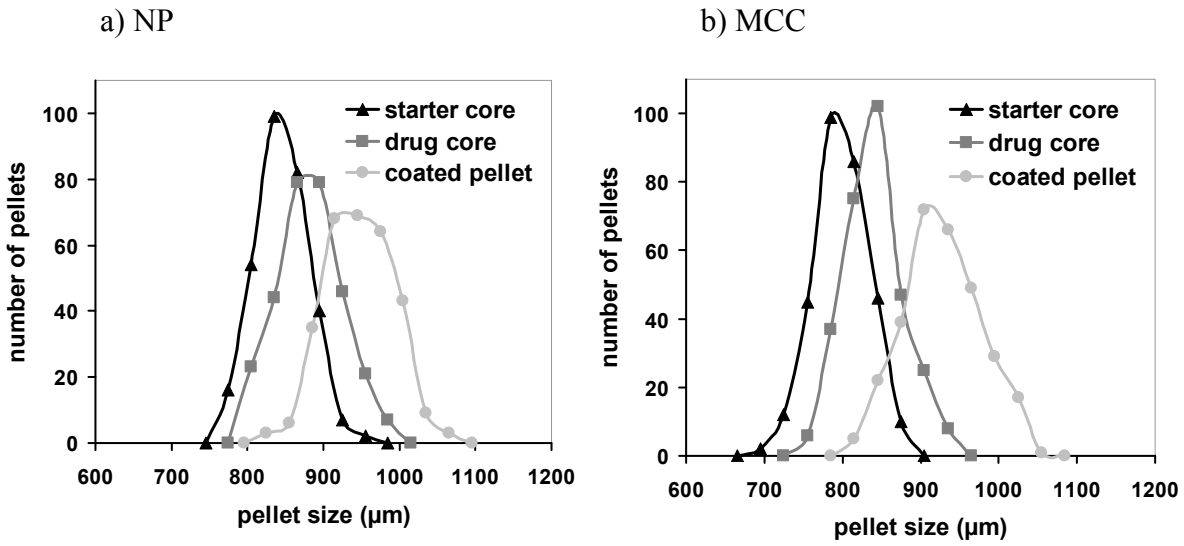


Figure 15. Exemplary size distributions of starter cores and their respective drug cores and coated pellets (10% carbamazepine loading, coating 3 mg/cm^2 RS/RL 65:35)

Size, size distribution and density inherently affected the batch surface area and thus the coating thickness (Heinicke, Matthews et al. 2005). Therefore, a surface area-normalized coating approach (mg/cm^2) was used in order to obtain comparable coating thicknesses for the different starter and drug cores. For this purpose, the surface area/weight ratio (A/m-ratio) of each drug core batch was estimated from the size and density data before coating (Table 2), assuming perfect sphericity and non-porous surfaces. In the majority, drug cores based on Celphere™-MCC starter cores had similar A/m-ratios compared to those based on nonpareils of the same sieving fraction. As expected, the A/m-ratio decreases with increasing drug loading.

loading / drug	0%		2%		10%		50%	
	NP	MCC	NP	MCC	NP	MCC	NP	MCC
—	54.3	52.8						
carbamazepine			54.4	53.4	53.2	52.4	46.7	46.6
theophylline					52.7	51.5		
diprophylline			54.4	52.5	52.7	51.7	45.0	45.3

Table 2. Surface area/weight ratios (cm^2/g) estimated from median diameter (D50) and weight of starter cores and drug cores

The aspect ratio of all cores was similar (Table 1) and in perfect agreement with previous reports (Gryczova, Rabiskova et al. 2008; Kallai, Luhn et al. 2010). Interestingly, distorted, platelet-like pellets were observed in MCC starter core batches. These flattened pellets were circular and indistinguishable from the top perspective and thus did not affect the aspect ratio (Figure 16a). However, when looking from the side, the non-spherical shape of the pellets became evident (Figure 16b). The content of distorted pellets was 35-37% for the Celphere lot (as determined by rolling on a tilted plane; see 2.2.2.3), and only about 10-12% in the Cellets lot. Sugar cores also contained ~10-12% distorted material but it mostly consisted of egg-shaped pellets or breakage.

a) top view b) side view

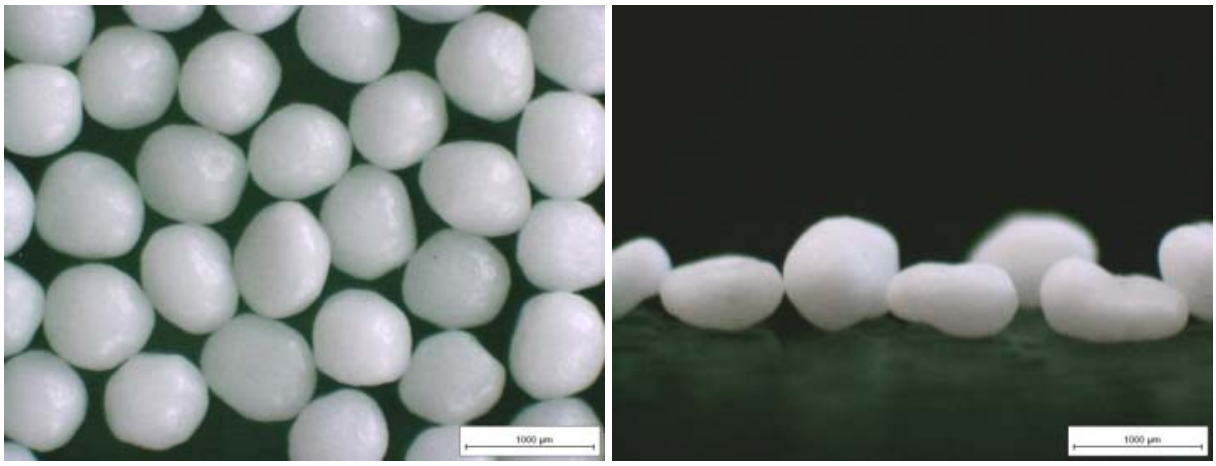


Figure 16. Macroscopic pictures of spherical and non-spherical MCC starter cores in a Celphere™ lot

The surface area/volume ratio (and hence A/m-ratio) of non-spherical particles is inevitably higher compared to spherical ones which could affect the batch surface area and finally the coating thickness. However, the effect of the increased fraction of distorted cores in the Celphere lot on the total batch surface area was estimated to be only 10% when assuming distorted cores as oblate spheroids of radial dimensions (r_a/r_b) 400 and 200 µm (Figure 17). Therefore the assumption of perfect sphericity of the cores was considered sufficiently valid for the calculation of the batch surface area.

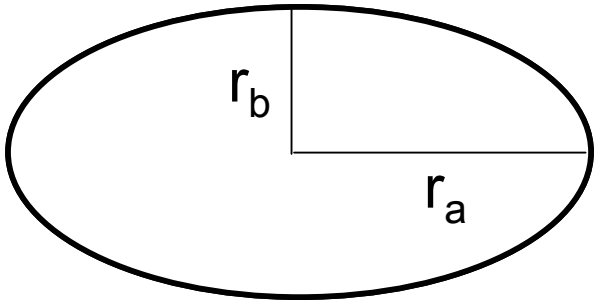


Figure 17. Schematic presentation of an oblate spheroid with radial dimension $r_a = 2r_b$

3.1.3 Drug release from pellets with a surface area-normalized coating

The drug release patterns of pellets coated with 3 mg/cm^2 RS/RL were characterized by a sigmoidal shape (Figure 18), which has been reported before for organically coated RS/RL pellets (Zhang, Zhang et al. 2003; Heinicke and Schwartz 2007; Heinicke and Schwartz 2007). The lag times were similar for both starter cores but surprisingly a faster release was obtained with the osmotically inactive MCC cores compared to sugar cores (Figure 18). The faster release of carbamazepine from MCC pellets was confirmed for all coating levels (Figure 19a) and RS/RL ratios (Figure 19b).

This was in contrast to the observations made in the preliminary study with celluloseacetate coatings. The difference was very likely attributed to the higher elasticity of organic Eudragit-coatings compared to the highly rigid CA coatings. For example, pronounced swelling without bursting was observed for unplasticized, organic RL-coatings (Ueda, Hata et al. 1994). The water uptake, swelling and cracking behaviour of the RS/RL-coated pellets will be evaluated later (3.1.6, 3.1.7).

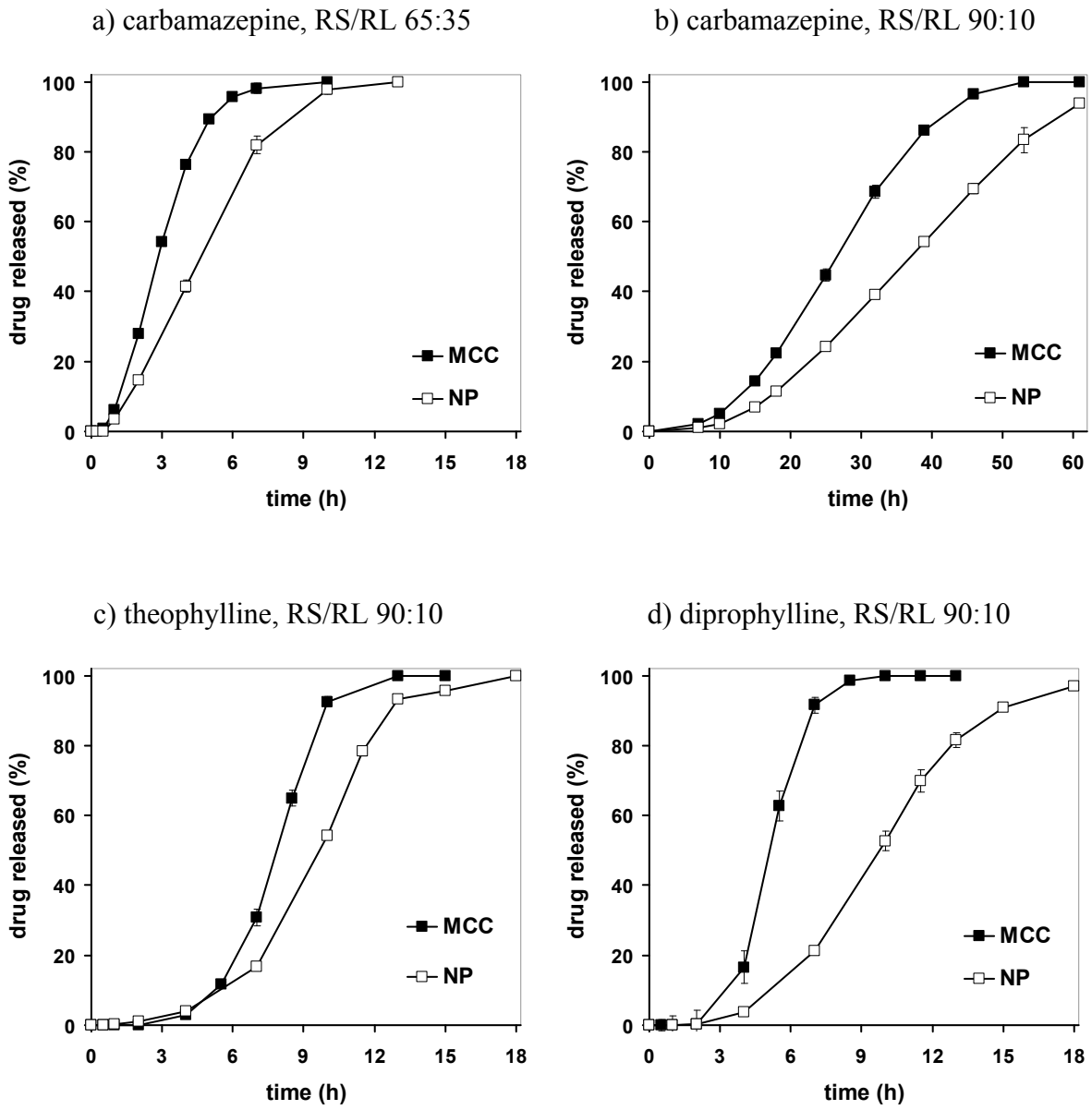


Figure 18. Drug release from RS/RL-coated pellets in deionized water as a function of the starter core type (10% drug loading, c.l. 3 mg/cm^2)

a) different RS/RL 65:35 coating levels

b) different RL-contents (at 3 mg/cm^2)

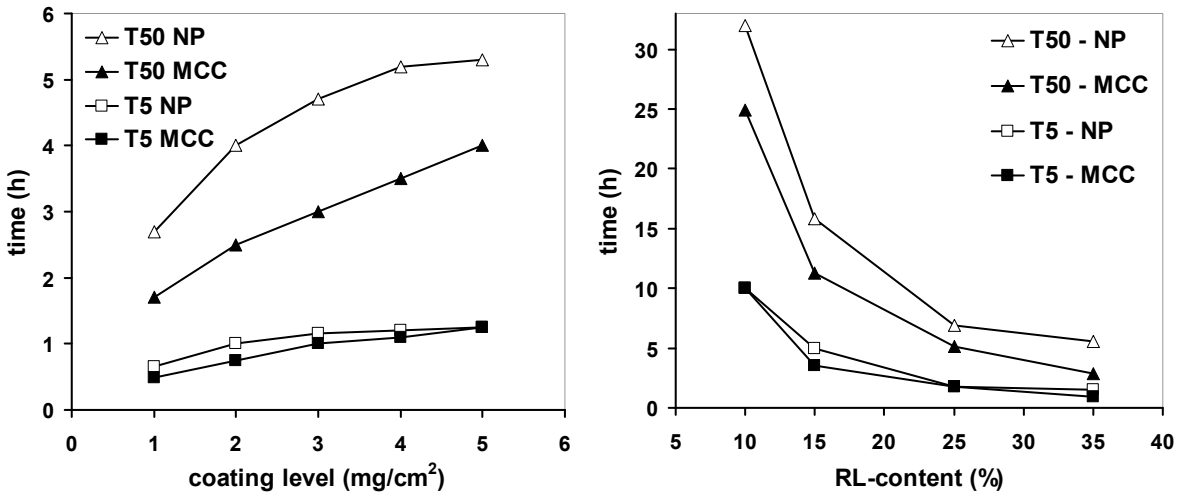


Figure 19. Effect of starter core type on lag time (T5) and T50 of carbamazepine release

This starter core effect could either be caused by differences in the applied polymer coating (its thickness, homogeneity or porosity) or by differences associated with the properties of the starter cores.

Thinner films on MCC pellets for example (and hence faster release) could have been the result of an underestimation of the batch surface area due to the higher fraction of non-spherical pellets in the Celphere raw material. However, similar average coating thicknesses of NP pellets (42 ± 2 µm) and MCC pellets (41 ± 3 µm) were determined by the median change resulting from a 5 mg/cm^2 RS/RL-90:10-coating on drug-cores. In addition, Cellets starter cores with a lower content of distorted pellets (similar to sugar cores, (Table 1), also exhibited a faster release which closely resembled the profile of the usual Celphere MCC cores (Figure 20). And hardly any difference in the release was observed for spherical versus non-spherical coated pellets (Figure 21). This indicated similar flight characteristics of the drug cores in the fluidized bed and thus similar coating thicknesses, despite their different sphericity. Therefore, a surface area artefact of the raw materials on coating thickness was ruled out.

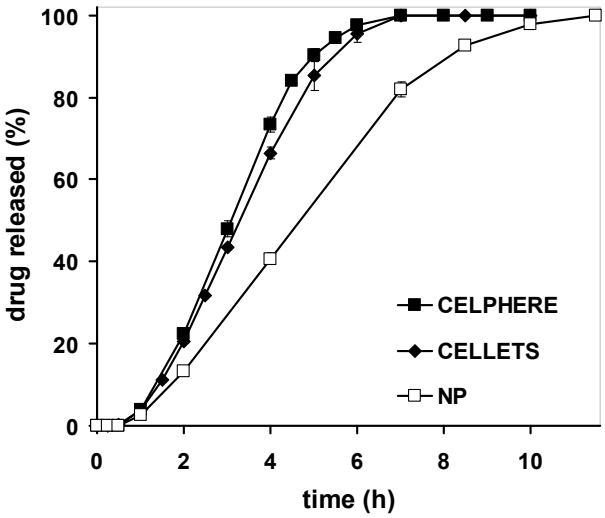


Figure 20. Carbamazepine release; comparison of nonpareils with MCC starter cores of different suppliers: Celphere™ / Cellets® (10-CBZ-RS/RL-65:35, c.l. 3 mg/cm^2)

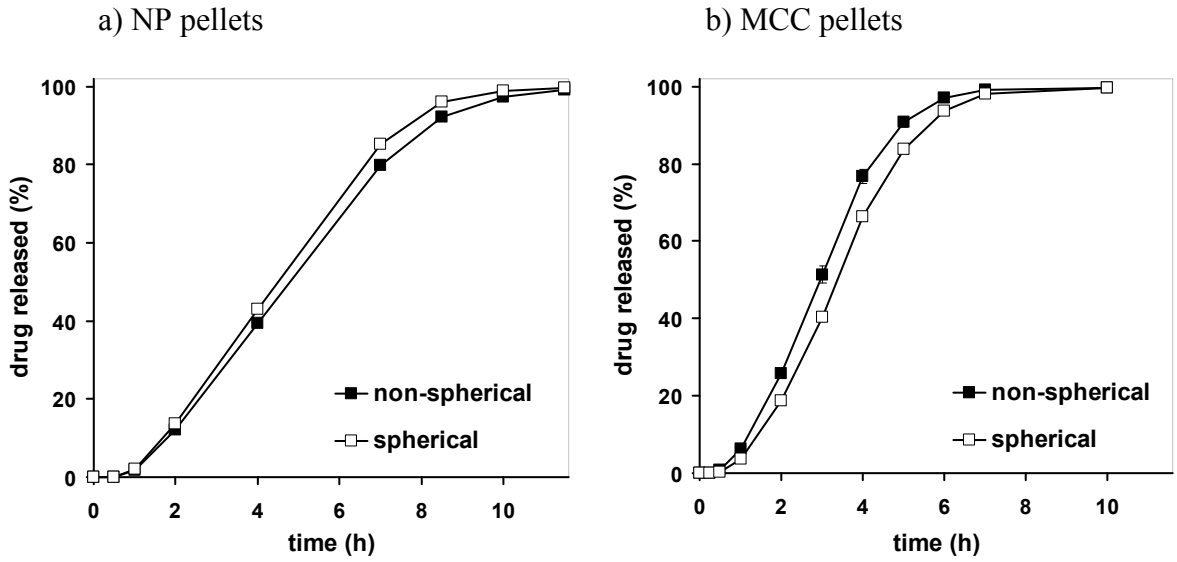


Figure 21. Effect of non-spherical material on carbamazepine release from coated pellets (10-CBZ-RS/RL-65:35; c.l. 3 mg/cm^2)

The very homogeneous distribution of the coating on all cores was again confirmed by the low inter-pellet-variability of the single pellet release profiles (Figure 22).

