

MATRIX- AND RESERVOIR-TYPE ORAL MULTIPARTICULATE DRUG DELIVERY SYSTEMS

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To my father.

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1. Introduction

1. Introduction

Major focus has been put in controlled drug delivery systems due to their therapeutic benefits. They include maximized coverage and minimized fluctuation in plasma concentrations, especially for drugs with a narrow therapeutic index, reduction in dosing frequency, improved efficacy and reduced adverse events, increased convenience and patient compliance, more uniform effect and reduction in gastro-intestinal irritation and other dose-related side effects. Furthermore, a clinically successful controlled release product with improved therapeutic effects also presents commercial benefits as product differentiation and/or line extension, maximized drug potential, market expansion and increased cost-effectiveness. (Getsios et al., 2004; Qiu et al., 2009; Qiu and Zhang 2000).

1.1 Coated Multiparticulate as Oral Drug Delivery Systems

Multiparticulates have gained much attention in the last two decades, due to their flexibility during formulation development, but also due to therapeutic benefits. In fact, multiparticulates present numerous advantages over single unit dosage forms. When taken orally, multiparticulates disperse in the gastro-intestinal tract, maximizing absorption, minimizing side effects, reduce the inter and intra-patient variability (Ghebre-Sellassie, 1997) and avoid the risk of local irritation (Bechgaard and Nielsen, 1978). Furthermore, the all-or-nothing effect can be circumvented and the gastric emptying time is less variable (Digenis, 1994; Karrout et al., 2009).

Pellets are defined as geometrical agglomerates obtained from diverse starting materials (sucrose, starch, microcrystalline cellulose, etc) and can be produced by different process conditions (Ghebre-Sellassie, 1989). Pellets loaded with different drugs can be blended and formulated in a single dosage form. This allows the administration of two or more types of drugs that may or not be chemically compatible, at the same or different sites within the gastro-intestinal tract. Furthermore, pellets with different release rates from the same drug can be combined in a single unit dosage form in order to achieve the desired drug release profile (Pearnchob, 2002). Due to low surface area to volume ratio, ideal shape for film coating, good flowability, low friability, narrow

particle size distribution, uniform and reproducible batches are obtained (Bianchini et al., 1992; Varshosaz et al., 1997). Coated pellets can be compressed into tablets (Bodmeier, 1997) or filled into hard gelatin capsules as final dosage form.

In order to achieve controlled drug release, pellets can be directly coated with a polymer: drug solution or dispersion (**matrix coated pellets**) or loaded with drug by a layering technique and further coated with a polymeric solution or dispersion (**reservoir coated pellets**) (Figure 1).

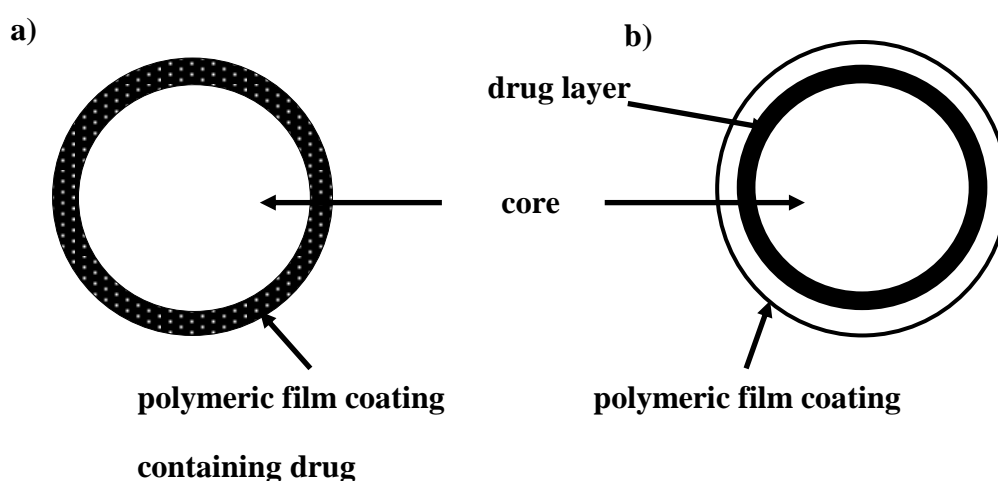


Figure 1. Schematic presentation of: a) matrix coated pellet and b) reservoir coated pellet.

1.2 Matrix Coated Systems

In matrix systems a polymer: drug solution or dispersion is sprayed onto pellets in order to achieve controlled drug release. The drug homogeneously distributed within the polymer is dissolved, dispersed or dissolved and dispersed. These systems present several advantages as easy-manufacture and low cost (1 step process), lower risk of dose dumping (if the coating accidentally ruptures) and the possibility of improvement of aqueous drug solubility. Besides, drug-polymer interactions can occur and bring benefits in terms of mechanical properties such plasticizing effect (Glaessl et al., 2009; Jenquin and McGinity, 1994). The main disadvantages include fast initial release (Huang and Brazel, 2001) and incomplete release in a defined time. The latter could be

avoided by coating sugar cores with different polymer: drug ratios, in which the drug was more concentrated in deeper layers of the matrix and so counteracting for the increased diffusion pathway (Scott and Hollenbeck, 1991). In addition, matrix coated systems were found suitable to control drug release of a highly soluble drug (Rahman and Yuen, 2005; Rahman et al., 2006).

1.2.1 Matrix solutions, matrix dispersions and drug release mechanisms

In matrix systems, the drug and polymer are dissolved or dispersed in a common solvent and upon solvent evaporation, a solid solution (drug dissolved in the polymer) or a solid dispersion (drug dispersed in the polymer) or a combination of both is obtained. If the initial drug concentration is below drug solubility in the polymer, drug is dissolved and drug release is mainly controlled by drug diffusivity in the polymer and can be simply described by

$$\frac{M_t}{M_\infty} = kt^n$$

Where M_t and M_∞ are absolute cumulative amount of drug released at time t and infinity, respectively and n is the diffusional exponent which is indicative of transport mechanism (Peppas, 1985; Ritger and Peppas, 1987). It is clear that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics (also termed as case II transport). When $n = 0.5$, Fickian diffusion is the rate-controlling step (case I transport). Values of n between 0.5 and 1 indicate that the contribution of both diffusion process as well as polymer relaxation control the release kinetics (non-Fickian, anomalous or first-order release). It should be noted that the two extreme values of $n = 0.5$ and 1 are only valid for slab geometry and $n = 0.43$ for a sphere. This model assumes that no significant changes occur in the matrix during drug release (constant porosity, no swelling and time independent permeability for the drug) (Siepmann and Siepmann, 2008).

In case of a solid dispersion, drug release rate can be approximately described by a square root of time kinetics (Higuchi, 1963).

$$\frac{M_t}{A} = \sqrt{D(2C_o - C_s)C_s t}, \text{ for homogeneous matrix}$$

$$\frac{M_t}{A} = \sqrt{D \frac{\varepsilon}{\tau} (2C_o - C_s) t}, \text{ for granular matrix}$$

where M_t is the cumulative absolute amount of drug released at time t , A is the surface area of the film exposed to the release medium, D is the drug diffusivity in the polymer (homogenous matrix) and the drug diffusivity through water filled pores (granular matrix), C_o represents initial drug concentration, C_s is the solubility of the drug in the carrier material for a homogenous matrix and aqueous drug solubility for a granular matrix, ε and τ represent the porosity and tortuosity, respectively. Higuchi law presents several assumptions as: 1) pseudo-steady state is maintained during release; 2) diffusion coefficient constant; 3) perfect sink conditions exist in external media; 4) drug concentration in the matrix is greater than drug solubility in the polymer and 5) no interaction between drug and polymer exist. One of the limitations of Higuchi law is the fact that linearity between amount of drug released per unit area per square root of time is just achieved until 60% drug release. Above 60%, drug release rate declines and the linearity is lost. This is due to increased path length for drug to diffuse with time (Tongwen and Binglin, 1998). Drug release from both solid solutions and solid dispersions are dependent on geometry of the device used.

1.3 Reservoir Coated Systems

A reservoir coated system consists of a drug layered core surrounded by a polymer. The major advantages of this system rely in the fact that very high drug loadings can be used and variable drug release profiles can be obtained, by just varying the type of polymeric membrane.