It had been suggested that different release profiles could also be obtained by mixing multiple units with a variety of lag times (Ueda, Hata et al. 1994). However, the similar lag times of the single pellets proved that the slower cumulative release from NP pellets is not caused by a wider range of lag times compared to MCC pellets (Figure 22).

a) NP single pellets b) MCC single pellets

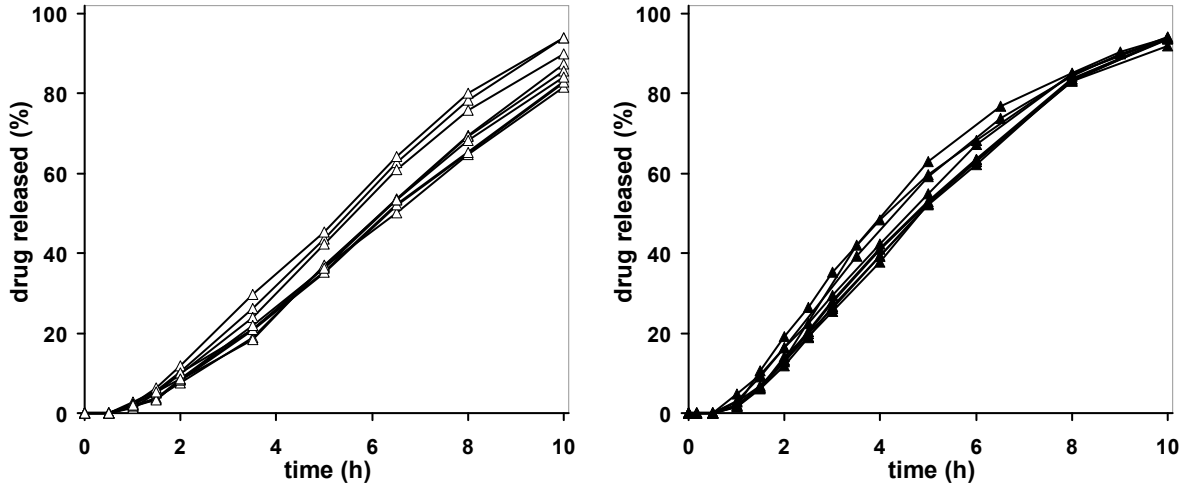
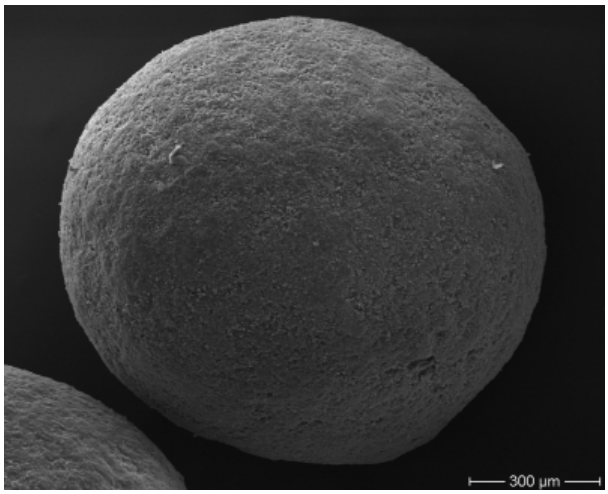


Figure 22. Single pellet release profiles of 10-CBZ-RS/RL-65:35 in deionized water (c.l. 1 mg/cm^2; shaker 80 rpm, 37 °C)

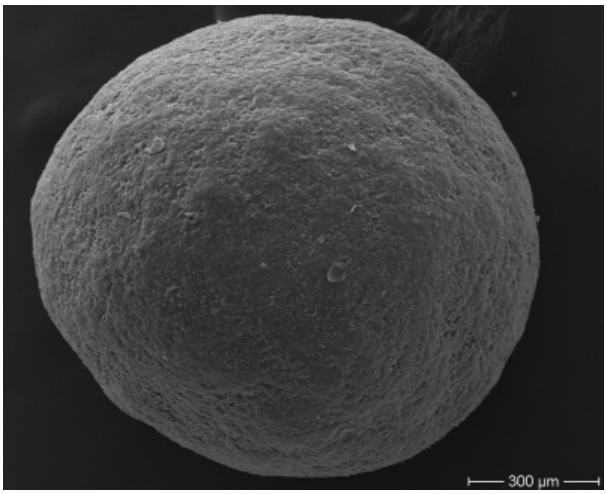
The application of the same drug or polymer formulation to cores with different solubilities or polarities could potentially lead to films with different porosities (Nesbitt, Mahjour et al. 1994; Baki, Bajdik et al. 2010). SEM-pictures of coated NP and MCC pellets, however, did not reveal any pronounced differences in the film structure (Figure 23, Figure 24). Even and slightly porous films, resembling orange-peel, were formed on all cores. This porosity was attributed to minor spray-drying during the organic coating process.

Apparently, neither the thickness of the coating nor inhomogeneities in its distribution on the cores or the porosity of the coating were accountable for the observed differences in release rates between NP and MCC pellets. It was thus reasonable to assume, that the faster release from RS/RL-coated MCC pellets was attributed to the inherent core properties of sugar cores and MCC starter cores.

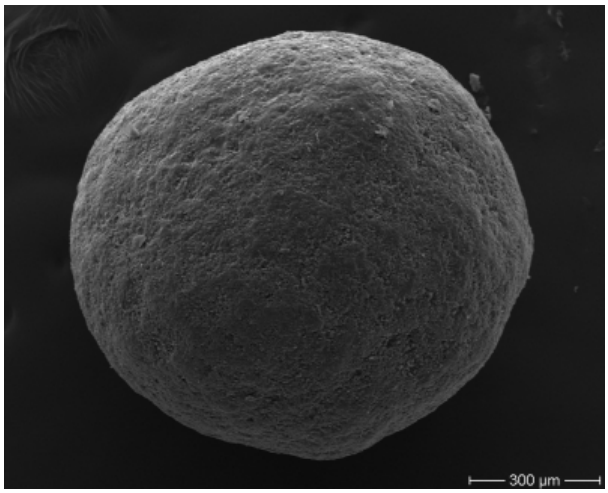
a) 10-CBZ-NP-RS/RL-90:10



b) 10-CBZ-MCC-RS/RL-90:10



c) 10-DPP-NP-RS/RL-90:10



d) 10-DPP-MCC-RS/RL-90:10

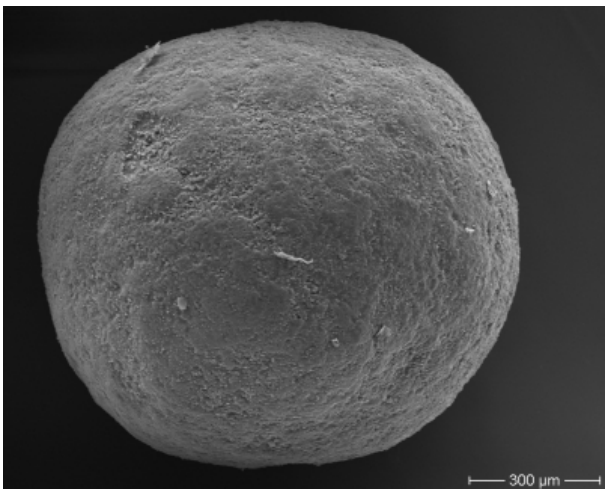
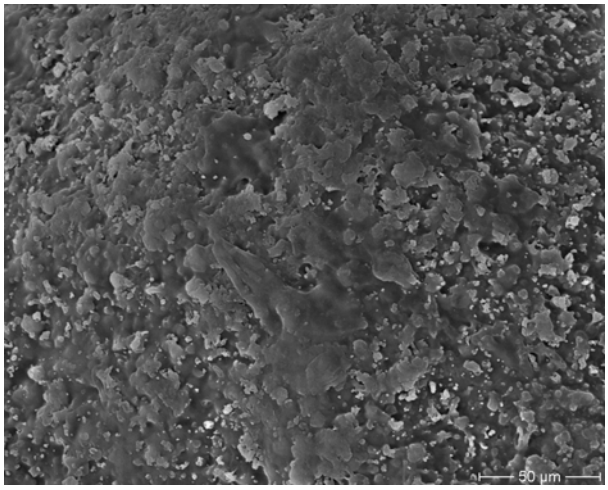
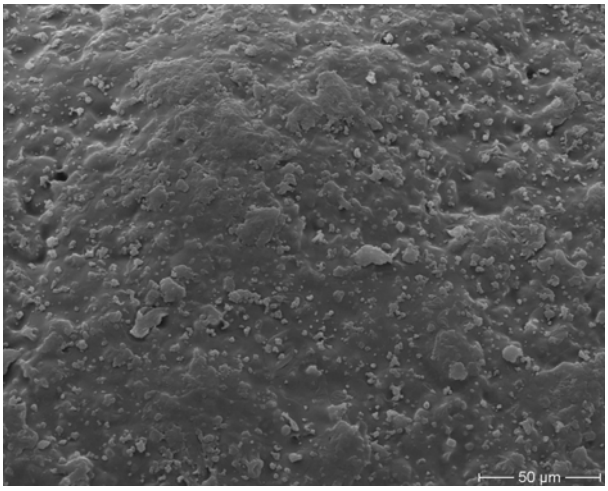


Figure 23. Scanning electron microscopy pictures (90x magnification) of the coating surface of pellets based on either NP or MCC starter cores (10% loading of carbamazepine or diprophylline; c.l. 3 mg/cm^2 RS/RL 90:10)

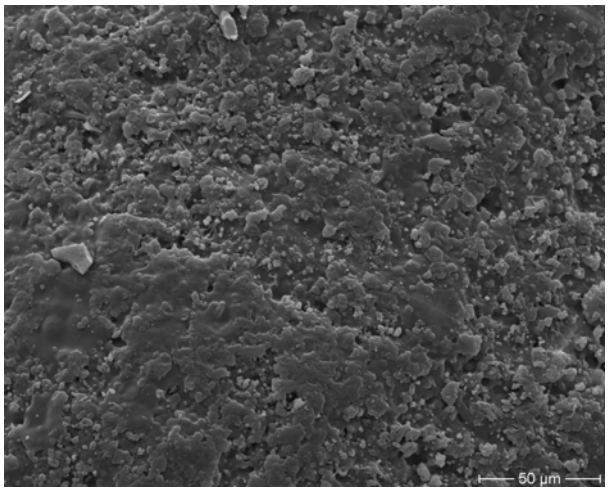
a) 10-CBZ-NP-RS/RL-90:10



b) 10-CBZ-MCC-RS/RL-90:10



c) 10-DPP-NP-RS/RL-90:10



d) 10-DPP-MCC-RS/RL-90:10

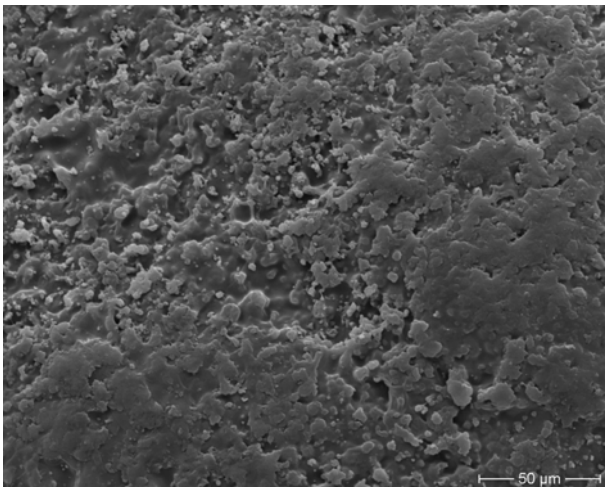


Figure 24. Scanning electron microscopy pictures (500x magnification) of the coating surface of pellets based on either NP or MCC starter cores (10% loading of carbamazepine or diprophylline; c.l. 3 mg/cm^2 RS/RL 90:10)

3.1.4 Potential effects of sucrose and MCC on drug release

Drug adsorption to the MCC starter cores which could affect the drug release (Okada, Nakahara et al. 1987; Rivera and Ghodbane 1994; AlNimry, Assaf et al. 1997) was not observed for any of the drugs used in the present work. The UV absorptions of drug solutions were unaffected by the addition of MCC starter cores (data not shown). Moreover, such adsorption would be expected to slow down drug release and hence was not indicated by the release results either.

However, the sucrose which contributes ~75% (w/w) in nonpareils led to changes in the drug solubility (Paruta 1964; Etman and Naggar 1990). In agreement with other reports, the solubility of theophylline was not affected by sucrose addition (Table 3 left, Paruta and Sheth 1966), but the solubility of diprophylline in deionized water decreased with increasing sucrose contents, whereas carbamazepine solubility increased (Table 3 left).

	sucrose content in % (w/w)				HPMC content in % (w/w)				
	0	10	30	50	0.5	1	2.5	5	10
carbamazepine	0.244	0.269	0.341	0.452	0.466	0.497	0.576	0.733	1.016
theophylline	11.1	10.3	10.6	10.3	11.1	11.4	11.8	12.3	12.6
diprophylline	210.2	204.0	147.0	91.0	207.9	205.8	213.0	208.6	209.7

Table 3. Effect of sucrose and HPMC concentration on the aqueous drug solubility in mg/mL (RSD<3%)

The reduced solubility of diprophylline in presence of sucrose could potentially decrease its diffusion gradient and hence its release from NP pellets. However, slower release from NP pellets was also observed for theophylline and carbamazepine, although their solubilities were not reduced by sucrose. Therefore additional factors influencing the release had to be considered.

HPMC which is contained in the drug layer (40% based on drug) has been reported to improve wettability, dissolution rate and solubility of poorly soluble drugs as well as prolonging supersaturation (by preventing recrystallization) in a variety of formulations (Usui, Maeda et al. 1997; Raghavan, Trividic et al. 2000; Gao, Rush et al. 2003; Verreck, Six et al. 2003; Matteucci, Brettmann et al. 2007; Kennedy, Hu et al. 2008; Gao, Akrami et al. 2009). HPMC also stabilized carbamazepine in its more soluble anhydrous polymorphic form (Katzhendler, Azoury et al. 1998; Otsuka, Ohfusa et al. 2000; Qu, Louhi-Kultanen et al. 2007). Such properties were reportedly correlating with the concentration of HPMC inside of the formulations (Usui, Maeda et al. 1997; Raghavan, Trividic et al. 2000; Matteucci, Brettmann et al. 2007; Gao, Akrami et al. 2009).

This was reconfirmed by the drug solubility in HPMC E5 solutions (Table 3 right). Carbamazepine solubility increased significantly with higher HPMC concentrations, whereas theophylline exhibited only a minor increase and diprophylline no effect, respectively. Although the HPMC content was the same for both starter core types (40% based on drug), these HPMC-induced solubility changes affected the release, as will be elucidated later.

Sucrose could also affect the hydration of Eudragit RS/RL (Heinicke and Schwartz 2007). In agreement, the values of water uptake after 48 h for free films of RS/RL 65:35 (or 90:10) decreased from 61.7 ± 1.9% to 15.7 ± 1.9% (or 47.0 ± 0.4% to 10.1 ± 0.3%) upon addition of 30% (w/w) sucrose to water. This pronounced dehydration was partially responsible for the slower release from NP pellets.

However, sucrose is a highly soluble substance (>2000 mg/mL) and could thus be released from the pellets rather quickly. Once the sucrose is released, the observed effects on drug solubility and coating hydration were likely becoming negligible.

3.1.5 Sucrose release

Sucrose release was determined by two methods: a gravimetric weight-loss method or an HPLC method, using a hydrophilic interaction chromatography column (HILIC) with evaporative light scattering detection (for more details see end of first chapter; 3.1.10).

The HPLC-ELSD method was specific for sucrose whereas the gravimetric method only allowed the determination of the total weight loss. In the present work, the amounts of sucrose released were determined from this total weight loss by subtracting the amounts of drug released (determined by UV). Compared to the HPLC-ELSD method, this gravimetric approach was found to be equally reliable (Figure 25). However, this was only valid because other excipients without UV-absorption (e.g. the HPMC binder or the 25% starch contained in nonpareils) were not released in parallel or only in negligible amounts.

While gravimetric weight loss studies were rather time-consuming and required far more pellet material (one set of pellets for every sample time point), they were very easy and economic. During the HPLC-ELSD analysis, many steps could be automated and a complete sucrose release profile was obtainable from just one set of pellets. However, the required expensive HILIC column (price ~2-3 times higher than regular RP-columns) and the need for solvents like acetonitrile rendered this method quite cost-intensive.

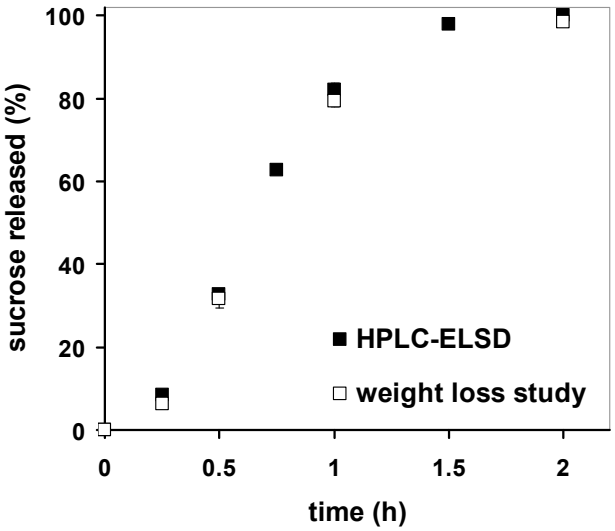


Figure 25. Comparison of HPLC-ELSD method vs. gravimetric weight loss method for determination of sucrose release from coated pellets (10-CBZ-NP-RS/RL-65:35; c.l. 3 mg/cm^2)

The sucrose release of drug-free nonpareils coated with either pure EC, pure RS or polymer blends (65:35) of EC/HPC or RS/RL indicated, that sucrose was released easier from cellulosic than from acrylic polymers (Figure 26).

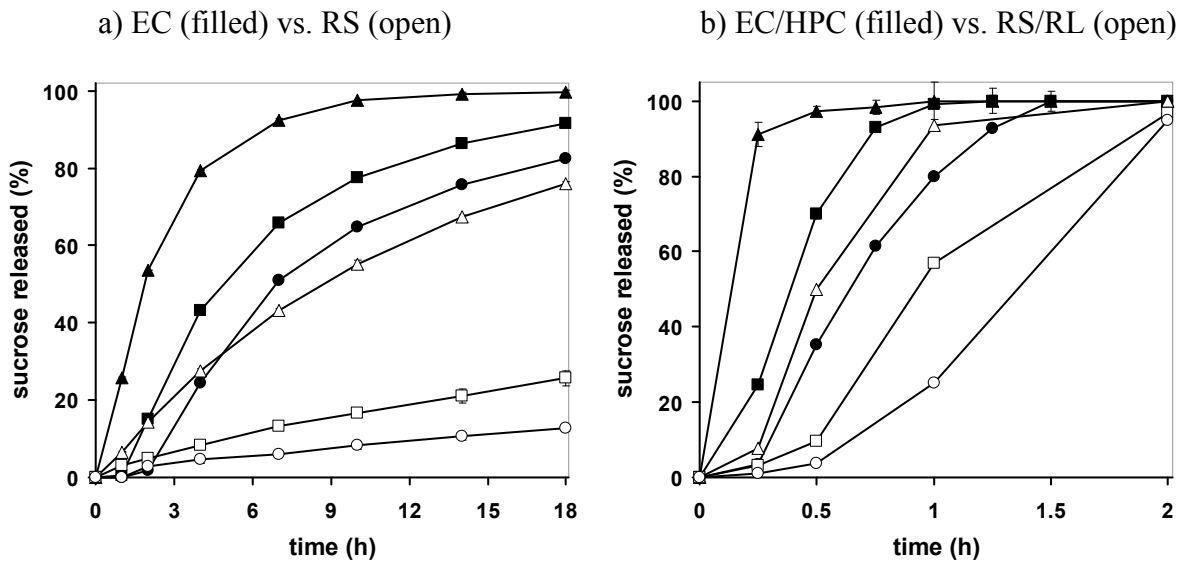


Figure 26. Sucrose release from nonpareils starter cores coated with a) pure polymer or b) 65:35 blends as a function of the coating level: ▲△ 1 mg/cm^2, ■□ 3 mg/cm^2, ●○ 5 mg/cm^2; method HPLC-ELSD

This was ascribed to the higher flexibility of acrylic versus cellulosic coatings. While pronounced expansion without ruptures was reported for pellet with the acrylic coating, pellets with the cellulosic coating did not swell but instead ruptured extensively (Ueda, Hata et al. 1994). In the present study, such pronounced rupturing was not observed for any of the coated nonpareils. However, smaller cracks may have formed. The highly soluble sucrose would then be released rather easily through these cracks, thereby preventing further pressure build-up and rupturing.

For the EC/HPC blend, the faster sucrose release compared to RS/RL was also explained by the solubility of HPC in aqueous media. At a content of 35%, the HPC was expected to leach from the EC-films, leaving behind water-filled channels which facilitate osmotic pumping (Hjärtstam, Borg et al. 1990). In contrast, water-insoluble, swellable RL would not create pores by leaching. The faster release in comparison to pure RS was only caused by the increased hydration of RL.

When monitoring the sucrose release from coated drug pellets, containing either highly soluble diprophylline (210 mg/mL) or poorly soluble carbamazepine (0.24 mg/mL) (Table 3), the sugar was released very similar to diprophylline, irrespective of the polymer (Figure 27a-b). However, carbamazepine release was a lot slower; at its lag time (T5) nearly 100% of sucrose was already released from the EC/HPC and RS/RL (65:35) coated pellets (Figure 27c-d).

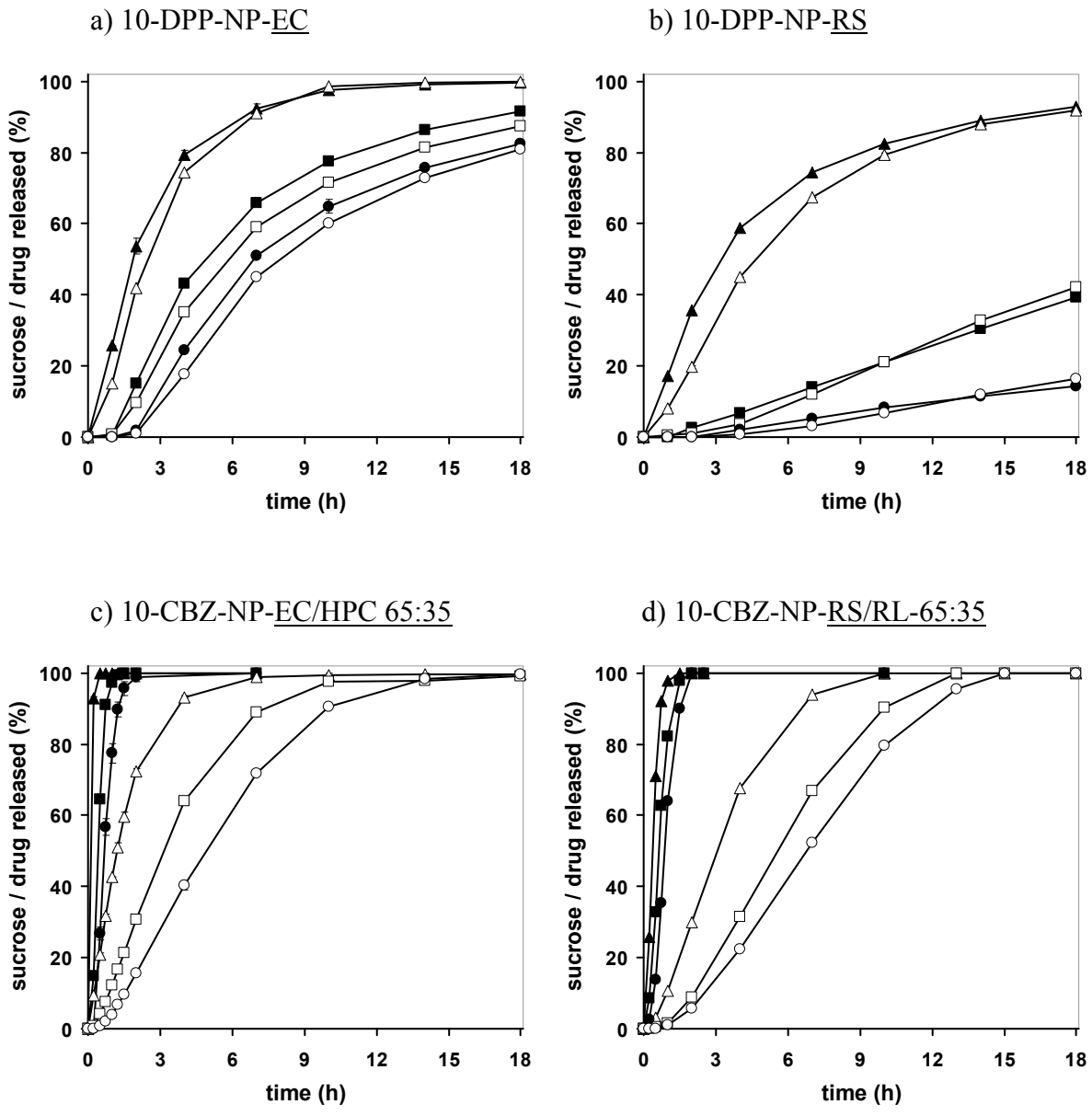
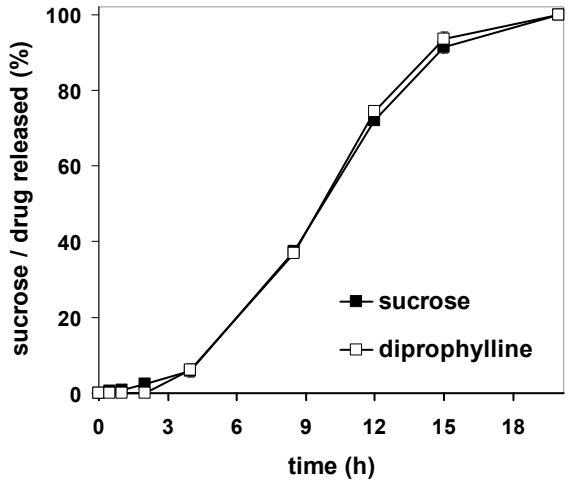


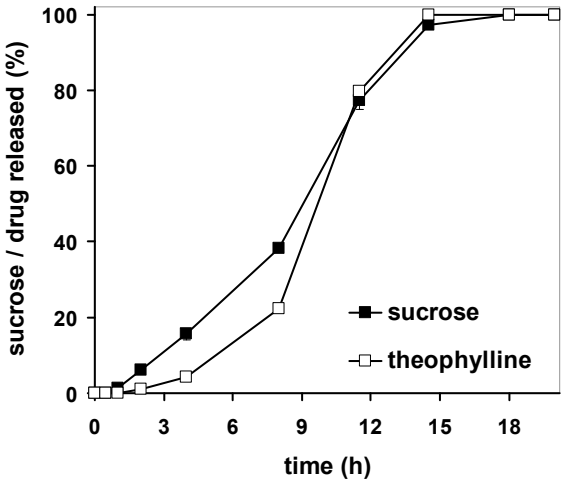
Figure 27. Sucrose (filled symbols) and drug (open symbols) release from coated pellets with 10% drug loading (c.l. ▲△ 1 mg/cm^2, ■□ 3 mg/cm^2, ●○ 5 mg/cm^2; method HPLC-ELSD)

Sucrose release data of RS/RL-90:10-coated pellets revealed that, similar to diprophylline, theophylline (11 mg/mL) was also released in parallel with the sugar (Figure 28). Both drugs could thus be affected by the afore-mentioned sucrose-induced changes in coating hydration and drug solubility. However, carbamazepine and sucrose were again released successively, with almost complete release of the sugar before the drug release.

a) 10-DPP-NP-RS/RL-90:10



b) 10-THP-NP-RS/RL-90:10



c) 10-CBZ-NP-RS/RL-90:10

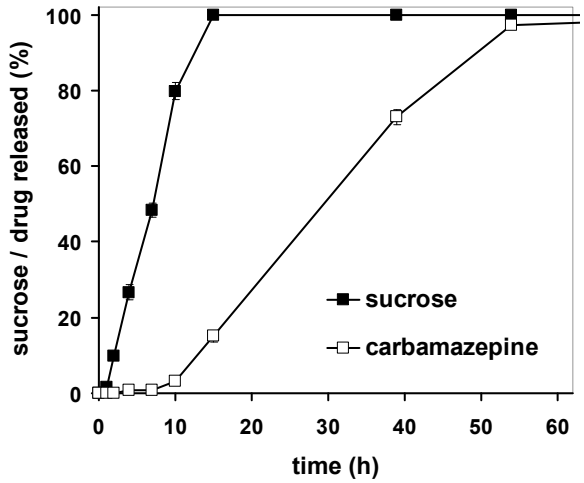


Figure 28. Sucrose and drug release from RS/RL-90:10-coated pellets (c.l. 3 mg/cm^2; method weight loss)

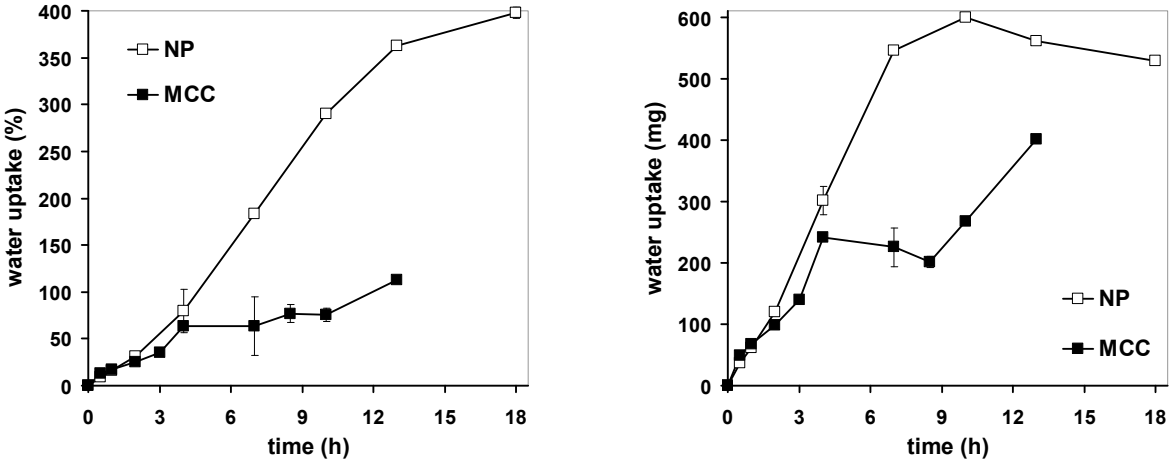
Whereas the effects of sucrose on RS/RL-coating-hydration and drug solubility decreased after its complete release, more permanent changes within the NP pellets were considered. Therefore their water uptake, swelling and cracking behaviour were studied in comparison to MCC pellets.

3.1.6 Water uptake studies

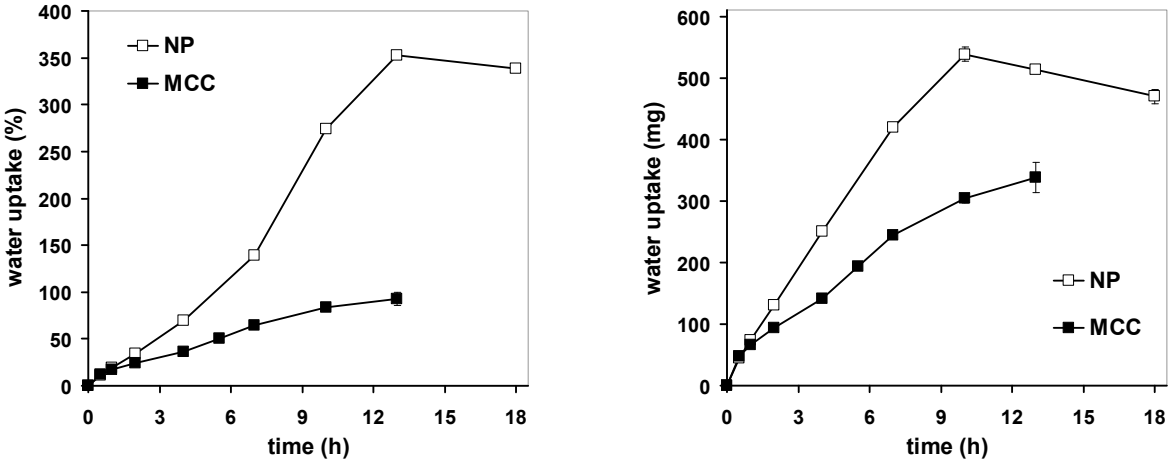
Due to their osmotic activity, NP pellets were proposed to have a higher water uptake than pellets based on osmotically inactive starter cores (Tang, Schwartz et al. 2000; Lecomte, Siepmann et al. 2005; Muschert, Siepmann et al. 2009 c). This could create higher tensile stress on the polymer coating (Hjärtstam, Borg et al. 1990; Hjartstam and Hjertberg 1998; Heng, Chan et al. 1999) or act like a counter current to the efflux of drugs (Narisawa, Nagata et al. 1997; Marucci, Ragnarsson et al. 2008; Muschert, Siepmann et al. 2009 b).

As expected, the relative water uptake (%) of RS/RL-90:10 coated pellets was higher for pellets based on nonpareils (Figure 29 left). The differences were slightly less pronounced in the absolute values (mg) (Figure 29 right), which was attributed to the release of the sugar and water gradually filling up the resulting volume. Initially, the relative water uptake was the same for both starter core types but it started to increase for NP pellets when the sugar dissolved and sucrose release set in (Figure 30).

a) diprophylline



b) theophylline



c) carbamazepine

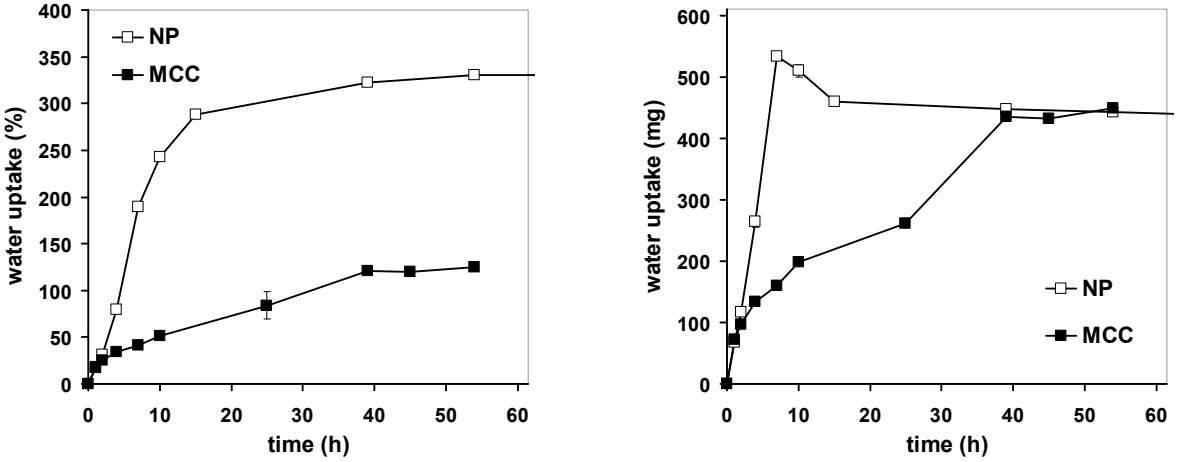


Figure 29. Relative (left) and absolute (right) water uptake of pellets coated with 3 mg/cm^2 RS/RL 90:10

a) theophylline b) carbamazepine

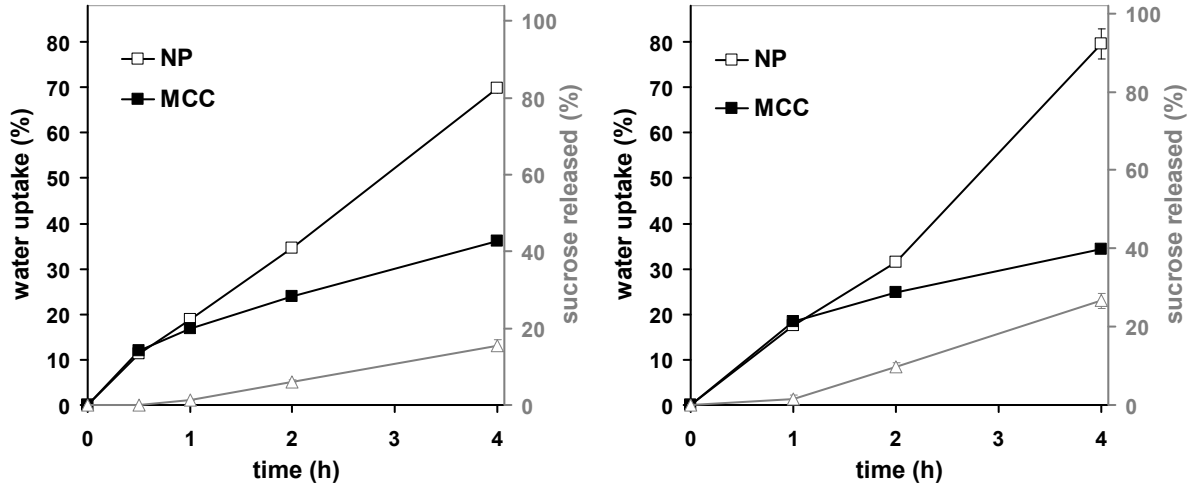


Figure 30. Detail of the early relative water uptake of pellets coated with 3 mg/cm^2 RS/RL 90:10 in correlation with the sucrose release

For soluble drugs like theophylline and diprophylline, the observed higher water uptake of NP pellets could lead to a dilution of the drug concentration inside pellets. Since this dilution would be equivalent to decreasing diffusion gradients, their release from NP pellets could potentially slow down.

However, estimates of the theoretical concentrations of theophylline and diprophylline inside NP pellets and MCC pellets did not provide conclusive evidence for such a dilution effect (Figure 31).

In theophylline pellets saturation was maintained for ~10 h irrespective of the starter core type. However, the release rate of NP pellets was already lower compared to MCC pellets after only 6 h (Figure 31a).

In diprophylline pellets on the other hand, saturation was not achieved at all (Figure 31b). Both NP and MCC pellets were not saturated anymore at the lagtime T5 and exhibited rather similar concentration profiles during the release.

Therefore a stronger dilution of soluble drugs in NP pellets due to their more pronounced water uptake could not be corroborated as the main reason for the lower release rate of NP pellets.

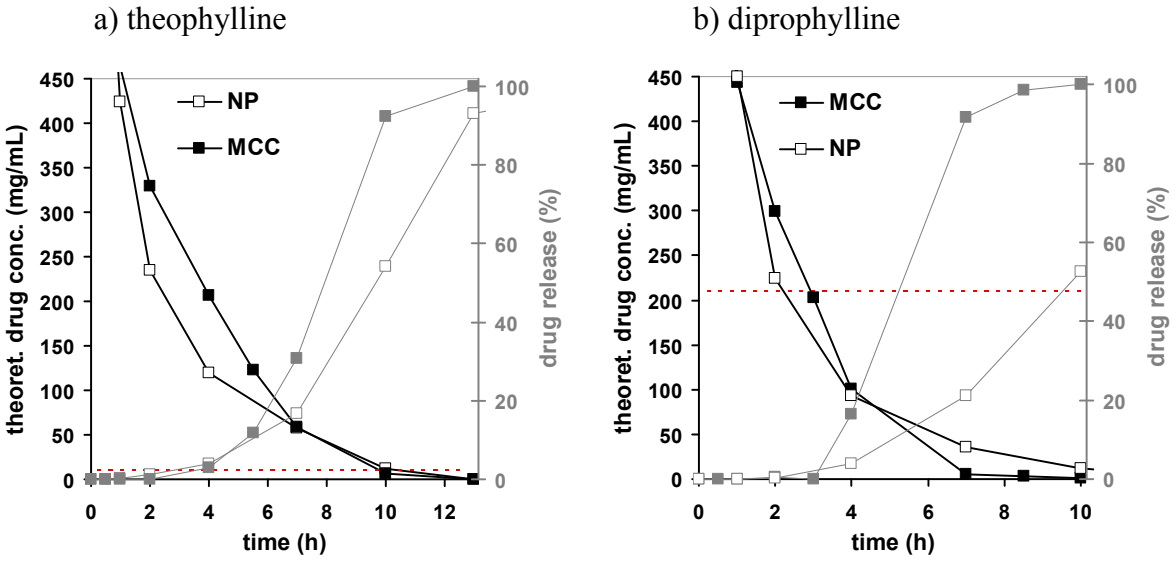


Figure 31: Theoretical drug concentrations inside NP and MCC pellets as estimated from water uptake and drug release data (dotted lines represent saturation concentration; 10% loading, 3 mg/cm^2 RS/RL 90:10)

Poorly soluble drugs like carbamazepine are expected to maintain saturation inside pellets, irrespective of the water uptake. A dilution-effect in NP-pellets could only occur if carbamazepine was released faster across the coating than it can be re-dissolved inside the reservoir. Considering that uncoated carbamazepine cores were 100% dissolved within less than 15 min (as described later in Figure 48) whereas RS/RL-coated pellets prolonged the release over 10-60 h (Figure 18), that was an unlikely case.

In some reports, higher water uptake of NP pellets was considered beneficial for the dissolution of drugs with low solubility (Muschert, Siepmann et al. 2009 c). However, in contrast to this theory, it was actually the lower water uptake of MCC pellets, which promoted carbamazepine release because it resulted in higher HPMC concentrations. HPMC in turn increased the solubility of carbamazepine (Table 3 right) and thus led to higher carbamazepine concentrations inside MCC pellets.

This was verified by retrieving RS/RL-65:35-coated carbamazepine pellets from their release vessels after 2h and squeezing out their internal fluid volume with a syringe (2.2.4.3). The carbamazepine concentration inside NP pellets was 0.264 ± 0.019 mg/mL (just slightly above the solubility in pure deionized water; Table 3) whereas inside MCC pellets higher values of 0.324 ± 0.013 mg/mL were found. Therefore, the diffusion gradient of carbamazepine was higher with MCC pellets.

3.1.7 Swelling and cracking studies

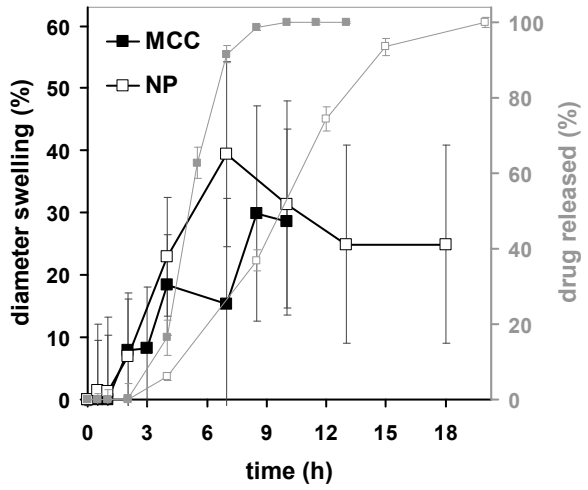
Depending on the porosity of the drug core and the rigidity of the applied polymer coating, imbibition of medium could also lead to swelling of the pellets. Especially semipermeable-coated systems tend to accumulate medium inside until the uptake is balanced by concurrent diffusional or convective release through an orifice. In consequence the system expands, the film is getting thinner and eventually can crack or rupture (Hjärtstam, Borg et al. 1990; Schultz and Kleinebudde 1997; Hjartstam and Hjertberg 1998; Heng, Chan et al. 1999).

Swelling as a function of release was determined during the water uptake study (Figure 32). Pellets coated with 3 mg/cm^2 RS/RL 90:10 were retrieved from the release vessels and a picture of 10 randomly chosen pellets was taken before blotting and drying the sample. Since a different set of pellets was thus measured for every time point (2.2.5), these swelling data were considered an estimation only.