1.3.1 Aqueous coating and organic coating

Pellets can be coated with an aqueous polymeric dispersion or an organic solution in order to achieve controlled drug release. Organic coatings present many disadvantages as the dependence of viscosity on molecular weight and the concentration of polymer used. In contrast, aqueous polymer dispersions are characterized by low viscosity even at high solid contents (Wheatley and C.R., 1997), leading to a decrease in coating process time. Organic solutions present additional disadvantages like the presence of residual solvents in the coating that can create changes in film properties, environmental pollution and explosion hazards. As a result, the use of aqueous polymeric dispersions is preferred for pharmaceutical coatings. However, film formation mechanisms (aqueous versus organic) are very different (Lehmann, 1994). With organic polymer solutions, polymer macromolecules are dissolved and this can create a high viscosity solution. During solvent evaporation, an intermediate gel-like phase is formed. After complete solvent evaporation, a polymeric film is obtained (Figure 2).

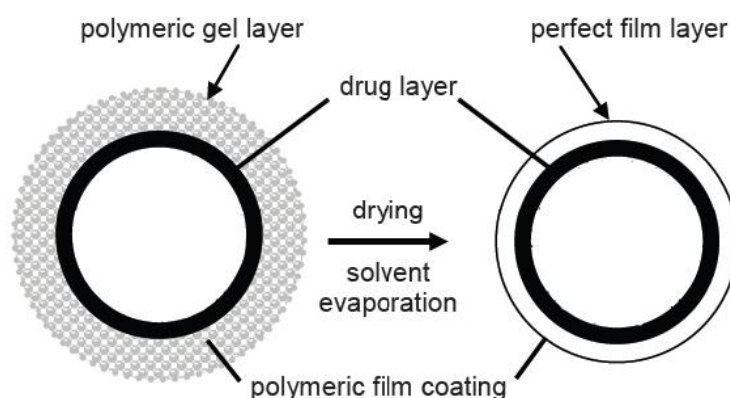


Figure 2: Schematic presentation of the film forming mechanism from organic polymer solution (Muschert, 2008).

In contrast, film formation from aqueous dispersions is a more complex process (Fukumori, 1994). During drying of aqueous dispersions, polymer particles come into contact with each other in a closed packed order. The high interfacial surface tension

between air and water leads to the formation of a layer of polymer spheres filled with water. The particle fusion or coalescence is then possible when the capillarity forces (air-water interfacial tension) are strong enough (Paeratakul, 1993; Wheatley and C.R., 1997) (Figure 3). Usually the coating process is performed at sufficient high temperatures to guarantee softness of the discrete polymer particles. The softening is related to the glass transition temperature (T_g) of the polymer (Augustine and York, 1988). A curing step (post coating thermal treatment) is carried out after coating process to assure complete film formation and avoid further gradual coalescence (Harris and I., 1997).

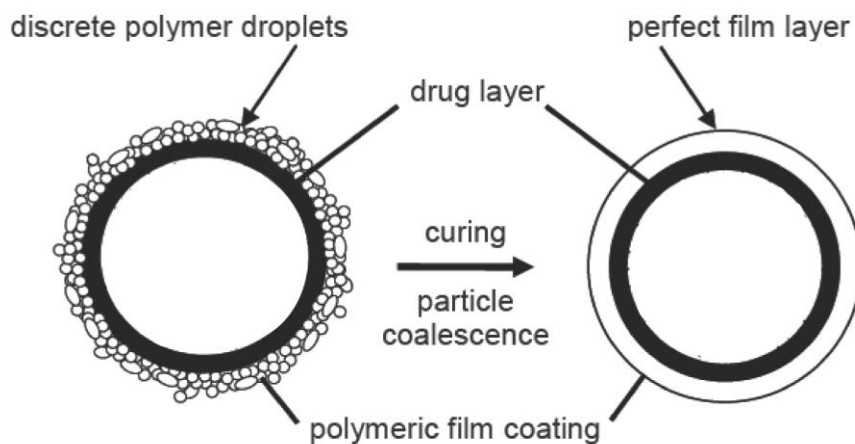


Figure 3: Schematic presentation of the film forming mechanism from aqueous polymer dispersions (Muschert, 2008).

The aqueous dispersions can have additional ingredients as surfactants that act as stabilizers during the production process. Other compounds as plasticizers and anti-taking agents are used to enhance the coating process and film properties. Plasticizers are added to promote the polymer particle coalescence, softening the particles and reducing minimum film formation temperature (MFT) (Wheatley and C.R., 1997). Film formation is related to glass transition temperature of the polymer or minimum film formation of the aqueous dispersion. The MFT is the minimum temperature above a

continuous film is formed during drying under standardized conditions (Wagner, 2002). Below this temperature the dry latex is opaque and powdery; however these conditions are different from drying during coating. Actually, water can decrease Tg of the some polymers (due to its plasticizing effect) and in this case the MFT is lower than the Tg of the polymer. Lippold and Monells Pages showed a linear relationship between the Tg and MFT for different polymer/plasticizer concentrations (Lippold and Monells Pages, 2001).

1.3.2 Formulation parameters

1.3.2.1 Polymer

1.3.2.1.1 Ethylcellulose

Ethylcellulose is a hydrophobic coating material used for controlled drug release, moisture protection and taste masking. It is a semi-synthetic polymer manufactured from cellulose and transferred with sodium hydroxide to alkali cellulose (Figure 4) (Rekhi and Jambhekar, 1995). Ethylcellulose is insoluble in gastro-intestinal tract (Siepmann et al., 2007) and assures pH independent drug release profiles due to its neutral side chains. It is widely used in oral drug delivery as film former, since it is non-toxic, non-allergenic and non-irritant. Ethylcellulose water permeability is very low, around one tenth of cellulose acetate (Bindschaedler et al., 1986).

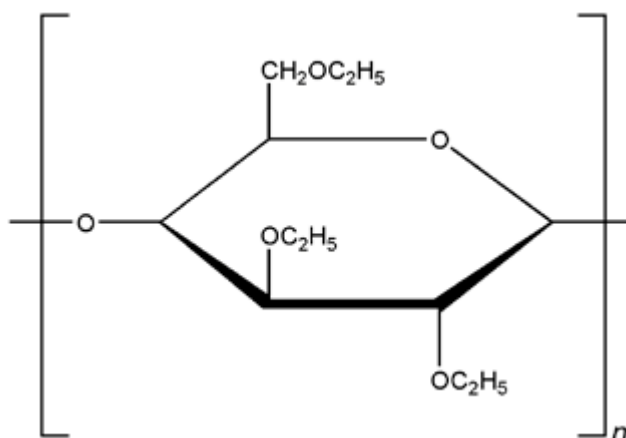


Figure 4: Chemical structure of ethylcellulose.

Ethylcellulose can be applied from organic solutions or from aqueous dispersions. It is soluble in several organic solvents and the nature of the solvent strongly affects the mechanical stability of ethylcellulose cast films (Jones and Medicott, 1995).

Aquacoat ECD and Surelease are aqueous dispersions of ethylcellulose available on the market. Aquacoat ECD has a solid content of 30% and contains 26% ethylcellulose, 2.4% cetylalcohol and 1.3% sodium dodecyl sulfate (FMC). Surelease has a solid content of 25% and it is pre-plasticized with dibutyl sebacate (3.5%) and oleic acid (1.9%) (Colorcon). The MFT of Surelease is 32°C and since it is pre-plasticized it does not require extra addition of plasticizer. In contrast, Aquacoat ECD requires a plasticizer to decrease the MFT (81°C) and improve film mechanical properties (Hyppölä et al., 1996).

1.3.2.1.2 Acrylate

Eudragit NE 30 D and Eudragit NM 30 D are ethylacrylate methylmethacrylate (2:1) copolymer (Figure 5)

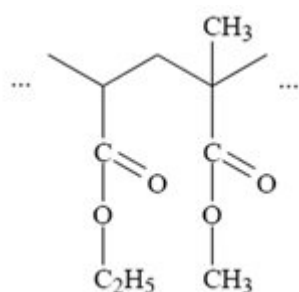


Figure 5: Chemical structure of ethylacrylate methylmethacrylate copolymer.

The main difference between both dispersions remains in the content and nature of emulsifier. Eudragit NE 30 D contains α -(4-nonylphenyl) ω -hydroxypoly-(oxy-1, 2-ethanediyl), namely nonoxynol 100 (1.5%) and Eudragit NM 30 D contains polyethylene glycol stearyl ether (0.7%) (Evonik, ; Evonik). Both aqueous dispersions have a solid content of 30% and a low MFT (5°C). Eudragit NE 30 D and Eudragit NM 30 D films are highly flexible and do not need addition of a plasticizer. These films are insoluble in gastro-intestinal tract, show very low permeability and a pH independent

swelling. For coating, anti-tacking agents are used to reduce the stickiness of the polymeric dispersion.

1.3.2.1.3 Polyvinylacetate

Kollicoat SR 30 D has a solid content of 30% and contains of polyvinylacetate (27%), polyvinylpyrrolidone (2.7%) and sodium laurylsulfate (0.3%) (BASF). If unplasticized, it has a MFT of 18°C and results in brittle films in dry state. Plasticizers are added to improve mechanical properties of the coating and the final MFT depends on the type and amount of plasticizer added (BASF). Since Kollicoat SR 30 D has no charge or ionizable groups (Figure 6), it results in pH independent film coatings (BASF).

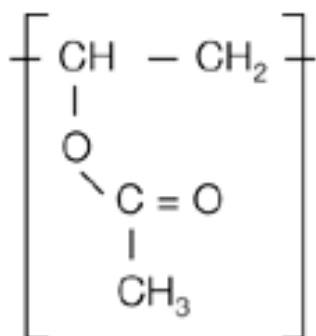


Figure 6: Chemical structure of polyvinylacetate.

In addition anti-tacking agents are also used to reduce the sticking tendency (Dashevsky et al., 2005). It can be used for controlled release formulations or taste-masking when in combination with pore-formers (Shao et al., 2002).

1.3.2.2 Additional additives

1.3.2.2.1 Plasticizers

When formulating a coating dispersion, the selection of plasticizer is of utmost importance. Plasticizers should remain in the films, exhibiting little or no tendency for

migration or volatilization and must be compatible with the polymer. Using a plasticizer that is incompatible with the aqueous dispersion can lead to poor film formation and unstable formulations during storage resulting in tremendous changes on drug release (Kucera et al., 2008; Pearnchob, 2002).

Plasticizers for film coating are excipients with high boiling point. They should be homogeneously distributed and give flexibility and mechanical resistance to the polymeric film. Plasticizers facilitate the process of polymer particle coalescence by increasing the mobility of the polymer chains and by weakening the intra and intermolecular attraction forces between the chains (Bodmeier et al., 1997). In fact, plasticizers increase the elongation and decrease the tensile strength and Young's modulus and thus have a great impact on mechanical properties of the coatings (Hutchings et al., 1994). Plasticizers also change other properties of film coatings like vapor transmission rates, moisture absorption and water penetration (Crawford and Esmerian, 1971; Johnson et al., 1991). If a hydrophilic plasticizer is added in high quantities it can lead to an increase in water diffusion in the polymer. In contrast, hydrophobic plasticizers may close the micro-voids in the film, leading to a decrease in water uptake (Turner and Abell, 1987).

The type and amount of plasticizer was found to affect drug release from aqueous coated pellets. Drug release from Aquacoat ECD and Eudragit RS/RL coated pellets decreased with increased plasticizer concentration (Saettone et al., 1995).

Drug release from Eudragit RS coated granules was faster with propylene glycol and polyethylene glycol 400 than tributyl citrate, as plasticizers. The faster release was attributed to higher hydrophilicity of plasticizers.

With Aquacoat ECD coated pellets, no change on drug release was observed when increasing the concentration of dibutyl sebacate and dibutyl adipate from 30 to 35%. It was hypothesized that saturation capacity of these plasticizers in the film coating had been exceeded (Dawn and Adel, 1994).

Plasticizers can be divided into water soluble and water insoluble. Water soluble plasticizers dissolve in the aqueous medium when they are added to polymer dispersions. Upon exposure to medium, they leach out from the film and may increase drug release rate (Bodmeier and Paeratakul, 1992). In contrast, water insoluble

plasticizers partition into the polymer. Complete uptake of insoluble plasticizer by the polymer can be achieved by an optimum stirring rate of the polymeric dispersion with the plasticizer. Increasing the time of standing for Aquacoat ECD (Lippold et al., 2008) plasticized with water insoluble plasticizer lead to a decrease in minimum film formation temperature. The extent and rate of distribution of different plasticizes between aqueous and polymer phase was studied by Bodmeier and Paeratakul. Water insoluble plasticizers showed a strong time dependent uptake rate in contrast with water soluble plasticizes (Bodmeier and Paeratakul, 1994a; 1997). A model was created to predict mass transfer mechanisms of water insoluble plasticizers emulsified in Aquacoat ECD dispersion. Dissolution of the plasticizer droplets and diffusion of plasticizer within the polymer was the main mass transfer mechanism. With this model it is possible to calculate the minimum stirring time (Siepmann et al., 1998).

In summary, the addition of plasticizers is required to reduce MFT of aqueous polymeric dispersions below the coating temperature and to enhance coalescence process. When adding a plasticizer to an aqueous dispersion it should be taken into consideration that the dissolution of the plasticizer in water, the convection through the aqueous phase and finally the diffusion into the discrete polymeric particles is a time dependent process (Paeratakul, 1993). Depending on water solubility, plasticizers are dissolved in the aqueous phase of the polymer dispersion after addition or emulsified therein. The type and the amount of plasticizer strongly affect the film formation from polymeric aqueous dispersions (Amighi and Moes, 1996b; Bodmeier et al., 1997; Yang et al., 2010).

1.3.2.2.2 Pore formers

Drug release from aqueous polymeric coatings may be very low and require the addition of hydrophilic polymers to act as pore formers. The amount and type of hydrophilic polymer used is related with the desired release profiles. A variety of pore formers can be applied and hydroxypropyl methylcellulose (HPMC) is widely used (Frohoff-Hülsmann et al., 1999a; Gunder et al., 1995; Tang et al., 2000). However addition of HPMC can lead to physical instability of coating dispersion, such Aquacoat ECD (Wong, 1994), leading to inhomogeneous film formation (Sakellariou et al., 1986). In

order to circumvent this problem, water-soluble polyvinyl alcohol–polyethylene glycol graft copolymer was used to obtain the desired drug release profile (Muschert et al., 2009b). Furthermore, drug release profiles were unchanged upon storage, if a curing step was performed before storage (Muschert et al., 2009c; Siepmann et al., 2007). In a recent study, polyvinyl pyrrolidone and polyvinyl alcohol-polyethylene glycol graft copolymer were added to Aquacoat ECD and Kollicoat SR 30 D. Stable dispersions were obtained with up to 50% hydrophilic pore formers (Dashevsky et al., 2010).

1.3.2.2.3 Anti-tacking agents and pigments

Anti-tacking agents are necessary to reduce the tackiness of aqueous coatings. Often talc and glyceryl monostearate are used to prevent sticking of the coated pellets to each other and to the wall of the coating chamber and to improve coating performance. In order to reduce tackiness, much higher amount of talc is needed in comparison with glyceryl monostearate, due to higher effectiveness of glyceryl monostearate as anti-tacking agent. The addition of talc and glyceryl monostearate can decrease film flexibility, becoming more pronounced when the content increases (Petereit et al., 1995; Wesseling et al., 1999).

Pigments are generally added to polymeric solutions and dispersions to provide easy product identification and to improve the elegance of pharmaceutical dosage form. In addition, titanium dioxide has been incorporated into film coating formulations as an opacifying agent to improve the stability of light-sensitive drugs (Bécharde et al., 1992; Rowe, 1983). The critical pigment volume concentration (CPVC) is an imperative concept in understanding the relationship between polymeric film coatings and insoluble excipients. When the pigment concentration increases, the amount of polymer necessary to surround the particles in the dry film increases. Consequently, insufficient polymer will surround all the filler particles at a particular pigment concentration, critical pigment volume concentration, CPVP. Once the CPVC is exceeded, several changes can occur in the mechanical properties, the appearance and the permeability of the film (Okhamafe and York, 1984). The CPVC is characteristic of each polymer-filler combinations (Felton and McGinity, 2002).