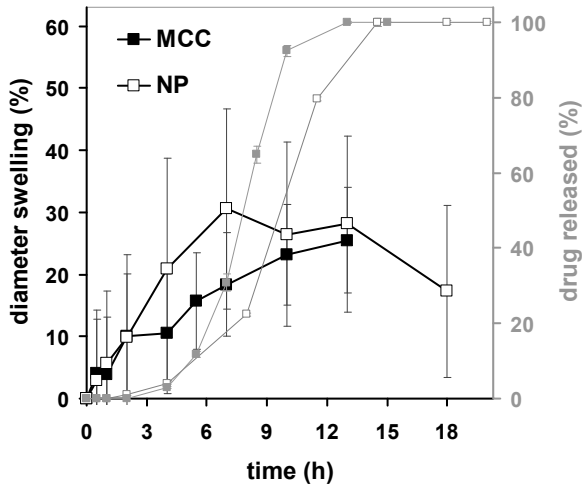
In agreement with the water uptake values and the release lag times (Figure 18 and Figure 29), the diameter swelling of NP and MCC pellets was similar in the beginning of release (Figure 32). The swelling of the NP pellets then reached a maximum after ~7 h, followed by a slight shrinkage which was attributed to the release of the osmotically active sucrose (Schultz and Kleinebudde 1997).

MCC pellets, on the other hand, exhibited a slower but more consistent swelling after the initial stage; and shrinkage of the pellets was not observed (Figure 32). This was due to the solid support offered by the insoluble MCC starter core.

a) diprophylline



b) theophylline



c) carbamazepine

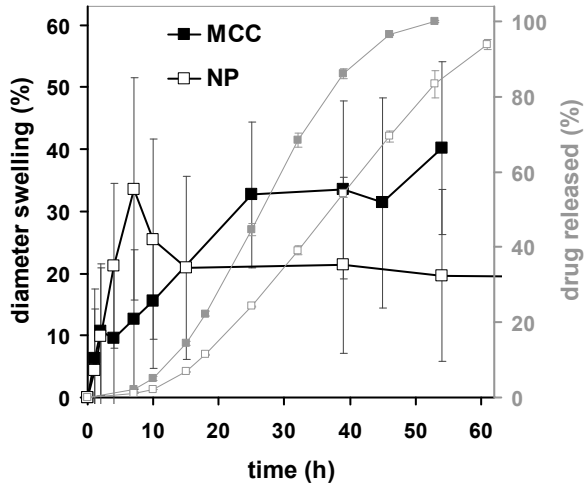


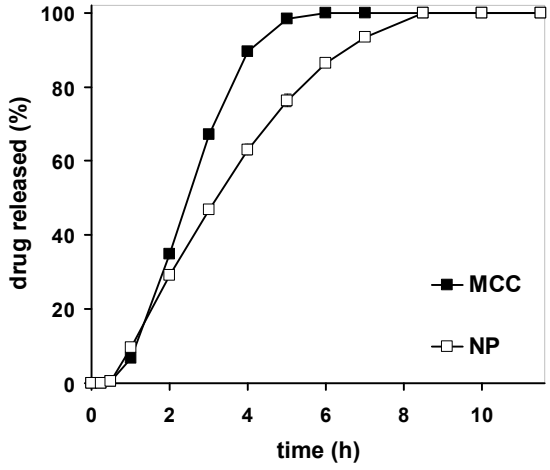
Figure 32. Diameter swelling and drug release of NP and MCC pellets during water uptake study (10% drug loading, 3 mg/cm^2 RS/RL 90:10)

Despite the pronounced swelling, ruptures or cracks in the coating were not visible at 60x magnification. Nonetheless, smaller cracks with a size of only a few micrometers could have been formed (Hjärtstam, Borg et al. 1990; Schultz and Kleinebudde 1997; Heng, Chan et al. 1999). In order to make those potential micro-cracks more noticeable, pigment containing pellets were prepared analogue to drug pellets by replacing 25% of the carbamazepine with a

micronized red pigment. Since iron oxide pigments are insoluble in water, they can not diffuse through the intact film coating but can only be expelled from pellets via micro-cracks or ruptures.

Drug release from pigment pellets was again faster with MCC cores (Figure 33a), similar to the release from pigment-free carbamazepine pellets (Figure 18a). Surprisingly, micro-crack formation and hence colouring of the release medium by expelled red pigment was noticeable for MCC pellets only after ~4 h whereas for NP pellets pigment release started after 45 min already. This difference is depicted for the 2 h sample time point (run with 1600 mg pellets for better visibility) (Figure 33b). The NP pigment pellets did not only exhibit earlier but also more pronounced micro-cracking; after two hours 23 out of 24 single pigment pellets with NP cores showed traces of expelled red powder but only one with MCC core.

a) carbamazepine release



b) release of red pigment at 2h time point

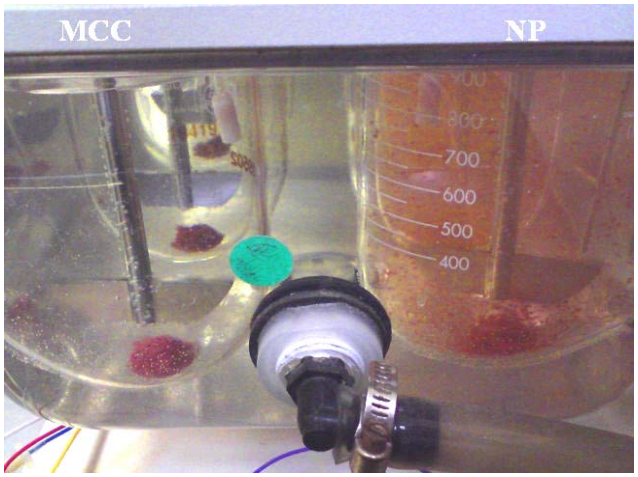


Figure 33. Release of carbamazepine and red pigment from pellets as a function of the starter core type (10% weight gain of drug and pigment 3:1, 3 mg/cm^2 RS/RL 65:35)

Macroscopic videos of pigment containing pellets at 60x magnification showed that both, NP and MCC pellets exhibited pronounced initial diameter swelling during the first 4 h (Figure 34). The swelling characteristics were similar to those of pure drug pellets (Figure 32): fast initial swelling followed by shrinkage for NP pellets; slower and more consistent swelling for MCC pellets.

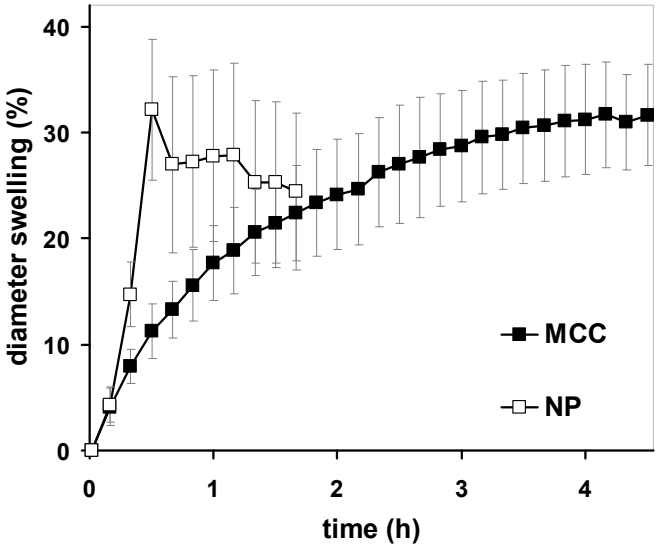


Figure 34. Initial diameter swelling of single pellets as a function of the starter core type (10% weight gain of carbamazepine and pigment 3:1; 3 mg/cm^2 RS/RL 65:35)

3.1.8 Release mechanism of RS/RL-coated NP pellets

The pigment release from NP pellets occurred by convective osmotic pumping in multiple very small pulses of sucrose solution from a single crack per pellet (Figure 35). Owing to the rapid water uptake and the poor hydration of RS/RL in presence of sucrose, the film apparently cracked at the weakest spot. This helped to relax the hydrostatic pressure on the film and potentially prevented further damages. However, the size of that crack was still so small that, without the pigment expelled, it would not have been noticeable at 60x magnification. Its area was negligible in comparison with the total surface area of the pellet.

The soluble drugs were predominantly released from NP pellets in parallel with the sugar by convection. This hypothesis was also supported by the similar release profiles of sucrose, theophylline and diprophylline despite their solubility differences (Figure 28). The convection was very slow, though, due to the small size of the orifice and the pronounced water uptake which potentially acted like a counter-current. Diffusion of soluble drugs was restricted by the reduced RS/RL-coating-hydration and diprophylline-solubility in presence of sucrose.

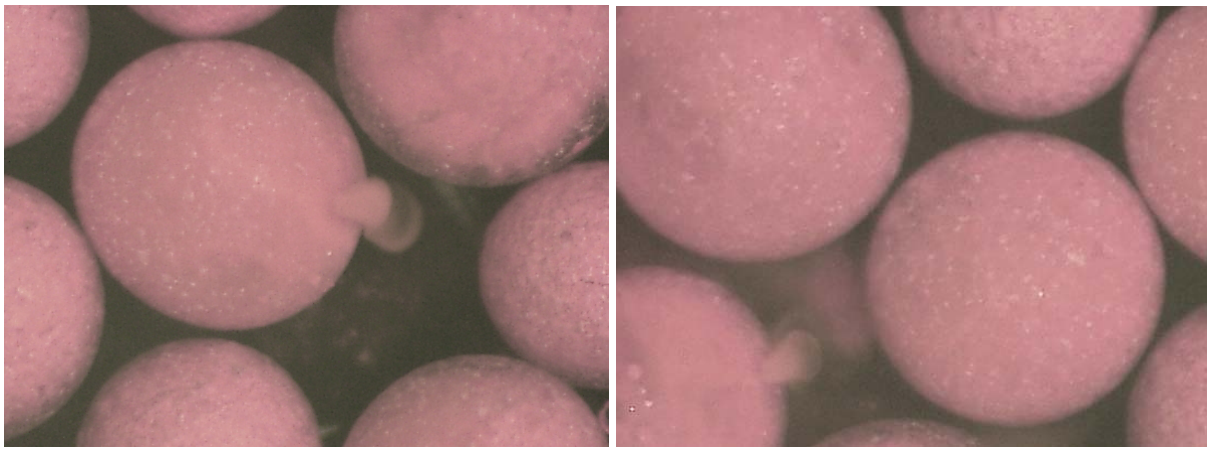


Figure 35. Convective release of red iron oxide pigment by osmotic pumping from NP pellets containing 10% carbamazepine and Sicovit red 3:1 (3 mg/cm^2 RS/RL 65:35)

The convective pulses slowed down after the first hour which was attributed to the nearly complete release of osmotically active sucrose (Figure 27d). And the concurrent shrinkage of the pellets may lead to pore closure and self-healing of the crack (Wool and Oconnor 1981). Therefore carbamazepine release from NP pellets, which occurred after the sucrose release, was predominantly by diffusion through the single crack and / or the intact polymer coating. This was confirmed by releases in different media.

3.1.8.1 Media dependence of carbamazepine release

Although all media were adjusted to the same osmolality (~330 mosmol/kg), and hence differed only with regard to their ionic strength and species, release rates of NP pellets decreased to different degrees (Figure 36a). The lag times were not affected, though, and similar observations were also made for osmotically inactive MCC pellets (Figure 36b). Hence the decreasing release rates were not caused by reduced osmotic gradients (Zentner, Rork et al. 1985; Ozturk, Ozturk et al. 1990; Ragnarsson, Sandberg et al. 1992; Schultz and Kleinebudde 1997; Zhang, Zhang et al. 2003; Sotthivirat, Haslam et al. 2007). However, the ion species is known to affect RS/RL-hydration and thus diffusion differently (Okor 1990; Bodmeier, Guo et al. 1996; Knop 1996; Wagner and McGinity 2002; Grützmann 2005).

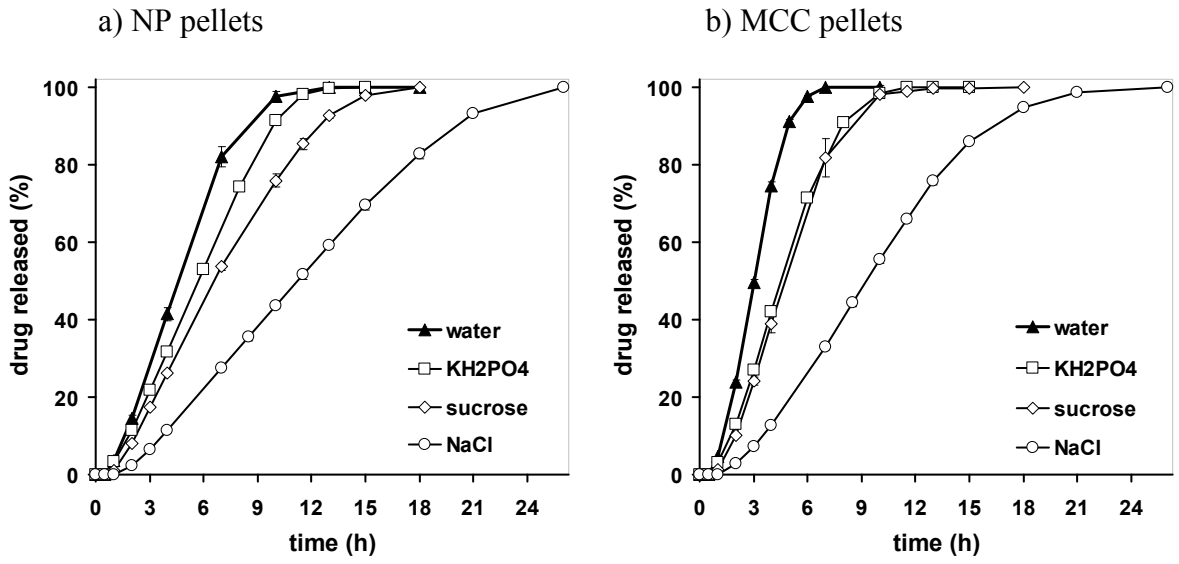


Figure 36. Media dependence of carbamazepine release from pellets coated with 3 mg/cm^2 RS/RL 65:35 (all media ~330 mosmol/kg)

3.1.9 Release mechanism of RS/RL-coated MCC pellets

Despite the lower release of pigment, crack formation on MCC pellets was considered highly probable, given that MCC pellets reached the same maximum swelling as NP pellets after the initial two hours (Figure 34). However, in absence of sucrose, the hydration of RS/RL-coatings was better. Hence numerous smaller micro-cracks were probably formed instead of just one as with NP pellets. Apparently the crack size on MCC pellets was too small to allow pigment release. However, the multitude of these micro-cracks created a larger cumulative 'crack-area' and thus enhanced drug release. The risk of pore closure was prevented by continuous swelling without shrinkage (Figure 34).

In addition, the lower water uptake of MCC pellets (Figure 29) resulted in more concentrated HPMC gels within the drug/pigment-binder-layer. In consequence, the insoluble pigment could have been trapped within the gel rather than being carried out by a convective stream of aqueous solution and the stronger gel probably acted like a plug in the micro-cracks, as it was reported for needle-pricked pellets (Heng, Chan et al. 1999). Equally important, though, was the effect of the more concentrated HPMC gel on the carbamazepine concentration which increased inside pellets as described earlier.

It was thus concluded that the starter core effect of RS/RL-coated NP and MCC pellets was resulting from i) sucrose-induced changes in coating hydration and drug solubility, ii) differences between the internal drug concentrations and iii) differences in the size and number of cracks formed in the coating during release.

Since mechanical properties as well as hydration behaviour of a film coating depend strongly on the polymer, the starter core effect observed with RS/RL-coated pellets could not simply be transferred to other coatings. For example, ethylcellulose (EC) was found to be less flexible and more prone to rupturing than RS (Ueda, Hata et al. 1994). Celluloseacetate (CA) is also less flexible than RS, as could be deduced from the polymers glass transition temperatures: CA ~190 °C (Guo 1993), EC ~ 133 °C and RS ~58 °C (Wagner, Maus et al. 2005; Terebesi and Bodmeier 2010). Comparing the starter core effect of RS/RL 65:35 to other batches coated with EC/HPC 65:35 or CA/PEG 65:35, only a minor difference between NP and MCC pellets was obtained with the EC/HPC blend (Figure 37b). Especially the release from NP pellets seemed to increase with EC/HPC. For CA/PEG, the release from NP pellets was even faster compared to MCC pellets (Figure 37c). More pronounced rupturing of the brittle blends as a consequence of the osmotic water uptake or a lower susceptibility to sucrose-induced coating dehydration were possible explanations.

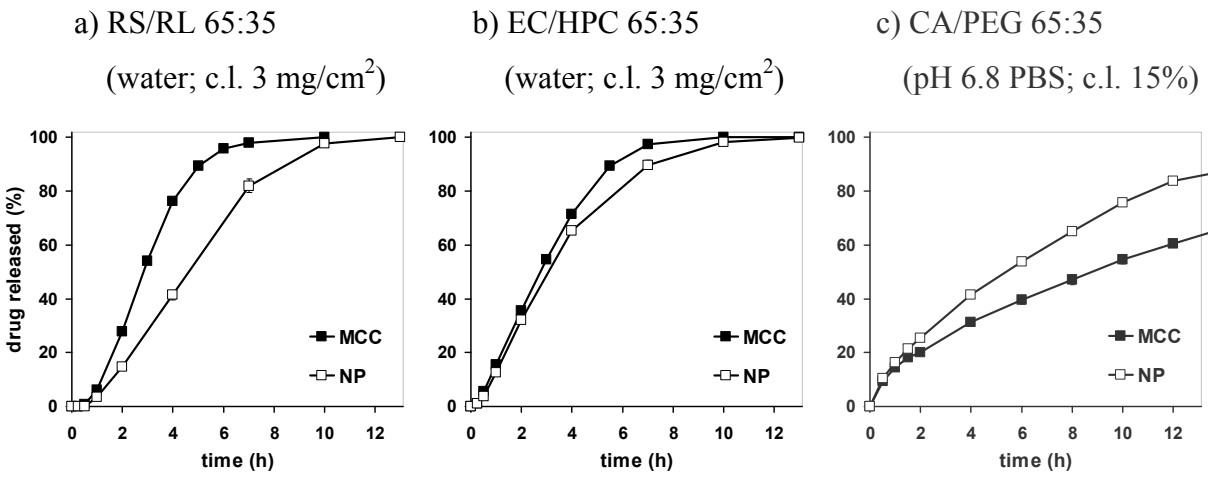


Figure 37. Effect of starter core on carbamazepine release from pellets coated with polymer blends of decreasing flexibility: RS/RL > EC/HPC > CA/PEG

3.1.10 Sucrose release determination by HPLC-ELSD

In contrast to most drugs, sucrose does not have a UV-absorbing chromophore. Therefore it was necessary to separate sucrose from the drug using an HPLC method, followed by evaporative light scattering detection (ELSD), in order to quantify the sugar selectively. Since sucrose is a hydrophilic substance, a zwitterionic HILIC-column (hydrophilic interaction liquid chromatography) was chosen for the separation step. As described earlier (1.3.1), these columns combine hydrophilic and electrostatic interactions to retain polar, hydrophilic analytes in the water-enriched layer which covers the porous silica particles of the stationary phase.

In agreement with recommendations of the supplier of the HILIC column, acetonitrile (ACN) and ammoniumacetate solutions in MilliQ-water (NH_4Ac) were chosen as the organic and aqueous eluents, respectively. In order to achieve sufficient retention of hydrophilic substances, the content of ACN should be at least 50% (SeQuant AB 2006). For the separation of sugars, ACN / NH_4Ac ratios of 80:20, 78:22 and 70:30 V/V had been suggested in the literature (Cardenas, Gallego et al. 1999; Steinike 2003; Bhandari, Kumar et al. 2008). However, with ACN contents above 73%, precipitation of the phosphate buffer salts contained in pH 6.8-samples was observed. Therefore, the ACN contents tested in the present work only ranged from 73-55% V/V.

Different settings of the ELS-detector and different NH_4Ac-buffer-concentrations have been evaluated previously (Risley and Pack 2006; Dashevska 2007; Rashan and Chen 2007). Following these recommendations, test injections with mixed samples were performed. These mixed samples contained carbamazepine, diprophylline, fructose, glucose and sucrose; all dissolved in either pH 6.8 phosphate buffer, 0.1N HCl or deionized water. A concentration of 25 mM NH_4Ac (yielding pH 6.8) in the aqueous eluent provided good separation of all peaks and was thus kept constant for the quantitative runs. The settings of the ELS-detector were chosen as follows: evaporator and nebulizer temperature 90 °C and 80 °C respectively, 1.0 SLM flow rate of the inert gas (filtered air) and vaporizing air pressure 4.5 bar. The injection volume was 60 µL of undiluted, aqueous sample.