The effect of insoluble materials as pigments is dependent not only on the concentration, but also on particle size and particle shape of the material. For example it was shown that adhesion of the polymer to tablet surface decreased with increasing particle size of the pigment. Moreover, increased adhesion occurred with increasing the pigment (titanium dioxide) concentration, due to increased interfacial contact between the tablet surface and polymeric dispersion (Felton and McGinity, 1999). The shape of pigments was found to influence the release rate. Generally platelet shaped pigments reduce the release rate due to longer diffusion pathways. Coatings with spherical titanium dioxide or needles of iron dioxide increased release rate (Maul and Schmidt, 1995).

1.3.3 Coating equipment and process conditions

1.3.3.1 Coating methods

There are different coating technologies to coat pellets (Christensen and Bertelsen, 2008; Jones, 1994). In order to get a better flow, drying capacity and coating uniformity, conventional coating pans (traditionally used for sugar coating) have been changed. Fluidized bed equipment is available for coating small cores or pellets. The fluid bed coating process, where particles are fluidized and the coating formulation sprayed onto the pellets (which are in permanent movement due to a strong air flow), assures an efficient drying of the devices (Jones, 1994). There are different techniques to spray the aqueous coating dispersion onto pellets, such top, bottom (wurster) or tangential (rotary granulator). With the top spray method the coating suspension is sprayed by the top. The bottom spray mode consists of a container containing the batch and an upper expansion chamber. A heated air stream, introduced into the product chamber through an orifice-bottom plate (air distribution plate), is fluidizing the batch and leaves the product chamber after passing a filter system. The wurster column is placed in the middle of the product chamber close to the bottom plate and is guiding the product flow to a uniform circulating motion (Glatt). The coating formulation is sprayed vertically upwards from the bottom plate by a spray nozzle. The liquid is supplied through an orifice in the center and is atomized into droplets by an air stream. The spray rate should be adapted to the evaporation capacity of the heating fluidizing air to enable

optimal drying conditions. All processes have in common essential coating steps: (i) the formation of suitable droplets from the coating formulation, (ii) contact and adhesion of the droplets onto the particles' surface and subsequently (iii) spreading and coalescence (Muschert, 2008).

1.3.3.2 Process parameters

The coating process includes several phases occurring at the same time, like atomization of the spray liquid and droplet formation, contact and spreading over the surface of the substrate, evaporation of liquid and coalescence of particles and film formation (Christensen and Bertelsen, 1997). The critical process parameters for application of aqueous dispersions include: 1) fluidization air volume, affecting the movement of the pellets; 2) fluidization air temperature, important for the evaporation of the solvent and the softening of the latex particles; 3) solids content of the dispersion, too high solid contents may cause strong variations on batch reproducibility; 4) spray rate, important parameter since a low spray rate leads to porous films due to partial drying on surface of pellets and film formation is comparable to spray drying. Too high spray rates lead to problems as sticking and agglomeration of pellets. The atomization air pressure affects the droplet size of the coating formulation (Wagner, 2002); 5) atomization air pressure, influences the droplet size and spraying pattern. The characteristics of substrate, as density, diameter and stickiness should also be taken in consideration for the coating process (Christensen and Bertelsen, 1997).

The product temperature should be 10°C to 20°C (Raymond and Ray, 1964) above MFT of the polymer dispersion in order to achieve sufficient water evaporation and complete film formation. The product temperature can be adjusted by varying the inlet air temperature (Bodmeier et al., 1997; Raymond and Ray, 1964). Too low temperatures can lead to incomplete coalescence and too high temperatures can originate very fast water evaporation on the pellet surface, leading to spray loss. Faster drug release rates can be a result of insufficient time necessary for the capillary forces to achieve complete coalescence. In addition, the mechanical properties of the films are related with the coalescence temperature (Parikh et al., 1993). Tackiness problems can occur at high coating temperatures as a result of interaction of drug and spray dispersion ingredients (Schmid et al., 2000).

Instability of coated dosage forms can also result of inappropriate conditions during coating process. The causes for instability can be exposure to humidity, light, higher temperatures and interaction between coating and core materials.

1.3.4 Drug release mechanisms

The mechanism controlling drug release from reservoir coated pellets is often a complex process (Ozturk et al., 1990) and it depends on coating type and thickness (Munday and Fassihi, 1989), drug type (Sadeghi et al., 2003) and core type (Kállai et al., ; Lecomte et al., 2005).

One of the mechanisms is diffusion through the continuous polymer film surrounding the drug loaded core (Dressman, 1994). Firstly, water penetrates through the coating until reaches the pellet core. Afterwards, drug is dissolved and released. The drug is released due to the concentration gradient inside the pellet (c_i) versus outside the pellet. In the case of perfect sink conditions the amount of drug released (dM) within a certain time period (dt) can be calculated as follows (according to Fick's law of diffusion):

$$\frac{dM}{dt} = D_m \cdot A \cdot K \cdot \frac{c_i}{d}$$

D_m is the apparent diffusion coefficient of the drug in the polymeric film, A the surface available for diffusion, K the partition coefficient of the drug (aqueous phase – polymeric phase), and d denotes the thickness of the film coating (Siepmann and Siepmann, 2008).

Drug release can occur through water filled pores. These pores can be due to leaching of water soluble compounds into the release medium or due to cracks formed by high hydrostatic pressure generated inside these systems upon water uptake. Drug release can be described as follows:

$$\frac{dM}{dt} = D_p \cdot A \cdot \frac{\varepsilon}{\tau} \cdot \frac{c_i}{d}$$

Where D_p is the diffusion coefficient of the drug in the aqueous phase present in the channels and pores, ε the volume fraction of the pores, τ the tortuosity of the channels (Ozturk et al., 1990)

Another possible mechanism controlling drug release from coated pellets is due to osmotic effects. For this mechanism to occur an osmotic active core should be surrounded by semi-permeable membrane and a difference in osmotic pressure between the inner and outer side of the membrane. Osmotically driven release depends on the porosity of the polymeric membrane and the osmotic pressure of the sugar core and the drug. Upon water uptake, drug is pushed out via pores in the coating. Drug release can be described as follows (Ozturk et al., 1990):

$$\frac{dV}{dt} = \frac{A\theta\Delta\pi}{l}$$

Where dV/dt denotes the water flow, A the membrane surface area, l the membrane thickness, θ the permeability of the polymeric membrane, and $\Delta\pi$ the difference in osmotic pressure (neglecting the counteracting hydrostatic pressure).

The overall drug release rate from coated pellets may be governed by one of the above mechanism or a combination of them (Frohoff-Hülsmann et al., 1999a; Ozturk et al., 1990). Parameters as core and coating swelling also contribute to the drug release rate.

Drug release mechanisms from ethylcellulose coatings are well described in literature (Ozturk et al., 1990; Rao and Murthy, 2002; Rekhi et al., 1995; Sadeghi et al., 2000; Shah et al., 1994; Tang et al., 2000; Zhang et al., 1991). Ozturk et al. investigated the mechanism of drug release from Aquacoat ECD coatings, by studying the effect of coating thickness, plasticizer and osmotic pressure. Drug release rate was mainly contributed by osmotic pressure developed by the core with less contribution from diffusion through pores or diffusion through the polymer.

The type of drug can strongly affect the resulting drug release rates. Ibuprofen diffused through the coating (due to high solubility in the polymer) while chlorpheniramine maleate diffused through microchannels in Aquacoat coated pellets, resulting from osmotic pressure developed by the core (Bodmeier and Paeratakul, 1993).

Drug release rate can be affected by changes in surface area (during dissolution study) of the pellets (Tang et al., 2000).

The coating level also changes the mechanism of drug release. At low coating levels, drug release occurred through pores in the coating, while at high coating levels drug release rate was controlled by diffusion through the coating (Sadeghi et al., 2000; Shah et al., 1994). Consequently the mechanism controlling drug release at higher coating levels was not just dependent on drug solubility but also on the polymer/dissolution medium partitioning coefficient of the drug.

Drug release mechanism from ethylcellulose coatings with pore formers was investigated by several researchers. At lower pore former content (HPMC) contents, drug release occurred through osmotic pumping, but above a certain value diffusion also contributed to overall drug release (Lindstedt et al., 1989). Addition of small amounts of polyvinyl alcohol-polyethylene glycol graft copolymer to ethylcellulose coatings was found to control drug release from coated pellets irrespective of the drug solubility and type of core formulation. The mechanism controlling drug release was shown to be diffusion through intact polymeric membranes (Muschert et al., 2009b).