Long runtimes up to 32 min were necessary for the separation of mixed samples in pH 6.8 phosphate buffer, although all drugs eluted early and well separated from the sugars (data not shown). However, the buffer ions had a low affinity to ACN and thus were strongly retained on the HILIC-column, causing peaks from 11-30 min run time. The first peak was

ascribed to (di)hydrogenphosphates and the double peak to sodium and potassium (Crafts, Bailey et al. 2009). Therefore two gradient runs were performed in which the NH_4Ac content was increased from 27% to 45% V/V over a gradient time tG of either 26 min (steep gradient) or 78 min (shallow gradient). Since water is the strong eluent in HILIC methods, increasing the aqueous eluent NH_4Ac was expected to shorten the runtime by faster elution of the phosphate buffer ions. However, even with the steep gradient, runtime was still in the range of 25 min (Figure 38).

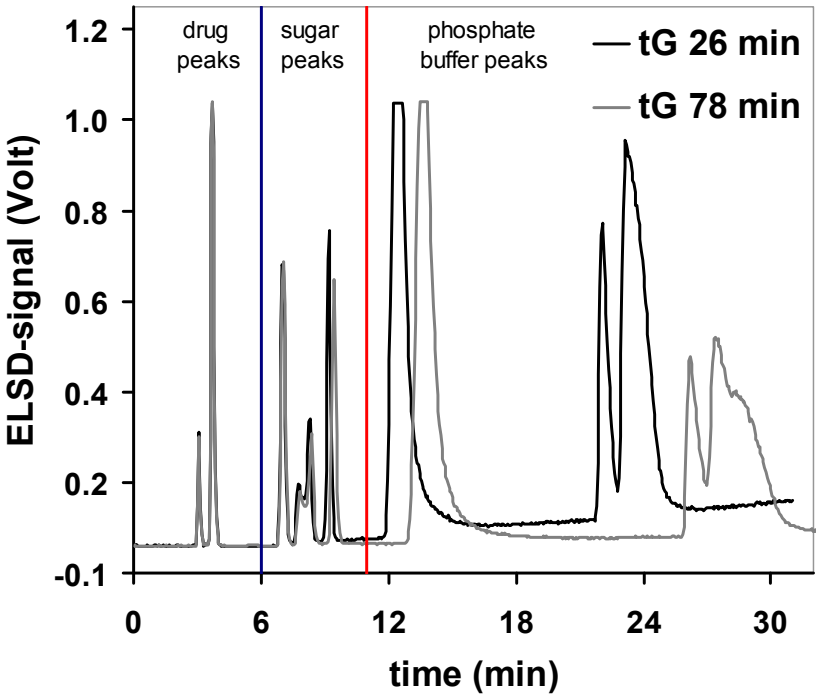


Figure 38. Gradient separation of a mixed sample dissolved in pH 6.8 phosphate buffer solution; content of 25 mM NH_4Ac increased from 27% to 45% V/V within a gradient time tG of either 26 min or 78 min; (mixed samples contained model drugs, sucrose, fructose and glucose)

Interestingly, the drug and sugar peaks were not affected by the gradient. Thus isocratic runs were considered feasible and avoided the need for re-equilibration of the column before injection of the next sample. In isocratic runs with ACN / NH_4Ac 73:27 V/V, retention of the phosphate buffer ions could be shortened further by adjusting the pH of 25

mM NH_4-Ac with acetic acid from 6.8 to 4.5 (Figure 39). At the lower pH, the runtime was now below 20 min which was considered appropriate for routine use. This could be attributed to the faster elution of sodium and potassium ions at lower eluent pHs (Risley and Pack 2006). The retention time of the (di)hydrogenphosphates on the other hand was hardly changed by the pH which was also in accordance with the report (Risley and Pack 2006).

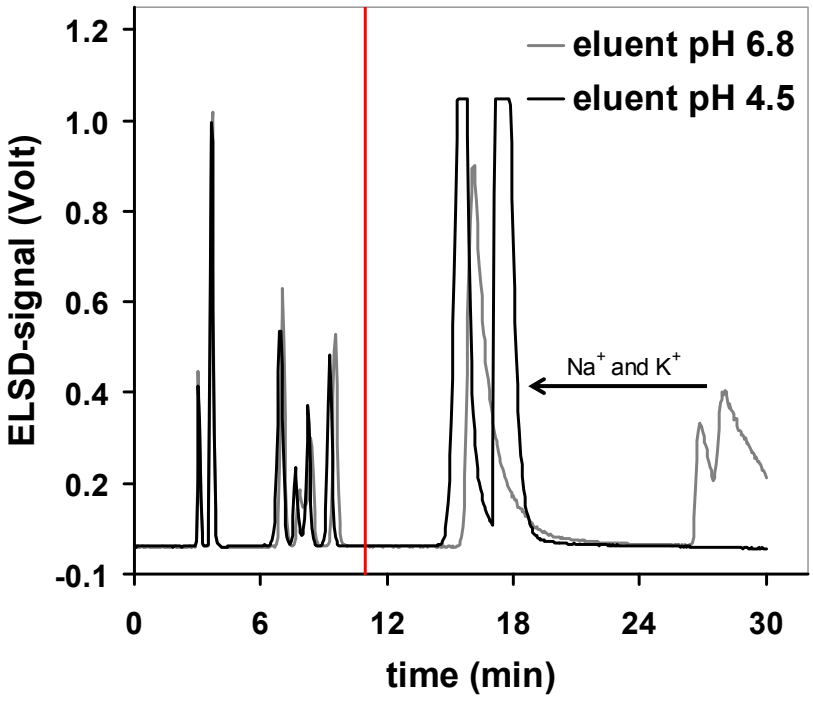


Figure 39. Effect of the pH of NH_4Ac (pH 6.8 vs. 4.5) on retention times of phosphate buffer ions in isocratic runs at eluent ratio ACN / NH_4Ac 73:27 V/V; (t_R > 11 min: (di)hydrogenphosphates, sodium and potassium)

The massive peak of chloride ions did not create problems for mixed samples dissolved in 0.1N HCl. It was positioned right between drug peaks and sugar peaks and thus did neither increase the runtime nor affect the detection of the sugars (Figure 40). Hence, a pH-adjustment of the NH_4Ac-buffer to pH 4.5 was not necessary for samples dissolved in 0.1N HCl.

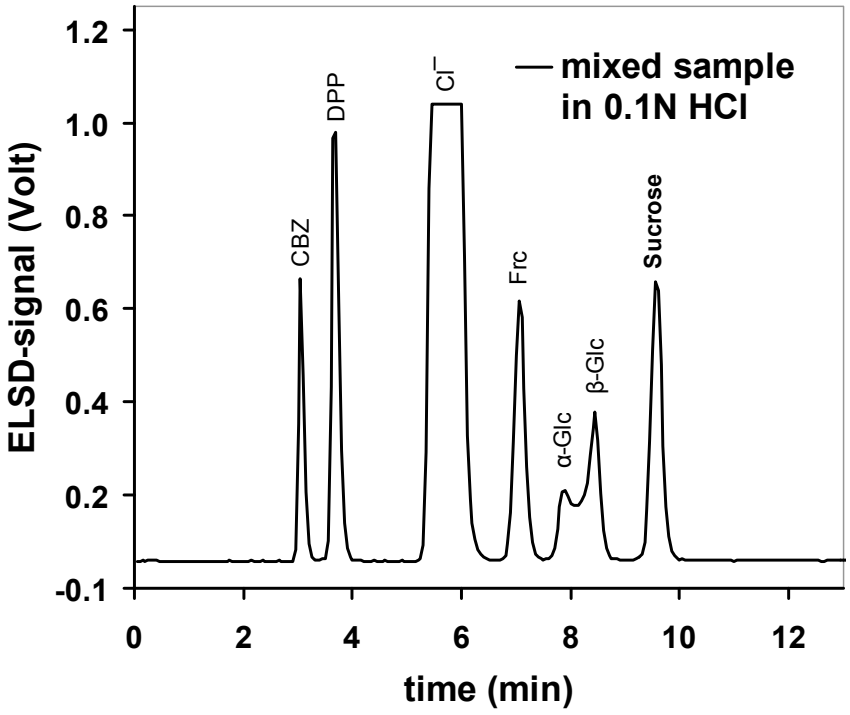


Figure 40. Isocratic elution of a mixed sample dissolved in 0.1N HCl with ACN / 25 mM NH_4Ac (pH 6.8) in a ratio of 73:27 V/V (mixed samples of test runs contained carbamazepine, diprophylline, sucrose, fructose and glucose)

However, sucrose was hydrolyzed in acidic media to its monomers fructose (Frc) and glucose (α-Glc and β-Glc) which then had to be quantified in lieu of sucrose. After just 1 h in 0.1N HCl at 37 °C, the monomer peaks became visible in the chromatogram while the sucrose peak decreased (Figure 41a). After 24 h sucrose was not detectable anymore. Tests with a semimicro-osmometer (2.2.12) allowed a quick and simple observation of sucrose hydrolysis (Figure 41b). It was almost complete after 9 h. Since this hydrolysis also happens during the drug release studies, samples before 9 h would contain mixtures of all sugars. Therefore early samples of releases in acidic media should be stored at 37 °C until at least 10 h 'age' in order to quantify sucrose completely via its surrogates fructose and glucose for all sample time points.

a) HPLC-ELSD b) semimicro-osmometer

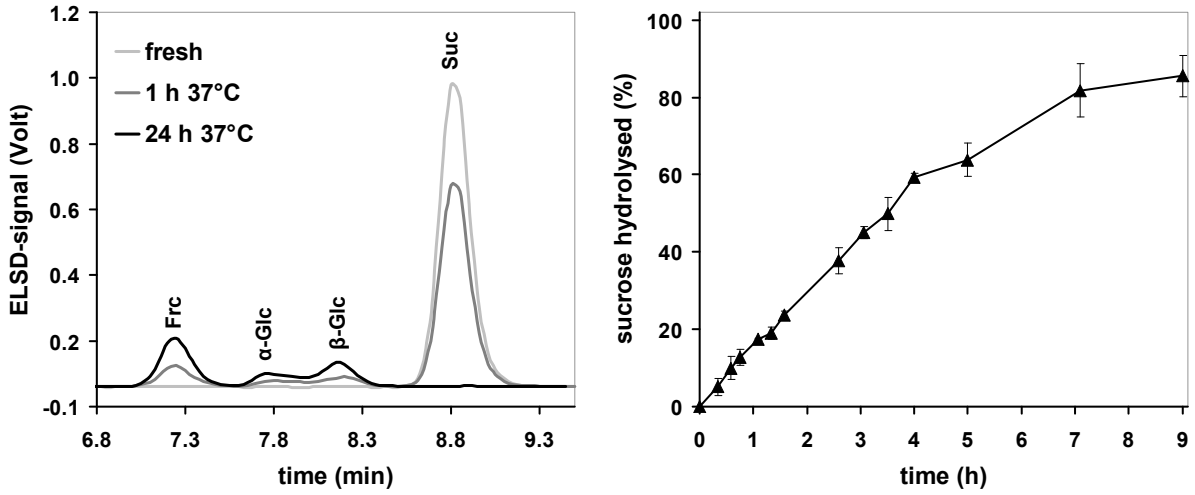


Figure 41. Hydrolysis of sucrose (Suc) to its monomers fructose and glucose (Frc, α-Glc and β-Glc) in 0.1N HCl at 37 °C as determined by two different methods

Hence, detection and quantification of sucrose in 0.1N HCl-samples and pH 6.8-phosphate-buffer-samples was feasible with isocratic runs in 11 min and 20 min, respectively, using ACN and 25 mM NH_4Ac 73:27 V/V as the eluent.

However, during routine use of the developed method, the large amounts of non-volatile buffer salts in each of the two media (chloride, sodium, potassium, phosphates) clogged the evaporation tube of the ELS-detector, despite regular, long-lasting water-vapour cleaning. This led to increasing interferences with the light scattering detection and finally necessitated a change of the release medium.

Since neither sucrose nor diprophylline and carbamazepine or the polymers RS/RL and EC/HPC were expected to exhibit pH-dependent behaviour, samples were henceforward tested in deionized water (Figure 42). Naturally, the peak separation and the order of elution were similar to the samples in buffer but lacking the disturbance of buffer salt peaks. The runtime was thus 11 min.

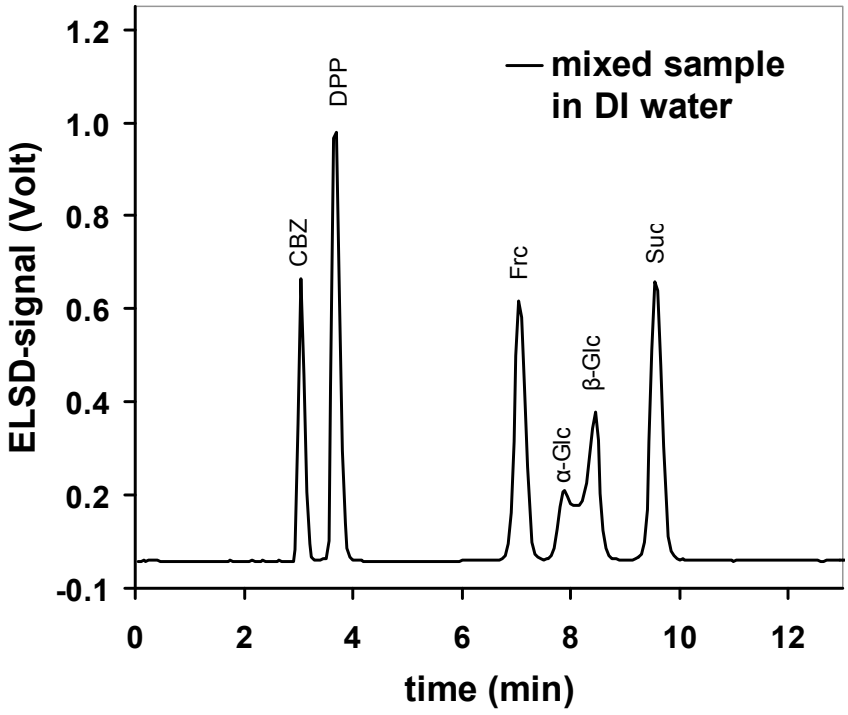


Figure 42. Isocratic elution of a mixed sample dissolved in deionized water with ACN / 25 mM NH_4Ac (pH 6.8) in a ratio of 73:27 V/V (mixed samples of test runs contained carbamazepine, diprophylline, sucrose, fructose and glucose)

A sucrose standard in deionized water (10 -1000 µg/mL) was tested, injecting 60 µL of all nine samples consecutively, then repeating the sequence (n=5 each). The mean retention time t_R of the sucrose peak was 9.41 ± 0.09 min (0.9% RSD). The RSD values of the measured peak areas ranged from 0.8% to 6.0% (Table 4).

The limits of detection and quantification, LOD (S/N=3) and LOQ (S/N=10), for sucrose were 0.6 µg and 1.5 µg respectively, which is in good agreement with other reports (Bhandari, Kumar et al. 2008).

As expected, a double-logarithmic correlation between sucrose concentration and ELSD peak area was found (R^2=0.9978) for concentrations between 25 and 1000 µg/mL (Figure 43) (Liu, Zhou et al. 2007; Rashan and Chen 2007). However, including the LOD concentration (10 µg/mL) in the standard as well, still yielded a sufficiently linear correlation (R^2=0.9948). Hence the linearity range for sucrose was from 10-1000 µg/mL.

sucrose conc. (µg/mL)	retention time (min)		peak area (µV·sec)	
	mean	RSD	mean	RSD
1000	9.50	0.6%	65283458	0.8%
750	9.39	1.5%	46952064	3.9%
500	9.41	1.0%	24429244	6.0%
250	9.43	0.7%	9205688	5.1%
100	9.44	1.1%	2582625	4.2%
75	9.39	0.8%	1887773	3.6%
50	9.43	0.6%	1160929	4.0%
25	9.40	1.2%	524154	4.8%
10	9.36	0.4%	213986	1.7%

Table 4. Retention times and ELSD peak areas for the sucrose standard in deionized water (n=5) (all 9 samples injected consecutively, then whole sequence repeated)

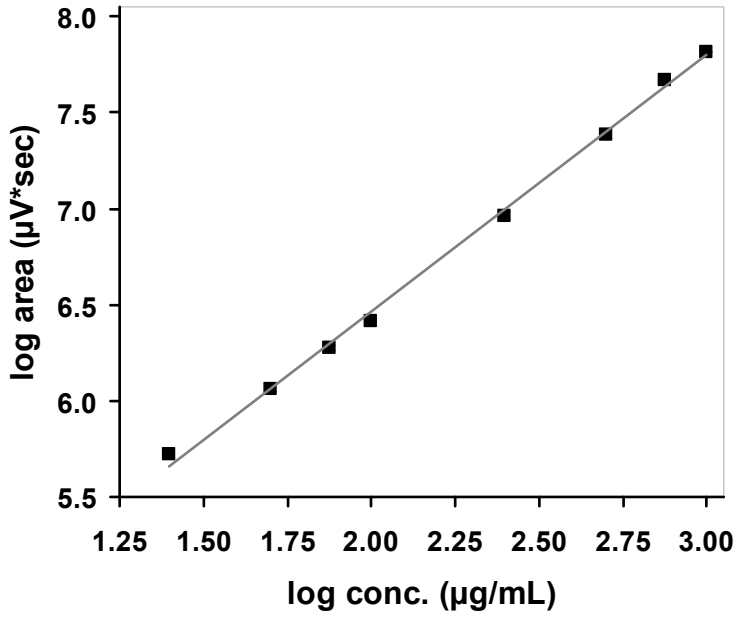


Figure 43. Log-log plot of the correlation of ELSD peak area (µV·sec) to sucrose concentration (µg/mL)

Due to the comparably low intraday-precision of the standard measurements (RSD values up to 6%, Table 4), sucrose content in release samples was quantified using external standards. For this purpose, sucrose solutions in deionized water (20, 200 and 600 µg/mL) were injected alternately after every fourth release-sample injection. In addition, a system suitability test (SST) was performed at the beginning of each sequence by injecting a 600 µg/mL sucrose solution three times in direct succession. The intra- and interday precision (expressed as the RSD value of n=4; n=3 for the SST) of these external standards on seven consecutive days range from 0.2% up to even 11.2% (Table 5).

sucrose conc. (µg/mL)	Intraday-precision [%]							Intrerday-precision [%]
	d1	d2	d3	d4	d5	d6	d7	
600	0.8	0.3	0.6	0.9	0.3	4.0	0.2	11.2
20	5.7	1.0	8.6	4.0	4.4	3.6	2.0	8.0
200	5.8	0.7	12.2	3.1	3.3	6.0	1.1	7.4
600	3.5	0.5	10.7	2.7	2.2	5.7	1.7	7.4

Table 5. Intra- and interday precision (RSD) of the peak areas measured for external sucrose standards (grey values obtained from system suitability test: 3 successive injections)

Comparing e.g. the run of day 2 with the next day, rather pronounced differences in precision were noticed. Since no changes were made on the equipment parameters or the external standard, this was attributed to fluctuations in the flow rate of the inert gas (pressurized, filtered air).

Naturally, not only sucrose but also the drugs could be quantified by their ELSD peaks. However, in drug release samples the amount of drug was only ~1/10 of the sucrose amount. In consequence, the ELSD peaks for drug were rather small and did not allow quantification with the same precision as by UV-absorption (Figure 44). While the release curves obtained from either an external UV or the diode array UV detector of the HPLC system were superimposing, a lower curve and larger deviations resulted from the ELS-detector.

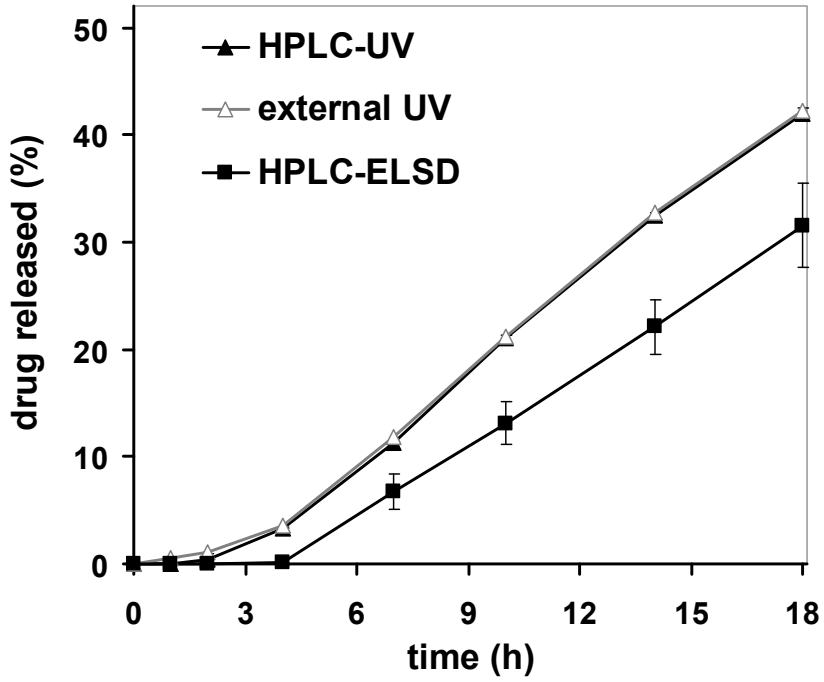


Figure 44. Comparison of different methods for diprophylline quantification during HPLC-ELSD runs (HPLC-UV, HPLC-ELSD or separate with external UV; batch 10-DPP-NP-RS, c.l. 3 mg/cm^2)

3.1.11 Summary – Effect of starter core type

Drug release from RS/RL-coated pellets was characterized by sigmoidal profiles. The lag time was similar for both starter core types but the release rate was higher for MCC pellets irrespective of the drug solubility, the RS/RL ratio or the coating thickness.

The sucrose contained in NP pellets induced several changes affecting the drug release; such as lowering RS/RL-hydration, reducing diprophylline solubility as well as diluting the HPMC concentration in pellets by pronounced, osmotically driven water uptake. The diameter swelling which resulted from this water uptake was more rapid for NP pellets compared to MCC pellets, especially during the early stages of release. This caused the in situ formation of a single small crack per pellet which helped to relax hydrostatic pressure and prevent further damages. The area of this single crack was large enough to permit convective release of sucrose solution via osmotic pumping, as visualised with an insoluble pigment. However, the crack-area was negligible compared to the surface area of the pellet and the shrinkage of NP pellets after complete sucrose release may allow pore closure. Thus, poorly soluble carbamazepine was released after the sugar and predominantly by diffusion whereas the more soluble drugs theophylline and diprophylline were released in parallel with the sugar by slow convection.

MCC pellets, on the other hand, exhibited less water uptake and a more gradual swelling which reached the same maximum as NP pellets. However, instead of one single crack, numerous smaller micro-cracks were formed on MCC pellets, due to the better coating hydration in absence of sucrose. Their size was too small for convective release; however, their multitude increased the cumulative area of cracks on the MCC pellets surface compared to NP pellets. Hence drug release from MCC pellets accelerated. The lower water uptake also led to a more concentrated HPMC gel within the drug-binder-layer. This increased the solubility of carbamazepine and its concentration inside pellets, thereby enhancing carbamazepine release from MCC pellets further.

The starter core effect was depending strongly on the mechanical properties and the hydration behaviour of the applied coating. For less flexible and /or less hydrated coating formulations like EC/HPC or CA/PEG, different effects of the starter core type were observed.

3.2 Effect of drug layer properties

In the first part of this work, the impact of the two most important starter cores (sucrose nonpareils and MCC starter cores) on drug release from reservoir pellets was evaluated (3.1). The second part is focused on the influence of drug layer properties such as drug solubility, binder content and drug loading on drug release. Since all pellets were prepared with starter cores of the same size (710-850 µm), different binder contents and drug loading levels inevitably caused changes in pellet size and density. Hence, only a surface area-normalized coating approach (mg/cm^2) ensured comparable coating thicknesses (3.1.3; (Heinicke, Matthews et al. 2005) . Data of the second part were usually obtained with the 3mg/cm^2 coating level which equalled coating levels of 14.0 - 16.8% for drug cores with 50% to 2% drug loading, respectively.

3.2.1 Influence of drug solubility

The drug solubility exhibited the strongest effect on drug release from coated reservoir pellets. In respective studies, the solubility of drugs was usually determined in pure aqueous media (Ragnarsson, Sandberg et al. 1992; Nesbitt, Mahjour et al. 1994; Ueda, Yamaguchi et al. 1994; Sadeghi, Ford et al. 2003; Sriamornsak and Kennedy 2007; Muschert, Siepmann et al. 2009 c). However, drugs could have different solubilities inside pellets containing sucrose and / or HPMC (Paruta 1964; Paruta and Sheth 1966; Etman and Naggar 1990; Raghavan, Trividic et al. 2000; Rane, Mashru et al. 2007). This was also observed in the present work using deionized water as the solvent (Table 3).

Similar results were obtained for other typical aqueous media, like 0.1N HCl and pH 6.8 phosphate buffer solution (Table 6). In all media, the solubility of theophylline was hardly affected, whereas the solubility of diprophylline decreased at higher sucrose contents. Carbamazepine solubility on the other hand increased by sucrose addition.

sucrose content	carbamazepine			theophylline			diprophylline		
	H_2O	0.1N HCl	pH 6.8	H_2O	0.1N HCl	pH 6.8	H_2O	0.1N HCl	pH 6.8
0%	0.244	0.276	0.244	11.1	15.7	13.1	210.2	215.4	173.8
10%	0.269	0.289	0.266	10.3	13.2	11.6	204.0	197.8	162.5
30%	0.341	0.379	0.342	10.6	13.5	11.6	147.0	151.2	109.3
50%	0.452	0.796	0.454	10.3	13.5	12.2	91.0	91.1	66.8

Table 6. Effect of release medium and sucrose on drug solubility in mg/mL (RSD < 3%)

In accordance with the reduced polarity of sugar solutions (proven by lower dielectric constants), there is a general trend of decreasing solubilities for highly soluble compounds and increasing solubilities for poorly soluble substances (Paruta and Sheth 1966) because the solvent properties become more favourable for relatively non-polar drugs and vice versa (Paruta 1964; Paruta and Sheth 1966; Shihab, Ezzedeen et al. 1988; Etman and Naggar 1990).

For most coated dosage forms, an increase in drug solubility was reflected by faster release and shorter lag times (Ragnarsson, Sandberg et al. 1992; Kim 1999; Neau, Howard et al. 1999; Sriamornsak and Kennedy 2007). This was usually attributed to steeper diffusion gradients and increased osmotic pressure which resulted in higher tensile stress on the coating and finally higher permeability, e.g. by film thinning and potential formation of micro-cracks in the coating (Ragnarsson, Sandberg et al. 1992; Schultz and Kleinebudde 1997; Heinicke and Schwartz 2007).

As expected, the poorly soluble carbamazepine was released much slower than the two soluble drugs theophylline and diprophylline from RS/RL-90:10-coated pellets (Figure 45), with complete release only after ~60 h. However, the twenty fold higher solubility of diprophylline compared to theophylline was not reflected in the release from NP pellets (Figure 45a). With MCC pellets, diprophylline exhibited a slightly earlier release (Figure 45b).

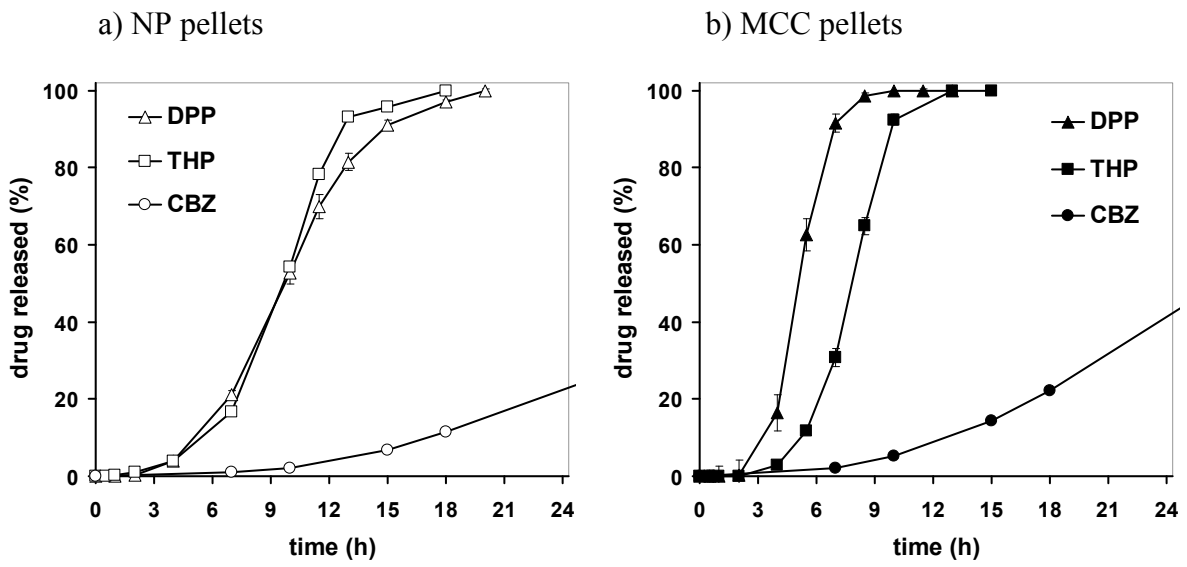


Figure 45. Effect of drug solubility on drug release in deionized water (10% drug loading, 40% binder, 3mg/cm^2 RS/RL 90:10)

Fast release of less water-soluble drugs from coated dosage forms has been reported before (Nesbitt, Mahjour et al. 1994; Sadeghi, Ford et al. 2003; Grassi, Zema et al. 2004; Muschert, Siepmann et al. 2009 c). This was attributed to the drug dissolution rate and the drug permeability of the polymer, which depends e.g. on the molecular size of the drug and its affinity to the polymer or potential interactions with it (Ragnarsson, Sandberg et al. 1992; Grassi, Zema et al. 2004; Muschert, Siepmann et al. 2009 c).

Theophylline for example exhibited a three times higher dissolution rate compared to diprophylline and up to ~20 times higher gel permeability in high viscosity HPMC matrices (Grassi, Zema et al. 2004). This finding was confirmed by the drug release from RS/RL-90:10-cast-films with a drug content of 1% (w/w, based on polymer; yielding solid solutions for all three drugs) (Figure 46). Theophylline permeated the RS/RL-90:10-film-matrix much quicker than diprophylline despite its twenty fold lower solubility in pure water. This was ascribed to the lower affinity of theophylline to RS/RL 90:10. In cast films containing 1 - 6% drug (w/w, based on polymer), theophylline already showed drug crystals in the dry film at only ≥ 2%, while diprophylline films were free of crystals even at 6%.

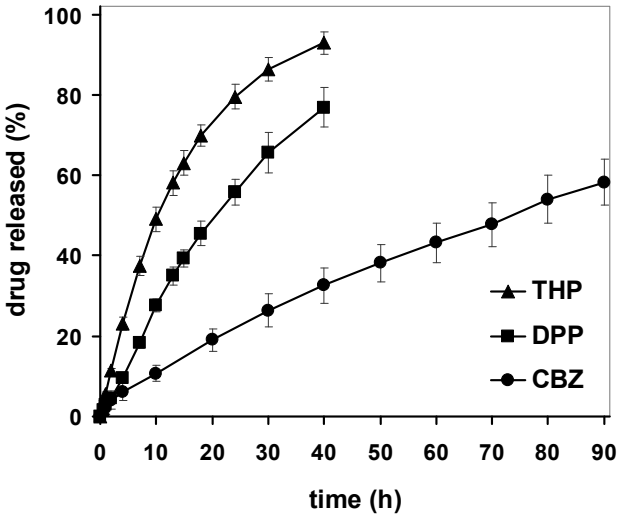


Figure 46. Drug release from RS/RL-90:10-cast films containing 1% dissolved drug

In addition, theophylline and diprophylline were released in parallel with sucrose from NP pellets (Figure 28). Thus, the solubility difference between the two drugs was clearly reduced during their release because sucrose decreased only the solubility of diprophylline but not theophylline (Table 6).

Earlier in this work, convective release of sucrose solution by osmotic pumping through a small, single micro-crack was observed for NP pellets containing carbamazepine and pigment (see 3.1.7). The similar release profiles of theophylline and diprophylline from NP pellets also suggested the same convective mechanism in their release. This theory was also supported by the sucrose release from theophylline and diprophylline pellets (Figure 28, Figure 47). The sugar was released similar to the drugs despite the even higher solubility of > 2000 mg/mL, because drug / sucrose solubility has only minor importance in dosage forms with convective release.

Interestingly, drug solubility did not only affect drug release but also the sucrose release. At lower drug solubilities the sugar was released slightly faster (Figure 47). This indicated a competition between the drugs and sucrose for the imbibed water to dissolve in (Heng, Chan et al. 1999; Bussemer, Peppas et al. 2003). With increasing drug solubility this competition was more pronounced because both substances aim to equilibrate their respective concentration gradients.

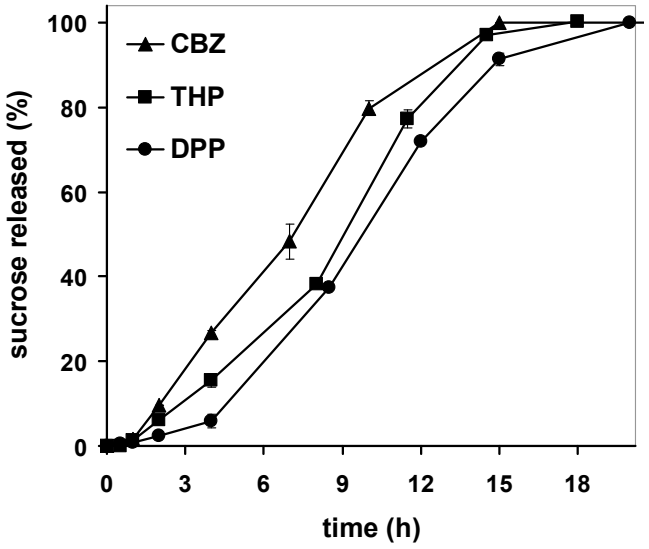


Figure 47. Influence of drug solubility on sucrose release as determined by weight loss (10% drug loading, 3 mg/cm^2 RS/RL 90:10)

3.2.2 Influence of binder content on carbamazepine release

Another drug layer parameter evaluated was the binder content which so far had rarely been studied (Iyer, Augsburger et al. 1993; Sinchaipanid, Chitropas et al. 2004). HPMC contents of 5%, 20% and 40% (based on drug weight) were investigated for the 10% drug loading of poorly soluble carbamazepine. Good layering efficiencies of 92-96% were obtained with all binder contents.

Dissolution profiles of uncoated carbamazepine cores were obtained at a reduced paddle speed of 50 rpm, in order to mimic the unstirred drug layer inside pellets. Increasing binder contents led to faster dissolution of uncoated carbamazepine cores (Figure 48). This was attributed to the improved solid dispersion of the poorly soluble drug inside the binder and the increased wettability. Drug cores based on soluble sugar nonpareils disintegrated. Hence their drug dissolution was even faster than for the insoluble MCC starter cores.

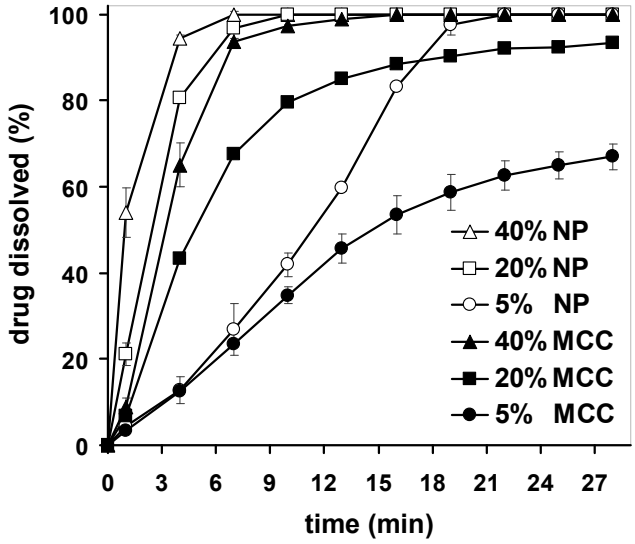


Figure 48. Effect of binder content (5, 20 or 40% w/w based on drug) on the dissolution of uncoated carbamazepine cores based on NP or MCC starter cores in deionized water at a reduced paddle speed of 50 rpm

In agreement with the core dissolution profiles, carbamazepine release from the respective RS/RL-65:35-coated MCC pellets increased slightly at higher binder contents (Figure 49). However, the release from NP pellets was unaffected.

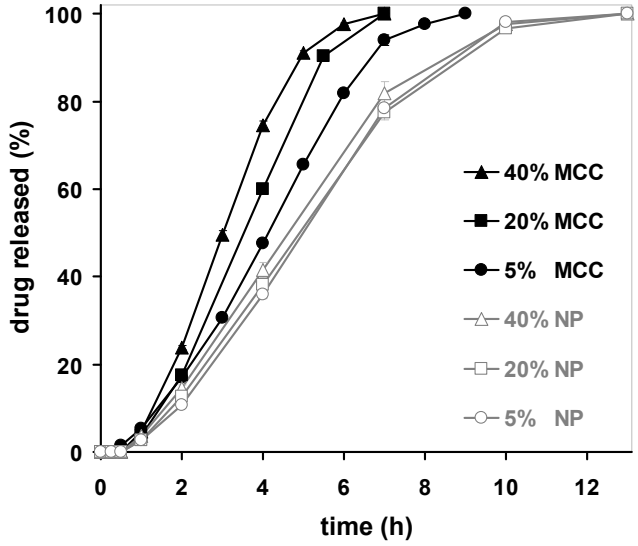


Figure 49. Effect of binder content (5, 20 or 40% w/w based on drug) on carbamazepine release from NP and MCC pellets (10% drug loading, 3 mg/cm^2 RS/RL 65:35)

This was mainly attributed to the observed differences in the water uptake behaviour of the two types of pellets. The lower water uptake of osmotically inactive MCC pellets led to higher HPMC concentrations inside pellets and thus increased the solubility of carbamazepine (Figure 29, Table 3 right). The resulting higher diffusion gradient led to the faster carbamazepine release from MCC pellets containing more binder. This was in agreement with other reports on the concentration-dependent supersaturation of poorly soluble drugs in presence of HPMC and the stabilization of carbamazepine in its more soluble anhydrous polymorphic form (Usui, Maeda et al. 1997; Katzhendler, Azoury et al. 1998; Raghavan, Trividic et al. 2000; Matteucci, Brettmann et al. 2007; Gao, Akrami et al. 2009).

In NP pellets, a similar dissolution enhancing effect of HPMC on carbamazepine was expected. However, the more pronounced water uptake of NP pellets diluted the HPMC concentration inside pellets to an extent, that the dissolution enhancement was not noticeable in the release profiles anymore.

A further potential explanation for the increasing release from MCC pellets at increasing binder contents was their swelling behaviour. HPMC is a swellable polymer and for higher viscosity grades (400 mPas) cracking has been induced in RS/RL pellet coatings (Heng, Chan et al. 1999). In the present work, MCC pellets, containing osmotically inactive carbamazepine and insoluble pigment only, showed swelling maxima similar to NP pellets (Figure 34). Hence, swelling of the HPMC in the drug layer was strongly indicated.

The initial diameter swelling of MCC pellets with and without drug-layer confirmed this HPMC swelling (Figure 50b). MCC pellets with the HPMC-containing drug layer exhibited a more pronounced swelling than coated MCC starter cores without it, despite the lower viscosity grade of HPMC used in the present study (5 mPas). This swelling could not be compensated in MCC pellets due to their solid starter core which directed the swelling force towards the coating. Therefore increasing binder contents could have resulted in higher tensile stress and micro-cracking for MCC pellets and thus increase their release. The same HPMC swelling was also observed for MCC pellets with increasing drug loading levels as follows (3.2.3). In NP pellets, however, HPMC swelling pressure could be absorbed in the fluid-filled centre, and moreover swelling of HPMC was reduced in presence of sugar (Williams, Ward et al. 2009). Accordingly, the initial diameter swelling of NP pellets was the same for pellets with and without drug-layer (Figure 50a).

a) NP pellets b) MCC pellets

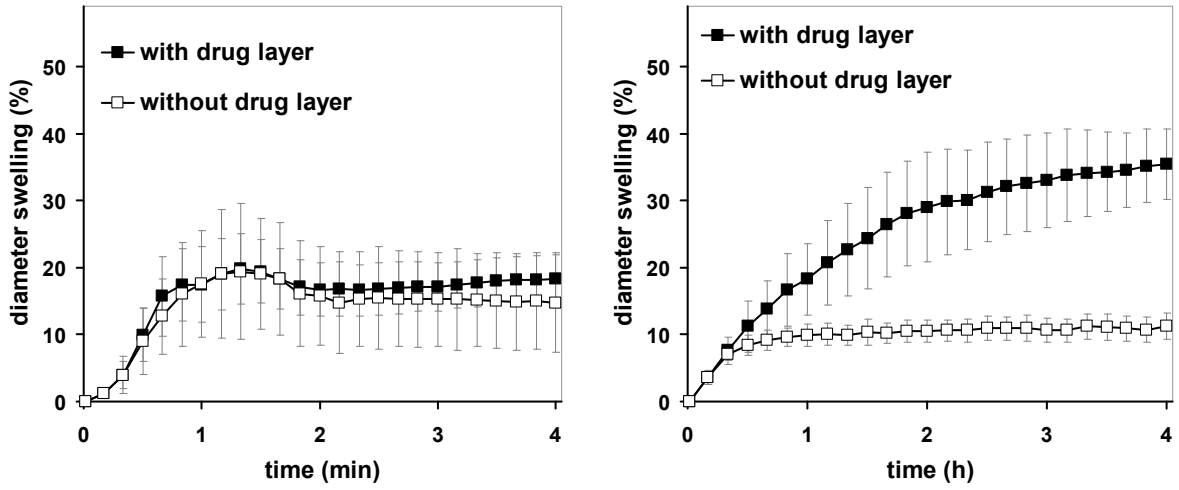


Figure 50. Initial diameter swelling of coated NP and MCC single pellets with and without drug layer (10% carbamazepine loading, 40% HPMC based on drug, 3 mg/cm^2 RS/RL 65:35)

3.2.3 Influence of drug loading

Whereas the effect of drug loading has been addressed numerous times for matrix systems (due to the associated percolation issues), it has to date received little attention for coated pellets (Bianchini and Vecchio 1989; Rekhi, Porter et al. 1995; Heinicke and Schwartz 2007).