The glass transition temperature of the polymer also affects the drug release mechanism. With water soluble plasticizers, the polymer was in glassy state after plasticizer migration and drug diffused through water filled pores. With water insoluble plasticizers, the polymer was in the rubbery state and a two phase release mechanism was found. In the first phase drug was released through pores created by leaching of HPMC and in the second phase pore shrinking occurred leading to a decrease of free volume in the polymer chains (Frohoff-Hülsmann et al., 1999a; Frohoff-Hülsmann et al., 1999b).

The type of coating technique (organic versus aqueous) was found to contribute to drug release mechanism in different ways. Drug release mechanism from coating with blends of a water-insoluble (ethylcellulose) and an enteric polymer (ethylcellulose:methacrylic acid ethylacrylate copolymer, Eudragit L) occurred by diffusion through the intact polymeric films and/or water-filled cracks. However, lower hydrostatic pressures were necessary to induce crack formation within aqueous coatings. Organic coatings were

mechanically strong with high degree of polymer-polymer interpenetration and thus higher hydrostatic pressure was required to induce crack formation.

The polymer particle size affects the film coating structure and properties. Blends of aqueous dispersions of a water-insoluble and an enteric polymer, ethylcellulose and hydroxypropyl methylcellulose acetate succinate (HPMCAS) and Eudragit L were used as coating materials to control theophylline release from matrix pellets. Drug releases were similar for both types of blends in 0.1 M HCl, but significant differences were observed in phosphate buffer pH 7.4. Eudragit L particles are smaller than HPMCAS particles (nano- vs. micrometer size range) and more effectively hinder the formation of a continuous and mechanically stable ethylcellulose network. Ethylcellulose structures remaining upon HPMCAS leaching are mechanically stronger and drug release is controlled by diffusion through the polymeric remnants. In contrast, ethylcellulose structures remaining after enteric polymer leaching at high pH are mechanically much weaker in the case of Eudragit L. Upon exposure to phosphate buffer, water-filled cracks are formed, through which the drug rapidly diffuses out (Siepmann et al., 2005).

1.3.5 Curing

After coating process and even with a product temperature 10°C-20°C above the MFT, complete film formation may not be achieved. Thus a short thermal treatment is required to complete polymer particle coalescence. At curing temperatures above the glass transition temperature, the mobility of the polymer chains increases and latex coalescence is accelerated. The curing step may be performed in an oven or in the fluidized bed coater immediately after the coating process. Too low curing temperatures can lead to incomplete film formation, whereas too high temperatures can lead to excessive tackiness and agglomeration of the solid dosage forms. The curing step can be performed at several temperatures or different times and in the presence of controlled humidity. All these factors can potentially affect drug release rate.

Drug release from Kollicoat SR 30 D coated pellets was unchanged by increasing the curing time (Dashevsky et al., 2005). This was attributed to complete film formation during coating process due to low MFT of plasticized Kollicoat SR 30 D coatings.

With other low MFT aqueous dispersion, Eudragit NE 30 D, increasing the curing time decreased ibuprofen release from coated pellets. The slower release rates with increasing curing time were attributed to a greater polymer particles coalescence (Bhattacharjya and Wurster, 2008). In another study, the curing temperature and time were investigated. Drug release decreased with increasing temperature. At 30°C, the decrease in drug release was small and not affected by the curing time. When temperature and time of curing were increased, the resulting changes in drug release rate increased. It was suggested that at higher temperatures, more polymer molecules can overcome the energy barrier and reach a stable state, reflected by the slower release. On the contrary, at low curing temperatures, few molecules can achieve a stable state, meaning that changes in drug release are expected to occur slowly over time until the stable state is reached (Lin et al., 2003).

With Aquacoat ECD coated pellets, a curing period of 8h was found to complete film formation (Wesseling and Bodmeier, 1999).

Controlled humidity can be used during the curing step. The presence of humidity was more effective to complete film formation than without. Water facilitates polymer particle coalescence and it acts as plasticizer for many polymers (Liu and Williams, 2002b; Williams III and Liu, 2000).

High content of plasticizer can minimize the curing effect (Amighi and Moes, 1996a), however there is a limit of plasticizer concentration to avoid problems as stickiness during coating process or forming agglomerates of pellets during curing.

With Aquacoat ECD, at low and intermediate plasticizer content a curing step was required whereas at high plasticizer content the curing effect was negligible (Bodmeier and Paeratakul, 1994b).

The curing effect on drug release can change depending on the type plasticizer and coating level. For example, drug release decreased with increasing harshness (time, temperature and relative humidity) of curing conditions, when using triethyl citrate as plasticizer. In case of dibutyl sebacate and Myvacet this relationship was only seen at low coating levels (Yang et al., 2010).

The curing step can lead to drug migration through the coating, usually resulting in an increase in drug release. A seal coat was used in order to protect drug migration and stabilize drug release profiles (Hamed and Sakr, 2003).

The effect of curing step on mechanical properties of films was evaluated. It was hypothesized that heating the plasticized ethylcellulose film coating above glass transition temperature resulted in film relaxation and stabilized film properties (Dressman et al., 1995). Moreover, increased adhesiveness of coating to the core tablet was attributed to a higher inter-diffusion of polymer chains upon curing (Felton and Baca, 2001).

1.3.6 Storage Stability

Although the curing step is performed in order to complete film formation, drug release rate was reported to decrease especially under elevated humidity (Siepmann et al., 2006; Wu and McGinity, 2000). This was mainly attributed to further gradual polymer coalescence, leading to denser films and decreased permeabilities for water and drug.

Continuous film formation was also observed with Kollicoat SR 30 D coated pellets stored at 40°C/75% RH (closed bottle), resulting in a decreased drug release (Shao et al., 2002). In contrast, extended lag time but no effect on release rate was observed with Kollicoat SR 30 D coated pellets upon 1 month storage at 40°C/75% RH (Ensslin et al., 2009).

Changes in drug release profiles were also observed with high glass transition temperature polymers. Physical instabilities in Aquacoat ECD coatings caused cracking and chipping of the film. Researchers attributed these problems to an increase in the water content of the films rather than a decrease (Chowhan et al., 1982). Unstable drug release profiles from Aquacoat ECD coated dosage forms are attributed to incomplete film formation and further gradual coalescence during storage. Uncured coated Aquacoat ECD coated pellets exhibited an increase in drug dissolution rate. Faster drug release may be caused by brittle films or the formation of microruptures in the film coat during storage (Wesseling and Bodmeier, 2001). In another study, drug release from

Aquacoat ECD coated pellets decreased after 4 months storage, even at room conditions (Gilligan and Li Wan Po, 1991).

Endogenous excipients usually are added to aqueous coating systems in order to stabilize the dispersion during storage. In other cases, excipients are used in the emulsion polymerization process of aqueous lattices, as is the case of nonoxynol 100 in Eudragit NE 30 D dispersions. Stability problems were reported with this emulsifier, as an increase in drug dissolution rate during storage. Crystallization of the surfactant can occur upon storage at room temperature due to its high melting point (~ 60°C) and this can increase drug release rate (Lin et al., 2001).

Thermal humidity curing was found to help to enhance coalesce of polymeric films, however presence of high levels of humidity during storage can destabilize films, originating changes in drug release rate over time (Liu and Williams, 2002a).

On the contrary, storage stability at 40°C/75% RH from Aquacoat ECD: HPMC coated pellets was improved only by using thermal/humidity curing or very high temperature (80°C) during 24h (Körber et al., 2009).

Some recent studies have shown an improvement of storage stability from aqueous polymeric systems, by adding hydrophilic polymers. Stable drug release profiles were obtained and attributed to the presence of more water trapped in these systems during film formation, facilitating particle coalescence (Kranz and Gutsche, 2009; Muschert et al., 2009a; Siepmann et al., 2008).

In another study, 200% talc was added to Eudragit RS/RL 30 D 95:5 plasticized with triethyl citrate. The acrylic polymer functioned as an effective binder for talc, resulting in a continuous film coat. Although film formation was incomplete, the coating still provided a sustained release of the drug. The high talc content in the films also resulted in no agglomeration of the coated pellets during storage at 40°C/75% RH in open containers. Moreover, addition of 10% or 20% of triethyl citrate to the coating formulation resulted in dosage forms that were physically stable and showed no significant change in drug release rate during storage for three months (Maejima and McGinity, 2001).

The degree of coalescence of latex particles at the completion of the coating process increases as the amount of plasticizer in the formulation increases, due to the plasticizer's ability to weaken polymeric intermolecular attractions. Consequently, it allows the polymer molecules to move more readily, increasing the flexibility of the polymer. While liquid plasticizers can be lost through evaporation during storage, solid-state plasticizers have the distinct advantage of remaining in the film throughout the shelf life of the dosage form. Studies have been conducted in which nonpareil beads were coated with Eudragit RS 30 D containing ibuprofen as the active ingredient and a solid-state plasticizer. The coated beads were cured at 40°C for a period of 24 hours and then stored at 23°C and 0% RH. No significant difference was found between the initial drug release rate and the drug release profiles of the stored samples. The authors reported that the presence of ibuprofen in the coating also served as an anti-adherent, preventing the agglomeration of pellets during the coating process and subsequent storage (Wu and McGinity, 2001).

1.4 Research objectives

1.4.1. Matrix Systems

- (i) the preparation of different types of matrix systems (solid solutions and solid dispersions);
- (ii) the identification and characterization of key parameters affecting drug release from matrix cast films and coated pellets.

1.4.2. Reservoir Systems

- (i) the preparation of different types of aqueous polymeric dispersions as well as organic ethylcellulose solutions coated sugar and MCC cores, using drugs with different solubilities;
- (ii) the characterization of drug release profiles;
- (iii) the identification and quantification of curing effect on drug release;

(iv) the investigation of the influence of storage conditions on drug release from coated pellets.

2. Materials and Methods

2.1 Materials

The following chemicals were obtained from commercial suppliers and used as received:

Model drugs

Paracetamol (BASF AG, Ludwigshafen, Germany), propranolol hydrochloride (Abott, Ludwigshafen, Germany), metoprolol tartrate (Moehs, Barcelone, Spain), diclofenac sodium (Farchemia, Treviglio, Italy) and ibuprofen (BASF AG, Ludwigshafen, Germany).

Polymers

Hydroxypropylmethylcellulose (HPMC) (Methocel E5, Colorcon, Dartfort, England), hydroxypropylcellulose (HPC) (Klucel EXF and JF, Hercules GmbH, Düsseldorf, Germany), povidone K90 (BASF AG, Ludwigshafen, Germany), polyethylene glycol 1500 (Lutrol E, Ludwigshafen, Germany), aqueous dispersion of polyvinyl acetate (Kollicoat SR 30 D; BASF AG, Ludwigshafen, Germany), aqueous dispersion of copolymer ethyl acrylate methyl methacrylate (Eudragit NE 30 D and Eudragit NM 30 D, Evonik Industries AG, Darmstadt, Germany), aqueous dispersion of ethylcellulose (Surelease, Colorcon, Dartfort, England) and Aquacoat ECD, FMC BioPolymer, Brussels, Belgium), ethylcellulose (Ethocel Standard premium 10, DOW Chemical Company, Midland, USA), ammonio methacrylate copolymer type A (Eudragit RS) and methacrylate copolymer type B (Eudragit RS).

Pellets

Non-pareil (Suglets, sugar spheres NF, 750-850 μm and 500-710 μm , NP Pharm S.A., c/o Gustav Parmentier, Frankfurt am Main, Germany), Celphere-MCC spheres (Microcrystalline Cellulose Spherical Seed Core, 700-850 and 500-630 μm , Asahi Kasei Chemical, Tokyo, Japan).

Solvents

Isopropranol (IPA) and ethanol (96%).

Other excipients

Talc (Luzenac GmbH, Düsseldorf, Germany), Silicon dioxide (Aerosil 200, Evonik Industries AG, Darmstadt, Germany), Triethyl citrate (TEC) (Citroflex-2, Morflex Inc., Greensboro, NC, USA).

2.2 Methods

2.2.1 Matrix Systems

2.2.1.1 Preparation of cast matrix films

Matrix films were prepared by dissolving diclofenac Na (30% w/w), ibuprofen (10-50% w/w) and metoprolol tartrate (10-50% w/w) in isopropanol: water 88:12 (w/w). After polymer addition (6% w/w, for ethylcellulose) and (10% w/w, for Eudragit RS and Eudragit RL), 7-28% (w/w) of HPC JF, PVP K90, mannitol and 6-30% (w/w) PEG 1500 were optionally added. Upon overnight stirring, matrix solutions/dispersions were cast on petri-dishes, covered with paper and dried at room temperature (2 days). The thickness of the films was measured using thickness gauge (Minitest 600, Erichsen, Hemer, Germany).

2.2.1.2 Preparation of coated matrix pellets

Matrix coated pellets were prepared by layering a matrix solution of ethylcellulose and drug (30% w/w, for diclofenac Na and ibuprofen and 20, 30 and 40% w/w, for metoprolol tartrate) in isopropanol: water 88:12 (w/w) onto drug-free sugar and MCC cores in a fluidized bed coater with a wurster insert (Uniglatt, Glatt GmbH, Germany) to a weight gain of 15% (w/w, based on the polymer). The coating conditions were batch size: 400 g, inlet temperature: 34-36°C (diclofenac Na), 38-40°C (ibuprofen) and 58-60°C (metoprolol tartrate), outlet temperature: 24-26°C (diclofenac Na), 28-30°C (ibuprofen) and 46-48°C (metoprolol tartrate), air flow: 28 m³/h, spray pressure: 2 bar, spray rate: 5-7 g/min (diclofenac Na), 4-5 g/min (ibuprofen) and 4 g/min (metoprolol tartrate) and a final drying for 15 min.

2.2.1.3 Drug release from matrix films

The edges of the films were sealed with vaseline to avoid drug diffusion through the film ends. Drug release was conducted in 900 ml (diclofenac Na and ibuprofen) and 500 ml (metoprolol tartrate) phosphate buffer pH 6.8 (75 rpm, 37°C, n=3) in a horizontal

shaker (GFL 3033). At predetermined time intervals, 3 ml samples were withdrawn and analyzed (directly or after appropriate dilution) with UV spectrophotometry (UV-2101 PC, Shimadzu Scientific Instruments, Columbia, MD, USA), diclofenac Na, $\lambda = 275$ nm; ibuprofen, $\lambda = 264$ nm; metoprolol tartrate, $\lambda = 274$ nm. The osmolality of the release media was determined based on the freeze point depression of the solutions compared to pure water.

2.2.1.4 Drug release from matrix coated pellets

The drug release from matrix coated pellets was investigated in a USP paddle apparatus (VK 700, Vankel Industries, Edison, NJ, USA), 900 ml (diclofenac Na and ibuprofen) and 500 ml (metoprolol tartrate) of phosphate buffer pH 6.8 (100 rpm, 37 °C, n = 3). The weight of pellets used was equivalent to about 2g. At predetermined time intervals, 3 ml samples were withdrawn and analyzed (directly or after appropriate dilution) with UV spectrophotometry (Shimadzu UV-2101PC UV-Vis Scanning spectrophotometer; Shimadzu Europe, Duisburg, Germany). The corresponding wavelengths were described in section 2.2.1.3. Optionally, the osmolality of the release medium was adjusted with Mannitol. The osmolality of the release media was determined based on the freeze point depression of the solutions compared to pure water.

2.2.1.5 Solubility measurements

Excess diclofenac Na and ibuprofen amounts were placed in contact with phosphate buffer pH 6.8 in a horizontal shaker (GFL 3033) (75 rpm, 37°C, n = 3) for at least 72h. Every 24h, samples were withdrawn, filtered and the pH of the saturated solution was adjusted with sodium hydroxide solution. The samples were then analyzed for their drug content as described in section 2.2.1.3, until equilibrium was reached.

2.2.1.6 Determination of the drug content

The residual drug content in the films was determined after extraction in ethanol (96%) for selected samples (diclofenac Na, $\lambda = 282$ nm; ibuprofen, $\lambda = 264$ nm; metoprolol tartrate, $\lambda = 276$ nm).