In accordance with the influence of the binder content on carbamazepine release (Figure 49), diameter swelling was also more pronounced at higher drug loading levels: 2% < 10% < 50% drug (based on starter core weight) (Figure 51a) since increases in drug loading inevitably lead to higher amounts of binder inside the pellets.

Interestingly, the swelling of diprophylline MCC pellets with 2% and 10% loading (Figure 51b) was slightly lower than for carbamazepine (Figure 51a), despite the higher osmotic activity at increasing diprophylline loadings. Although inducing a more pronounced water uptake, osmotically active substances may be competing with the HPMC for this water and thus reduce its swelling rather than increasing it (Heng, Chan et al. 1999). And secondly, the dissolving diprophylline particles may offer less solid support to the swelling HPMC and thus partially compensate swelling pressure similar to soluble nonpareils.

a) CBZ-MCC-RS/RL-65:35 b) DPP-MCC-RS/RL-90:10

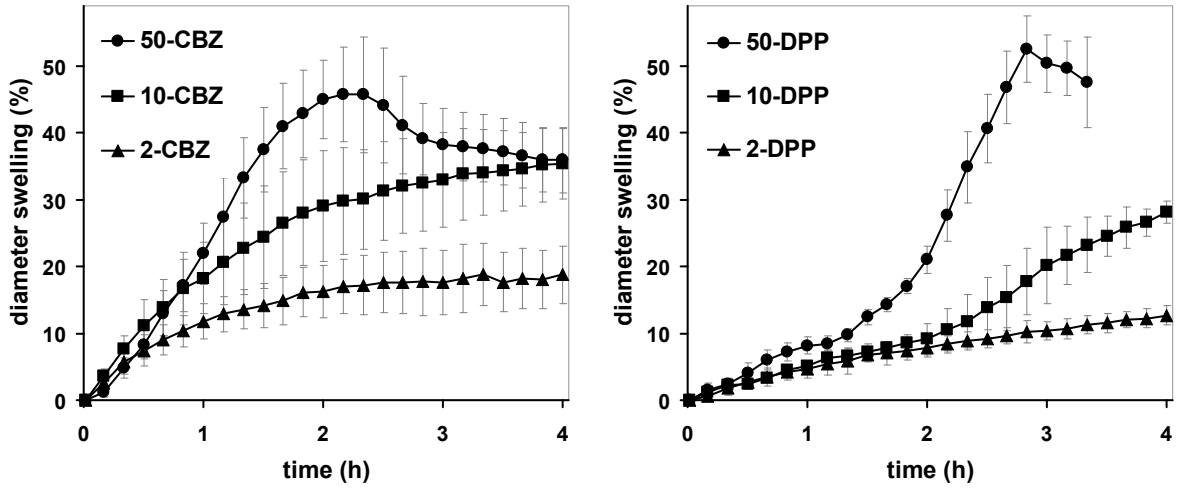


Figure 51. Effect of drug loading on initial diameter swelling of MCC single pellets (2, 10 and 50% drug loading, all 40% binder content, 3 mg/cm^2 RS/RL)

The partial shrinkage of MCC pellets which was observed only at the 50% drug loading was caused by a slightly more pronounced crack formation compared to 2% and 10%. These cracks, although barely visible at 60x magnification, were noticed by expelled 'powder clouds' of undissolved carbamazepine (Figure 52). For diprophylline no such clouds were seen owing to its high solubility but the shrinkage indicated a rapid drug release, likely in form of solutions. Apparently some HPMC is released through these cracks, too, explaining the loss in swelling pressure and the slight shrinkage for this particular high drug loading.

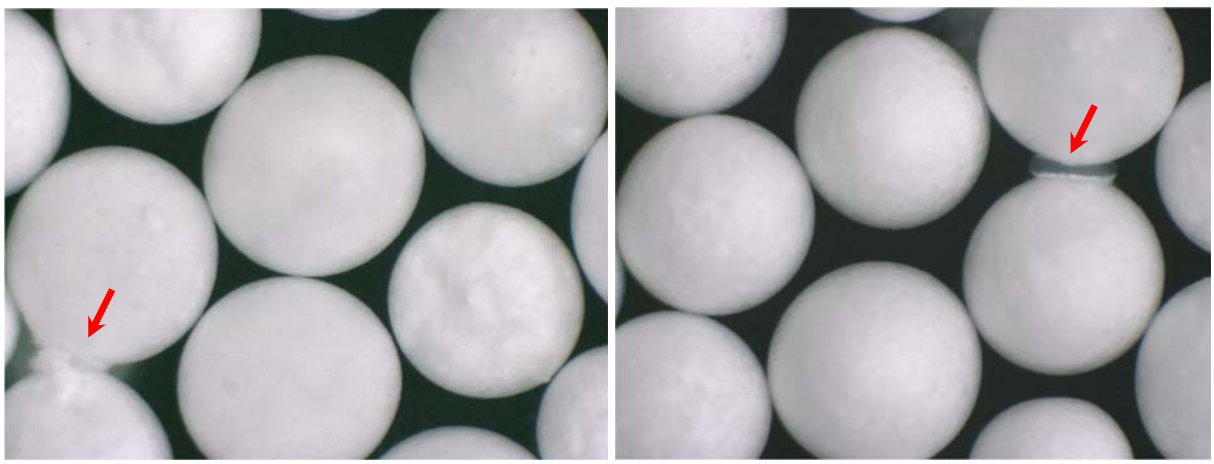


Figure 52. Exemplary pictures of micro-cracking for 50-CBZ-MCC-65:35 during release; solid carbamazepine expelled from minute cracks as white 'drug powder clouds'

In contrast to the increased swelling, the percent release of carbamazepine from MCC pellets decreased at higher drug loadings (Figure 53a and b), whereas the exact opposite was observed for diprophylline (Figure 53c). The same result was obtained with the respective NP pellets (Figure 54).

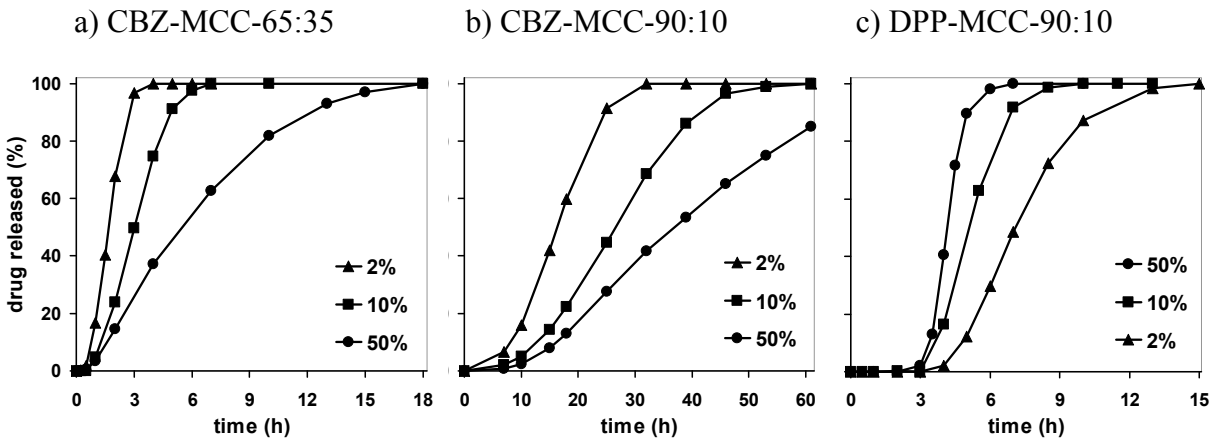


Figure 53. Effect of drug loading on release from MCC pellets coated with 3 mg/cm^2 RS/RL

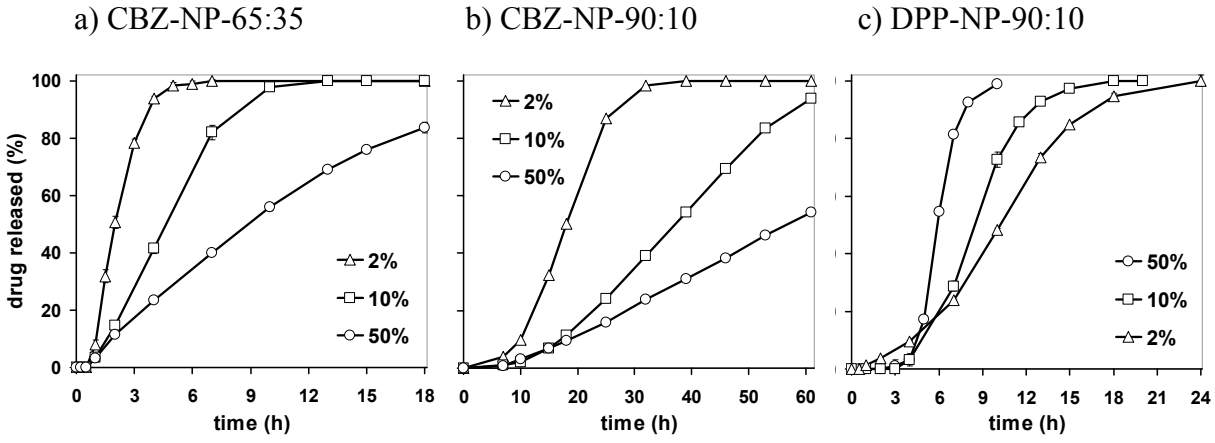


Figure 54. Effect of drug loading on release from NP pellets coated with 3 mg/cm^2 RS/RL

Other authors who observed faster release at higher drug loading levels for coated pellets attributed their finding to an increased surface area (Bianchini and Vecchio 1989). However, for reservoir pellets higher drug loading levels inevitably equate to lower surface area/dose ratios since a fixed dose is delivered by less particles. The surface area/dose ratio was estimated from the weight and size of the drug cores, and the values decreased with increasing drug loading as expected (Table 7 left). The percent release of carbamazepine was thus in good agreement with the surface area available for its release.

drug loading	core surface area / dose ratio [cm^2/g]	release rates normalized to core surface area [$\mu g/cm^2 \cdot h$]		
		DPP-90:10	CBZ-90:10	CBZ-65:35
50%	0.156 ± 0.003	2860	110	578
10%	0.60 ± 0.01	413	49	357
2%	2.76 ± 0.05	52	18	157

Table 7. Surface area/dose ratios versus surface area-normalized release rates of RS/RL-coated MCC pellets for different drug loading levels (40% binder, c.l. 3 mg/cm^2)

However, when the release rates (linear slope of the release profile) were normalized for the surface area of the drug cores, both drugs exhibited increased release rates per area at higher drug loading levels (Table 7 right). As indicated before, this was probably attributed to the more pronounced swelling which resulted in higher tensile stress acting on the coating (Figure 51). The resulting film thinning and the formation of micro-cracks were thus responsible for the increased release rates per surface area.

This effect was far more pronounced for diprophylline, due to its high solubility. Whereas carbamazepine could achieve only negligible osmotic pressure at all drug loadings (~1-2 mosmol/kg at saturation), diprophylline release rates per area were additionally increased at higher loadings due to the distinct increase in osmotic pressure (Heinicke and Schwartz 2007). This increase was so pronounced that, in contrast to carbamazepine, the decreased surface area-to-dose ratio associated with higher diprophylline loadings was overcome (Table 7); thus resulting in the observed faster percent release.

For highly soluble drugs, faster release at higher loadings was also ascribed to longer periods of saturation (Heinicke and Schwartz 2007). Profiles of theoretical diprophylline concentrations inside MCC pellets were estimated from drug weight divided by water uptake in a fixed amount of pellets over time (Figure 55). Diprophylline pellets with 50% loading kept the reservoir saturated until 30-40% drug release, whereas the 2% and 10% loading were not saturated anymore at the lag time T5.

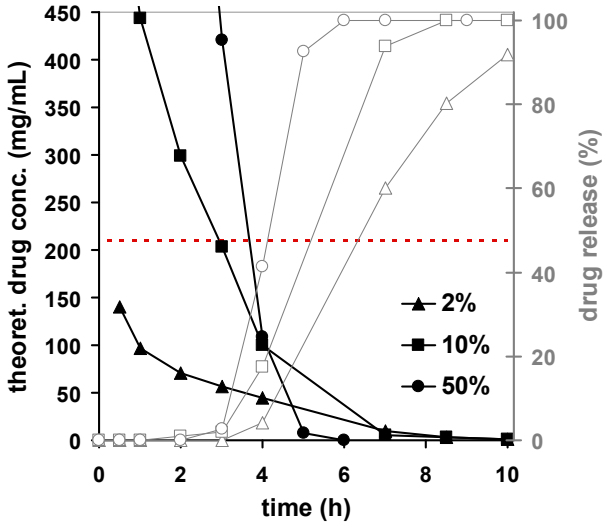


Figure 55. Theoretical diprophylline concentrations inside MCC pellets at 2%, 10% or 50% loading as estimated from water uptake and drug release data (the dotted line represents saturation concentration; 40% binder, 3 mg/cm^2 RS/RL 90:10)

Interestingly, the sucrose release was equally affected by the drug loading although the 'sucrose loading' was not changed by using the same size of nonpareil starter core for all drug loadings (Figure 56). Sucrose release also increased with increasing drug loading in the order 2% < 10% < 50% which was most likely attributed to the same swelling induced changes in coating permeability. Moreover, the application of increasing amounts of drug to the same-sized sucrose starter cores also resulted in an increased surface area/dose ratio for the sugar. The small exception of 50%-loaded carbamazepine pellets, where sucrose release set in with a slight delay, could be due to a 'barrier effect' that the thick poorly soluble drug layer exerts on sucrose release.

a) carbamazepine pellets b) diprophylline pellets

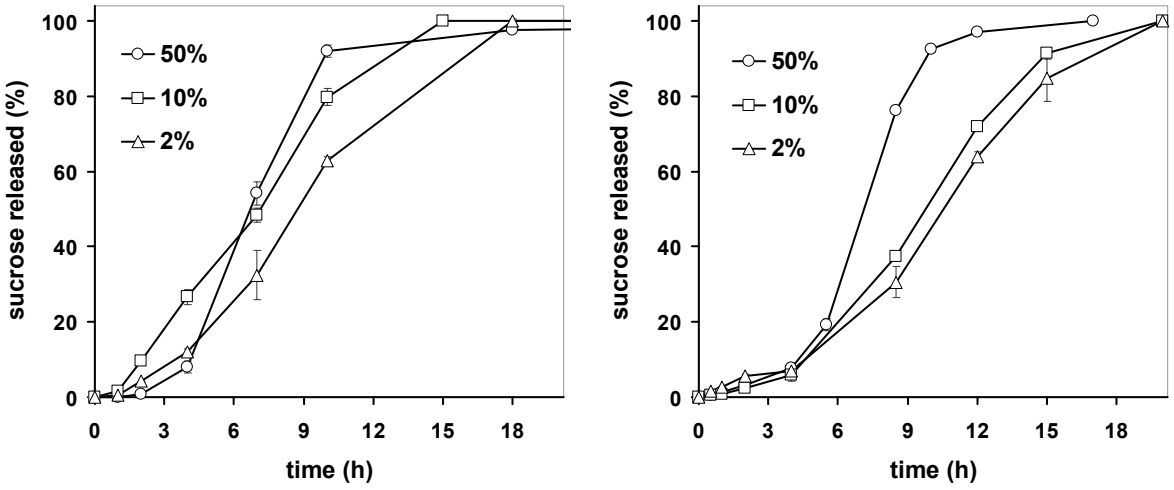


Figure 56. Sucrose release from pellets coated with 3 mg/cm^2 RS/RL 90:10 as a function of drug loading

For reservoir systems it was thus concluded, that increases in drug loading generally lead to slower release profiles due to the decreased surface area/dose ratio of the drug. However, if the drug layer provides sufficient osmotic pressure and / or swelling force, the coating permeability can be increased to such extents that the reduced surface area is overcome and faster release is achieved.

The extension of this concept would result in rupturable systems, where the osmotic pressure, the swelling force or both lead to complete destruction of the membrane. For such systems neither drug solubility nor binder content or drug loading have an influence on drug release (Ueda, Yamaguchi et al. 1994).

3.2.4 Summary – Effect of drug layer properties

The second part of this work evaluated the effect of drug layer properties such as the drug solubility, the binder content and the drug loading on the release of drugs from RS/RL-coated reservoir pellets.

Irrespective of the aqueous medium, theophylline solubility was unaffected by sucrose whereas the values increased for carbamazepine and decreased for diprophylline as a function of sucrose concentration. While poorly soluble carbamazepine was released significantly slower than the more soluble drugs theophylline and diprophylline, the twenty fold solubility difference of the latter two was not reflected by their similar release profiles. This was mainly attributed to the convective release mechanism of both drugs from NP pellets and also to the reduced solubility of diprophylline in presence of sucrose as well as the greater affinity of diprophylline to the RS/RL coating, which reduced its permeability. Sucrose release decreased slightly with increasing drug solubility; likely due to a competition of drug and sugar for the imbibed water.

Increasing the binder content led to improved wettability, higher dissolution rates and increased solubility of carbamazepine. This was also reflected in a slightly faster release from MCC pellets, but showed no effect on the carbamazepine release from NP pellets. That was attributed to the stronger dilution of the HPMC concentration, the reduced swelling of HPMC in presence of sucrose as well as to the absorption of HPMC swelling pressure inside NP pellets.

Despite the low viscosity grade used in the present work, swelling studies of pellets with either increasing binder contents or increasing drug loadings strongly suggested a participation of the binder HPMC in the pellets diameter swelling. Pellets with increased drug loading levels exhibited more pronounced diameter swelling, owing to the associated higher amounts of swellable binder and the higher osmotic activity. This resulted in higher tensile stress on the coating and in consequence enhanced drug release rates per surface area. However, only for highly soluble diprophylline this increase was pronounced enough to overcome the decreased surface area/dose ratio which is inevitably linked to higher drug loading levels of reservoir pellets. Therefore diprophylline exhibited a faster percent release at higher drug loading levels, while the release of poorly soluble carbamazepine decreased. This can also be attributed to prolonged saturation at increasing diprophylline loadings.

Summary

4 Summary

Reservoir pellets consisting of a drug-layered starter core and a water-insoluble polymer coating to control the release of the active compound, have become increasingly important for oral drug delivery. Although a number of studies indicate the potential effects of the drug core on the release, the research to date focuses predominantly on the properties of the coating. However, drug release is a complex interplay of the coating and the drug core. While factors like e.g. the stress sensitivity and permeability of a film coating are mainly governed by the polymer (its inherent rigidity, the type and amount of added plasticizers or pore formers, the mode of application, etc.), release steps like coating hydration, medium uptake, drug dissolution, build-up of hydrostatic pressure and potential crack formation are also depending on the properties of the drug core. Nonetheless, there is still surprisingly few data available on that matter or comparison is hampered by insufficient consideration of the coating thickness.

Hence, the major aim of this work was to evaluate how drug release from coated pellets is affected by changes in their drug cores. In the first part, the effect of the two most common types of starter cores, soluble sucrose nonpareils (NP) versus insoluble microcrystalline cellulose (MCC) beads, on drug release and release mechanism was investigated. (The respective coated pellets are referred to as NP pellets and MCC pellets.) The second part was aimed at the influences of the drug layer which is applied onto these two starter cores. The properties investigated were drug solubility, binder content and drug loading.

The majority of tests were performed on pellets coated with blends of Eudragit RS/RL, a cationic, water-insoluble ammonio-polymethacrylate polymer. Hence, in order to avoid ionic incompatibilities, three non-ionisable drugs were chosen as model drugs representing different solubilities in deionized water at 37 °C: poorly soluble carbamazepine (0.24 mg/mL), highly soluble diprophylline (210 mg/mL) and theophylline with an intermediate solubility (11 mg/mL). The test set-up with different starter cores, drugs, binder contents and drug loading levels inevitably led to drug cores with different weights, sizes and densities. Therefore, all drug cores were characterized closely for those parameters, because only a surface area-based coating approach ensured comparable film thicknesses for all the different drug cores.

Weight loss studies as well as a new HPLC-ELSD method have been successfully applied to monitor the release of sucrose from NP pellets in the present work. The HPLC-ELSD method was more specific for sucrose (or its monomers fructose and glucose); however, it was cost-intensive and not transferable to non-volatile release media like 0.1N HCl or USP pH 6.8 phosphate buffer solutions. Weight loss studies proved to be the equally precise method of choice.