2.2.1.7 Drug partition into polymer

Ibuprofen partition into ethylcellulose, Eudragit RS and Eudragit RL was determined as follows: a known amount of drug was dissolved in a known amount of phosphate buffer pH 6.8. Accurately weighted polymer was added to drug solution and stirred during 24h (75 rpm, 37°C, n=3) in a horizontal shaker (GFL 3033). 3 ml samples were withdrawn and analyzed (directly or after appropriate dilution) with UV spectrophotometry (Shimadzu UV-2101PC UV-Vis Scanning spectrophotometer; Shimadzu Europe, Duisburg, Germany). The corresponding wavelengths were described in section 2.2.1.3. Drug partition into the polymer was calculated as follows:

$$\text{drug partition into polymer} = 100 - \left(\frac{C_f}{C_i} \right) * 100$$

Where C_i is the initial drug concentration and C_f is the final drug concentration.

2.2.1.8 Differential scanning calorimetry (DSC)

Thermograms of PEG 1500, ethylcellulose, diclofenac Na, matrices of ethylcellulose: diclofenac Na 60:40 (cast film and physical mixture) with and without PEG 1500 were obtained by differential scanning calorimetry (Mettler DSC 821[°]) and STAR software (Mettler Toledo, Giessen, Germany) to determine the melting point. The samples (10-20 mg) were sealed in aluminum pans. All tests were run under a nitrogen atmosphere at a scanning rate of 5°C/min over a temperature range of 0 to 80°C.

2.2.1.9 Scanning electron microscopy (SEM)

The morphology of the surfaces and cross section of the coated pellets was examined by scanning electron microscopy (SEM). The dried samples were mounted onto the stages prior to coating for 230 s under an argon atmosphere with gold-palladium (SCD 040, Balzers Union, Lichtenstein) and then were observed with a scanning electron microscope (PW 6703/SEM 515, Philips, Eindhoven, The Netherlands).

2.2.1.10 Microscopic analysis

Matrix films were analyzed by polarizing light microscopy. The microscope was equipped with an imaging system (EasyMeasure; INTEQ Informationstechnik, Berlin, Germany).

2.2.1.11 Water uptake and weight loss

Matrix coated pellets, cast film (pieces of 5 x 5 cm) and MCC cores were accurately weighed, placed into a bottle filled with pre-warmed phosphate buffer pH 6.8 and horizontal shaken (GFL 3033) (75 rpm, 37°C, n=3). At pre-determined time intervals, samples were accurately weighed (W_{wet}) and dried to constant weight at 105°C (W_{dry}). The water uptake (%) and weigh loss (%) at time t were calculated as follows:

$$\text{water uptake (\%)} (t) = \frac{W_{\text{wet}} (t) - W_{\text{dry}} (t)}{W_{\text{wet}} (t)} * 100$$

$$\text{weight loss (\%)} (t) = \frac{W_{\text{dry}} (t)}{W_{\text{initial}} (0)} * 100$$

2.2.2 Reservoir Systems

2.2.2.1 Preparation of reservoir coated pellets

Drug loaded cores (33%, w/w drug loading) were prepared by layering drug-binder (HPMC) solutions (composition indicated in Table 1) onto drug-free sugar and MCC cores in a fluidized bed coater (metoprolol tartrate and propranolol HCl - Aeromatic Strea-1 and paracetamol- Glatt-GPCG-1). The process parameters are described in Table 2.

Table 1: Composition of drug-binder solutions used for the drug layering of pellets:

ingredients	amount, %
metoprolol tartrate/paracetamol	15.0
HPMC E5	3.8
isopropanol	71.5
water	9.8
total	100.0
propranolol HCl	15.0
HPMC E5	3.8
isopropanol	40.6
water	40.6
total	100.0

Table 2: Process parameters for the drug layering of pellets:

process parameters	metoprolol tartrate	propranolol HCl	paracetamol
batch size, g	1200	1200	1200
inlet air temperature, °C	60	52	38-40
outlet air temperature, °C	46-48	40-45	31
product temperature, °C	53-54	42-44	30
air flow, m ³ /h	80	90	80
spraying pressure, bar	1.2	1.2	1.2
spray rate, g/min	5	6	16

Drug loaded cores were coated with polymeric aqueous dispersions of Kollicoat SR 30 D 30 D, Eudragit NE 30 D, Eudragit NM 30 D, Surelease, Aquacoat ECD and organic

ethylcellulose solution in a fluidized bed coater Mini Glatt (Glatt, GmbH, Binzen, Germany) to a weight gain of 25% (w/w). Kollicoat SR 30 D and Aquacoat ECD were plasticized with 10 and 20% TEC (w/w, based on the dry polymer weight), respectively. 50% Talc (w/w, based on the dry polymer weight) was added to Kollicoat SR 30 D, Eudragit NE 30 D and Eudragit NM 30 D as antitacking agent. The polymer content was adjusted to 15% (w/w) with purified water. For all coatings, the batch size: 100g, air flow: 0.2 bar and spray pressure: 0.9 bar. Product temperature and spray rate for each coating are described in Table 3:

Table 3: Process parameters for the coating of drug layered pellets:

coatings	product temperature, °C	spraying rate, g/min
Kollicoat SR 30 D	28-30	9
Aquacoat ECD	40-42	12
Surelease	40	17
Eudragit NE 30 D	19-20	8
Eudragit NM 30D	19-20	9
organic ethylcellulose	40-42	15

The organic coating formulation consisted of ethylcellulose (7% w/w), plasticized with and 5% TEC (w/w, based on the dry polymer weight) solution of isopropanol: water 88:12 (w/w). 30% HPC (w/w, based on the polymer) was added to the coatings of paracetamol and propranolol HCl loaded cores. For all coatings, the batch size: 100g, air flow: 0.2 bar, spray pressure: 0.9 bar. Product temperature and spray rate are described in Table 3.

For all coatings, 0.5% (w/w) Aerosil was added prior to any experiment.

2.2.2.2 Drug release

The drug release from coated pellets was investigated in a USP paddle apparatus (VK 700, Vankel Industries, Edison, NJ, USA), 900 ml of phosphate buffer pH 6.8 (100 rpm, 37°C, n = 2 or 3). The weight of pellets used was equivalent to about 50 mg of paracetamol, 150 mg of propranolol HCl and metoprolol tartrate. At predetermined time intervals, 3 ml samples were withdrawn and analyzed with UV spectrophotometry (Shimadzu UV-2101PC UV-Vis Scanning spectrophotometer; Shimadzu Europe, Duisburg, Germany); paracetamol, $\lambda = 245.6$; propranolol HCl, $\lambda = 288$ nm; metoprolol tartrate, $\lambda = 274$ nm. The osmolality of the release media was determined based on the freeze point depression of the solutions compared to pure water.

2.2.2.3 Water uptake and weight loss

Coated propranolol HCl pellets were accurately weighed (W_{initial}) and placed into a bottle filled with pre-warmed phosphate buffer pH 6.8 and horizontal shaken (GFL 3033) (75 rpm, 37°C, n=2). At pre-determined time intervals, samples were accurately weighed (W_{wet}) and dried to constant weight at 105°C (W_{dry}). The water uptake (%) and weight loss (%) at time t were calculated as follows:

$$\text{water uptake (\%)} (t) = \frac{W_{\text{wet}} (t) - W_{\text{dry}} (t)}{W_{\text{initial}} (0)} * 100$$

$$\text{weight loss (\%)} (t) = \frac{W_{\text{dry}} (t)}{W_{\text{initial}} (0)} * 100$$

2.2.2.4 Pellets observation

Observation of the pellets before and after dissolution was performed under light microscope using image analyzing software (Inteq, Berlin, Germany).

2.2.2.5 Curing

After coating, pellets were cured in an oven for 24h at 40°C, 60°C and 60°C/75% RH. Upon curing at each condition, pellets were weighed, observed (macroscope) and drug release was performed. The moisture uptake (%) was calculated as follows:

$$\text{moisture uptake (t) (\%)} = \frac{W_{\text{cured (t)}} - W_{\text{initial (0)}}}{W_{\text{initial (0)}}} * 100$$

After curing, the pellets were equilibrated in a dessicator filled with silica gel at least for 24h at room temperature.