In the first part of this work, release of all three drugs from RS/RL-coated pellets was characterized by sigmoidal profiles. The short lag time was always similar for both starter core types but surprisingly the release rate was higher for the insoluble MCC pellets compared to NP pellets; irrespective of the drug solubility, the RS/RL ratio or the coating thickness. This was unexpected because other studies mainly reported a faster release for NP pellets, which was commonly explained by their osmotic activity.

In agreement with this suggestion, NP pellets did show a higher water uptake and, especially during the initial stages of release, a more pronounced diameter swelling. This higher water uptake was attributed to the dissolution and the release of sugar from NP pellets, which created osmotic pressure and a larger volume inside the pellets that was filled with the imbibed water. However, the higher water uptake and fast initial swelling did not result in faster release from RS/RL-coated NP pellets. Owing to the dehydration of RS/RL in presence of sucrose, a single small crack per pellet was formed. The resulting convective release of sucrose solution via osmotic pumping (confirmed by visible release of a water-insoluble, red iron oxide pigment) allowed the relaxation of the hydrostatic swelling pressure and hence prevented the coating from further damages. However, the area of that single crack was negligible compared to the total surface area of a pellet, and after most of the osmotically active sucrose was released, the pumping slowed down. The concurrent shrinkage of NP pellets potentially led to pore-closure and self-healing of the small crack. Therefore, poorly soluble drugs like carbamazepine were released after sucrose and predominantly by diffusion. Soluble drugs like theophylline and diprophylline, on the other hand, were released in parallel with the sugar mainly by convection. This parallel release of sucrose and soluble drugs was very slow due to the competition of all soluble substances for water, the small size of the orifice and the pronounced water uptake which may have acted as a counter-current. Diffusion of soluble drugs was restricted by the sucrose-induced dehydration of the RS/RL-coating as well as the reduced diprophylline solubility in presence of sugar.

In contrast, MCC pellets exhibited less water uptake and a slightly slower, more gradual diameter swelling. Although this swelling reached the same maximum as NP pellets, a far less pronounced pigment release indicated smaller cracks for MCC pellets. Apparently numerous smaller micro-cracks were formed on MCC pellets instead of one single crack, due to the better coating hydration in absence of sucrose. Since MCC pellets did not shrink, these micro-cracks were also prevented from closing. And their multitude increased the cumulative cracked area on MCC pellets, thereby enhancing the drug release. In contrast to the expectation, the lower water uptake of MCC pellets was even benefitial for the release of poorly soluble carbamazepine. The resulting higher concentrations of HPMC within the drug layer increased the solubility of carbamazepine and its concentration inside pellets.

In conclusion, the starter core effect of RS/RL-coated pellets was caused by a combination of several factors: i) sucrose-induced reduction of RS/RL-coating hydration and diprophylline solubility, ii) differences in the size and number of cracks formed in the coating and in consequence different release mechanisms and iii) HPMC-induced increase of carbamazepine solubility. Due to the dependence of the starter core effect on the mechanical properties of the coating, different starter core effects were obtained for NP and MCC pellets coated with less flexible polymer blends, such as EC/HPC 65:35 and CA/PEG 65:35. For these two blends, the release from NP pellets was increased, very likely due to more pronounced cracking or lower susceptibility to sucrose-induced dehydration.

The second part of this work evaluated the effect of drug layer properties such as the drug solubility, the binder content and the drug loading on the release of drugs from RS/RL-coated reservoir pellets. Diprophylline and carbamazepine solubility in deionized water, 0.1 N HCl and pH 6.8 phosphate buffer at 37 °C was affected by the presence of sucrose. In agreement with the reduced polarity of sucrose solutions with increasing sucrose contents, solubility values increased for carbamazepine and decreased for diprophylline. Theophylline with its intermediate solubility was unaffected.

While poorly soluble carbamazepine exhibited the slowest release, as expected, the significant solubility differences between theophylline, diprophylline and sucrose were not reflected in their similar release profiles. This was attributed to the convective release mechanism from NP pellets but also to the sucrose-induced decrease in diprophylline solubility and to the higher affinity of diprophylline to the RS/RL coating, which reduced its permeability. Theophylline on the other hand exhibited a very low affinity to RS/RL. Less

than 2% of the drug dissolved in the RS/RL polymer. Therefore, theophylline was released faster from RS/RL solid solutions than diprophylline, despite its twenty fold lower solubility. Interestingly, drug solubility did not only influence drug release. In combination with soluble drugs, the release of sucrose decreased slightly, likely due to a competition of drug and sugar for the imbibed water.

Increasing the binder content for carbamazepine cores led to improved wettability and increased dissolution rates. In case of MCC pellets, this was noticeable in slightly faster release rates at higher binder contents, due to the increased carbamazepine solubility at higher HPMC concentrations. In addition, swelling data suggested a higher diameter increase and hence more pronounced crack formation for MCC pellets due to the swelling of the HPMC. For NP pellets, though, no effect on the carbamazepine release was observed. This was attributed to the stronger dilution of HPMC, the reduced swelling of HPMC in presence of sucrose as well as to the potential to swell bidirectional towards the coating and the fluid-filled core and thus compensate most of the pressure.

Higher drug loading levels are intrinsically tied to decreased surface area/dose ratios. In agreement with this, the percent release of carbamazepine decreased with increasing loadings. However, owing to higher amounts of swellable binder and to higher osmotic activity, pellets with increased drug loading levels also exhibited more pronounced diameter swelling. This resulted in a higher tensile stress on the coating and in consequence increased absolute release rates per surface area. In contrast to carbamazepine, this increase was so pronounced for highly soluble diprophylline, that the reduced surface area of high loadings was overcome and faster percent release was observed. The latter was additionally attributed to the longer saturation periods of highly soluble substances at increased drug loading levels.

Zusammenfassung

5 Zusammenfassung

Die Bedeutung multipartikulärer Arzneiformen wie z.Bsp. sog. Reservoir-Pellets ist in den letzten Jahren stetig gestiegen. Sie bestehen üblicherweise aus einem wirkstoff-beladenen Kern, welcher zwecks gesteuerter Wirkstofffreisetzung mit einem Polymer-Überzug versehen ist, dem sog. Coating. Obwohl in einigen Studien bereits auf den potenziellen Einfluss der Arzneistoffkerne auf die Freisetzung hingewiesen wurde, liegt der Forschungs-Schwerpunkt weiterhin stark auf Seiten der Polymereigenschaften. Nichtsdestotrotz ist die Wirkstofffreisetzung aus Reservoir-Pellets ein komplexes Zusammenspiel von Polymerüberzug und Arzneistoffkern. Während Faktoren wie die mechanische Belastbarkeit oder die Permeabilität des Überzuges überwiegend von den Eigenschaften des Polymers bestimmt werden (seiner Festigkeit, der Art und Menge zugesetzter Weichmacher oder Porenbildner, der Überzugsweise, etc.), hängen Freisetzungsschritte wie die Hydratation des Polymerfilms, die Aufnahme des Mediums, die Auflösung des Wirkstoffes, der Aufbau von hydrostatischem Druck und die möglicherweise daraus resultierende Bildung feiner Risse auch von den Eigenschaften des Arzneistoffkerns ab. Ungeachtet dessen gibt es immer noch überraschend wenige Studien zu diesem Thema oder der Vergleich der Daten ist durch eine unzureichende Berücksichtigung von Faktoren wie z. Bsp. der Schichtdicke des Überzuges erschwert.

Daher war das Hauptziel der vorliegenden Arbeit zu beurteilen, wie (stark) die Wirkstofffreisetzung und der Freisetzungs-Mechanismus von den Eigenschaften des Arzneistoffkernes beeinflusst wird. Im ersten Teil der Arbeit wurde der Effekt der zwei gängigsten Starterkerne untersucht; lösliche Zucker-Nonpareils (NP) oder unlösliche Kerne aus mikrokristalliner Cellulose (MCC). (Die jeweiligen überzogenen Reservoir-Pellets werden im Rahmen dieser Arbeit als NP Pellets und MCC Pellets bezeichnet.) Der zweite Teil der Arbeit ist dem Einfluss der Arzneistoffschicht gewidmet, welche auf diese beiden Starterkerne aufgetragen wird. Die untersuchten Eigenschaften waren Arzneistofflöslichkeit, Bindemittel-Gehalt sowie Arzneistoffbeladung in Prozent.

Die Mehrzahl der Tests wurde an Pellets mit Eudragit RS/RL-Mischüberzügen durchgeführt; kationischen, wasser-unlöslichen Polymethacrylat-Copolymeren. Um Inkompatibilitäten mit den positiv geladenen Ammonium-Gruppen der beiden Polymere zu vermeiden, wurden drei nicht-ionisierbare Arzneistoffe ausgesucht, als Modell-Substanzen mit unterschiedlichen Löslichkeiten (in entionisiertem Wasser bei 37°C): das schwer lösliche

Carbamazepin (0.24 mg/mL), das hochlösliche Diprophyllin (210 mg/mL) und Theophyllin mit einer mittleren Löslichkeit (11 mg/mL). Die Ausrichtung der Arbeit auf Pellets mit verschiedenen Starterkernen, Arzneistoffen, Bindemittel-Gehalten und Arzneistoff-Beladungen führte unweigerlich zu Unterschieden in Größe, Gewicht und Dichte der Pellets. Daher wurden alle Arzneistoffkerne diesbezüglich charakterisiert, da nur durch einen auf der Chargen-Oberfläche basierenden Überzug, gleiche Schichtdicke der aufgetragenen Filme für alle Arzneistoffkerne gewährleistet werden konnte.

Masseverlust-Studien sowie eine neue HPLC-ELSD Methode wurden in der vorliegenden Arbeit erfolgreich genutzt, um die Freisetzung des Zuckers aus NP Pellets zu verfolgen. Die HPLC-ELSD Methode war zwar spezifischer für Sucrose (oder ihre Monomere Fruktose und Glukose); allerdings war sie auch vergleichsweise kostenintensiv und konnte nicht problemlos auf nicht-volatile Freisetzungs-Medien wie 0.1N HCl oder USP pH 6.8 Phosphat-Puffer übertragen werden. Daher waren Masseverlust-Studien die universellere aber ebenso präzise Methode der Wahl.

Im ersten Teil der Arbeit wurden für alle drei Arzneistoffe sigmoidale Freisetzungsprofile aus den RS/RL-überzogenen Pellets beobachtet. Die kurze lag-Zeit vor Beginn der Freisetzung war nahezu identisch für beide Starterkerne. Jedoch war die Freisetzungsrate für die MCC Pellets überraschenderweise höher als für die NP Pellets; unabhängig von der Arzneistoff-Löslichkeit, dem RS/RL-Mischungsverhältnis oder dem Überzugslevel. Dies entsprach nicht unbedingt der Erwartung, da in anderen Studien häufig schnellere Freisetzungen mit NP Pellets beobachtet wurden, was gewöhnlich der Löslichkeit und der daraus resultierenden osmotischen Aktivität ihrer Kerne zugeschrieben wurde.

Übereinstimmend mit dieser Annahme, wurde tatsächlich eine höhere Wasseraufnahme für NP Pellets beobachtet, und insbesondere zu Beginn ein ausgeprägterer Quellungs-Zuwachs im Durchmesser. Die höhere Wasseraufnahme wurde sowohl durch die Auflösung als auch durch die Freisetzung des Zuckers verursacht. Der osmotische Druck bedingte einen stärkeren und schnelleren Wassereinstrom, während die Freisetzung des Zuckers zu einem freien Volumen innerhalb der Pellets führte, das von dem einströmenden Medium gefüllt wurde. Trotzdem führten weder der höhere Wassereinstrom noch der höhere Durchmesser-Zuwachs zu einer schnelleren Freisetzung. Aufgrund der Dehydratation von RS/RL-Überzügen durch den gelösten Zucker, bildete sich ein einzelner feiner Riss. Die dadurch ermöglichte konvektive Abgabe von Zuckerlösung durch osmotisches Pumpen

(nachgewiesen durch den sichtbaren Ausstrom von unlöslichem, roten Eisenoxid-Pigment) führte dazu, dass sich der im Innern aufgebaute, hydrostatische Druck entspannen konnte und dadurch weitere Risse im Film vermieden wurden. Allerdings war die Fläche dieses Risses verschwindend gering im Vergleich zur Gesamt-Oberfläche eines Pellets. Zudem wurde das osmotische Pumpen mit fortschreitender Zuckerfreistzung immer geringer. Das damit einhergehende Schrumpfen der NP Pellets führte möglicherweise zum Verschluss des Risses. Daher wurden schwer lösliche Substanzen wie Carbamazepin erst nach dem Zucker und vorwiegend diffusiv freigesetzt, während lösliche Arzneistoffe wie Theophyllin und Diprophyllin parallel zum Zucker und vorrangig mittles Konvektion freigesetzt wurden. Allerdings war diese parallele Freisetzung von Zucker und löslichen Wirkstoffen erschwert durch die Konkurrenz aller löslichen Stoffe um das einströmende Wasser, die geringe Größe der Ausstrom-Öffnung sowie die ausgeprägte Wasseraufnahme, welche potentiell wie ein Gegenstrom wirken kann. Diffusion der löslichen Arzneistoffe war nur eingeschränkt möglich, aufgrund der reduzierten Hydratation des RS/RL-Überzuges sowie der geringeren Diprophyllin-Löslichkeit in Anwesenheit von Sucrose.

Im Gegensatz dazu zeigten MCC Pellets eine geringere Wasseraufnahme und einen etwas gemäßigteren Durchmesser-Zuwachs. Obwohl die Quellung zum selben Maximalwert wie bei NP Pellets führte, wurde kaum Pigment freigesetzt, was auf kleinere Risse schließen ließ. Anstelle eines einzigen Risses bildete sich anscheinend eine Vielzahl kleinerer Mikro-Risse, bedingt durch die bessere Hydratation des Überzuges. Da MCC Pellets, anders als NP Pellets, nicht wieder schrumpften, kam es auch nicht zum Verschluss dieser Mikro-Risse. Aufgrund ihrer großen Anzahl, verteilt über die gesamte Oberfläche eines Pellets, wurde die kumulative Fläche der Risse deutlich vergrößert und die Freisetzung somit beschleunigt. Zusätzlich stellte sich heraus, dass im Gegensatz zur Erwartung, der geringere Wassereinstrom sogar förderlich war für die Freisetzung von schwer löslichem Carbamazepin. Die dadurch bedingte höhere HPMC-Konzentration innerhalb der Arzneistoffschicht führte zu einer deutlich erhöhten Löslichkeit sowie einer höheren Carbamazepin-Konzentration innerhalb der Pellets.

Zusammengefasst war der beobachtete Effekt der Starterkerne das Result mehrere Faktoren: i) die Reduktion der Diprophyllin-Löslichkeit sowie der Überzugs-Hydratation in Anwesenheit von Sucrose, ii) die Unterschiede in Größe und / oder Anzahl der während der Freisetzung gebildeten Risse im Überzug (und als Konsequenz Unterschiede im Freisetzungsmechanismus) und iii) die durch HPMC bedingte höhere Carbamazepin-

Löslichkeit. Da somit der Starterkern-Effekt von den mechanischen Eigenschaften des Polymers abhing, wurden auch unterschiedliche Effekte für NP-und MCC Pellets mit anderen, weniger flexiblen Überzügen beobachtet, z.Bsp. EC/HPC oder CA/PEG. Beide Überzugssysteme wiesen eine erhöhte Freisetzung aus den NP Pellets auf; sehr wahrscheinlich aufgrund ausgeprägterer Riss-Bildung oder aufgrund ihrer geringeren Anfälligkeit für zucker-bedingte Dehydratation.

Der zweite Teil dieser Arbeit beschäftigte sich mit dem Einfluss der Arzneistoff-Löslichkeit, dem Bindemittel-Gehalt sowie der Arzneistoff-Beladung auf die Freisetzung von RS/RL-überzogenen Pellets. Die Arzneistoff-Löslichkeit in entionisiertem Wasser, 0.1 N HCl und pH 6.8 Phosphatpuffer war teilweise in Abhängigkeit von der Zucker-Konzentration verändert. In Übereinstimmung mit der sinkenden Polarität von wässrigen Sucrose-Lösungen bei steigendem Sucrose-Gehalt, war die Löslichkeit von Carbamazepin erhöht, während die Werte für Diprophyllin sanken. Theophyllin war aufgrund seiner intermediären Löslichkeit kaum beeinflusst.

Während das schwer lösliche Carbamazepin wie erwartet am langsamsten freigesetzt wurde, waren die deutlichen Löslichkeitsunterschiede zwischen Theophyllin, Diprophyllin und Sucrose kaum merklich in ihren sehr ähnlichen Freisetzungsprofilen. Dies war auf ihren konvektiven Freisetzungs-Mechanismus aus NP Pellets zurückzuführen, aber auch auf die reduzierte Diprophyllin-Löslichkeit sowie die höhere Affinität von Diprophyllin zu dem RS/RL-Überzug, wodurch sich die Permeabilität dieses Arzneistoffes verringerte. Theophyllin hingegen zeigte eine deutlich niedrigere Affinität zu RS/RL. Weniger als 2% ließen sich in dem Polymer lösen. Zudem wurde Theophyllin trotz seiner ca. 20-fach geringeren Löslichkeit schneller aus sog. festen Lösungen (d.h. Wirkstoff molekular gelöst im Polymer) freigesetzt als Diprophyllin, was auf eine höhere Permeabilität und weniger Interaktionen mit dem Polymerfilm schließen ließ.

Interessanterweise beeinflusste die Arzneistofflöslichkeit nicht nur die Freisetzung des Wirkstoffes selbst, sondern auch die des Zuckers aus NP pellets. In Kombination mit den löslichen Arzneistoffen sank die Zuckerfreisetzung geringfügig, wahrscheinlich weil alle löslichen Substanzen im Kern um das einströmende Wasser konkurrierten.

Eine Erhöhung des Bindemittel-Gehalts in Carbamazepin-Pellets führte zu besserer Benetzbarkeit und erhöhter Auflösungsgeschwindigkeit der nicht-überzogenen Kerne. Bedingt durch die ebenfalls erhöhte Löslichkeit von Carbamazepin bei höherem Bindemittel-

Gehalt, resultierte dies im Fall der MCC Pellets in einer geringfügig schnelleren Freisetzung. Zudem legten Quellungs-Studien nahe, dass der erhöhte Bindemittel-Gehalt auch zu einem erhöhtem Durchmesser-Zuwachs und somit ausgeprägterer Riss-Bildung geführt haben könnte. Für NP Pellets, dagegen, war kein Einfluss des Bindemittel-Gehalts zu verzeichnen. Dies lag an der stärkeren Verdünnung der HPMC, der deutlich reduzierten Quellbarkeit von HPMC in Anwesenheit des Zuckers sowie an der Möglichkeit, bidirektional zu quellen, d.h. sowohl zum Überzug hin als auch ins flüssigkeits-gefüllte Pellet-Innere und dadurch den meisten Quelldruck zu kompensieren.

Naturgemäß ist eine höhere Arzneistoff-Beladung im Fall von Reservoir-Pellets untrennbar verbunden mit einem niedrigeren Oberfläche-zu-Dosis Verhältnis. Dementsprechend sank die prozentuale Freisetzung von Carbamazepin bei steigender Beladung. Andrerseits führte eine höhere Beladung aber auch zu mehr quellbarem Bindemittel in den Pellets und potentiell zu höherer osmotischer Aktivität, was sich in einem stärkeren Durchmesser-Zuwachs der Pellets äußerte. Aufgrund der daraus resultierenden, stärkeren Zugbelastung auf die Filme, erhöhte sich wiederum die freigesetzte Arzneistoffmenge pro Zeit und Oberfläche. Im Gegensatz zu Carbamazepin, war dieser Anstieg für das hochlösliche Diprophyllin so ausgeprägt, dass sogar die reduzierte Oberfläche überwunden und somit eine schnellere prozentuale Freisetzung erzielt wurde. Letzteres kann ebenfalls der längeren Diprophyllin-Sättigung bei hohen Beladungen zugeschrieben werden.

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Publications / Presentations

7 Publications and presentations

Publications

Steiner, K., Körber, M., Bodmeier, R.; The effect of starter cores on drug release from Eudragit RS/RL 100 coated reservoir pellets; - Article in preparation

Steiner, K., Körber, M., Bodmeier, R.; The effect of drug layer properties on drug release from Eudragit RS/RL 100 coated reservoir pellets; - Article in preparation

Poster presentations

Steiner, K., Bodmeier, R.; Influence of drug and core material on drug release from extended release reservoir pellets; Annual meeting of the American Association of Pharmaceutical Scientists (AAPS), San Diego, USA, 2007, # 2125

Steiner, K. Dashevska, V., Dashevsky, A. and Bodmeier, R.; Monitoring sucrose release from NonPareil-based reservoir pellets using Evaporative Light Scattering Detection (ELSD); Annual meeting of the American Association of Pharmaceutical Scientists (AAPS), Atlanta, USA, 2008, # 1271

Curriculum vitae

8 Curriculum vitae

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.