2.2.2.6 Storage

A known amount of coated pellets (uncured and/or cured) (W_{initial}) were filled in glass bottles and stored in stability test chambers: 40°C/75% RH (Simulationsanlage, Weiß Umwelttechnik GmbH, Lindenstruth, Germany), RT/60% RH (NaBr saturated solution) and 40°C (dessicator with silica gel) for 1 and 3 months. After storage, pellets were weighed (W_{stored}), observed (macroscope) and drug release was performed. The moisture uptake (%) was calculated as follows:

$$\text{moisture uptake (\%)} (t) = \frac{W_{\text{stored (t)}} - W_{\text{initial (0)}}}{W_{\text{initial (0)}}} * 100$$

After storage, the pellets were equilibrated in a dessicator filled with silica gel at least for 24 h at room temperature.

2.2.2.7 Swelling under storage

After 1 and 3 months storage at 40°C/75% RH and RT/60% RH, the bulk volume of pellets was measured using a graduated syringe of 1 ml. The swelling (%) at time t was calculated as follows:

$$\text{swelling (\%)} (t) = \frac{V_{\text{stored}}(t) - V_{\text{initial}}(0)}{V_{\text{initial}}(0)} * 100$$

2.2.2.8 f_2 , similarity factor

The similarity of drug release profiles was evaluated using the f_2 similarity factor:

$$f_2 = 50 \log \left(\left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right)$$

where n is the number of observations, R_t denotes the percentage of drug released from the reference formulation, and T_t the percentage of drug released from the test formulation.

3. Results and Discussion

3.1 Matrix Systems

The objective of the study was the investigation of the key parameters affecting the drug release from matrix cast films and coated pellets.

3.1.1 Effect of drug type

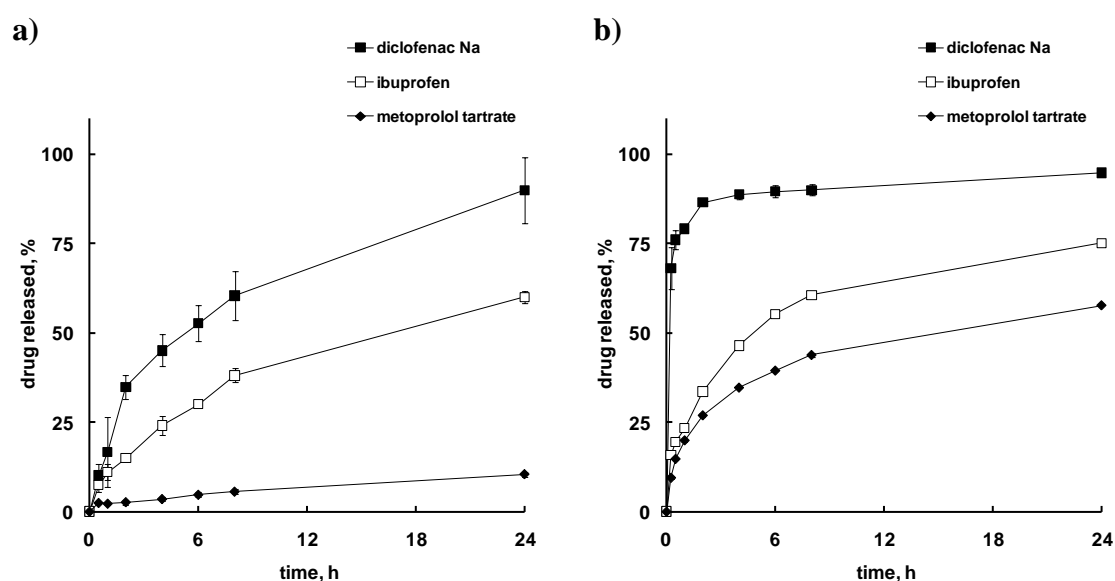


Figure 7: Effect of drug type on release from ethylcellulose matrix systems (30% drug loading). a) cast films and b) coated pellets (15% coating level).

Drug release from ethylcellulose matrix cast films and coated pellets was in the following order: diclofenac Na > ibuprofen > metoprolol tartrate (Figure 7a and b). Interestingly, the rank order of the observed release rates did not follow the rank order of aqueous drug solubility (metoprolol tartrate, 3630 mg/ml (Glaessl et al.) >> ibuprofen, 11.1 mg/ml > diclofenac Na, 1.0 mg/ml). Drug solubility in the matrix was: ibuprofen, 50% > diclofenac Na, 10% > metoprolol tartrate, 5% (determined by occurrence of drug crystals in the cast films). At 30% drug loading, diclofenac Na was

dissolved and dispersed (large crystals on matrix surface), ibuprofen was completely dissolved and metoprolol was dispersed in the matrix (Figure 8).

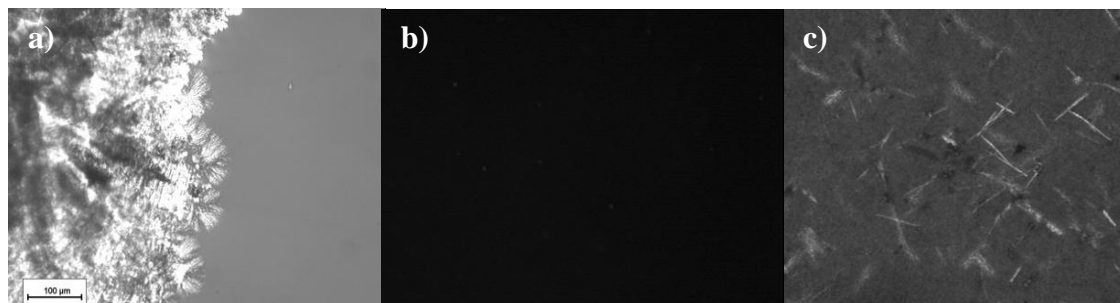


Figure 8: Polarizing light microscope images from ethylcellulose matrix cast films (30% drug loading). a) diclofenac Na, b) ibuprofen and c) metoprolol tartrate.

The fast release of diclofenac Na was attributed to rapid dissolution and release of drug crystals at matrix surface. Due to high solubility of ibuprofen in the matrix, diffusion through the matrix was the mechanism controlling drug release. Metoprolol tartrate, although very high soluble drug, released very slow due to drug entrapment in the matrix. Drug release from cast films and coated pellets was in the same order (diclofenac Na > ibuprofen > metoprolol tartrate), however with different extents (Figure 7a and b). The reasons for faster drug release from coated pellets could be attributed to higher surface area to volume ratio, shorter diffusion pathways and the method of preparation (coating method produces more porous matrices and the casting method originates denser matrices). The difference between drug release from matrix cast films and coated pellets was much less pronounced for ibuprofen than metoprolol tartrate or diclofenac Na. Since ibuprofen is dissolved in the matrix, drug diffusivity through the polymer should remain constant (cast films and coated pellets) with low contribution of porosity and drug release difference between films and coated pellets is mainly attributed to higher surface area to volume ratio from coated pellets (Fig 7a and b). In case of metoprolol tartrate, drug is dispersed in the matrix and drug release occurred by drug diffusion through water filled pores, consequently in a more porous matrix, drug diffusion significantly increases and drug release increases. Besides the

effect of geometry, the porosity factor is determining the increase in drug release from matrix coated pellets in comparison with the corresponding cast films.

3.1.2 Effect of drug loading

3.1.2.1 Solid solution

Drug release increased monotonically with increasing drug loading, due to higher drug amount in the matrix able to diffuse (Figure 9a). Ibuprofen release could be linearly described by a square root of time relationship, indicating a diffusion controlled mechanism (Figure 9b). Since drug is dissolved (solid solution), drug diffusion occurred through the polymer for all drug loadings and drug release rate constant (determined by the slope of linear portion of the curve of cumulative amount of drug release versus square root of time) increased in a direct proportion to the drug concentration, except with the lowest drug loading (Figure 9c). The amount of ibuprofen remaining in the matrix at 24h was plotted against the initial drug loading and a linear relationship was obtained, as well. The amount of drug not released was directly correlated with initial loading. By extrapolation of the curve, approximately 65% ibuprofen loading is necessary to achieve complete release (Figure 9d). On the other hand, it is clear from Figure 9a, that increasing the drug loading to 65% would increase as well the initial drug release.

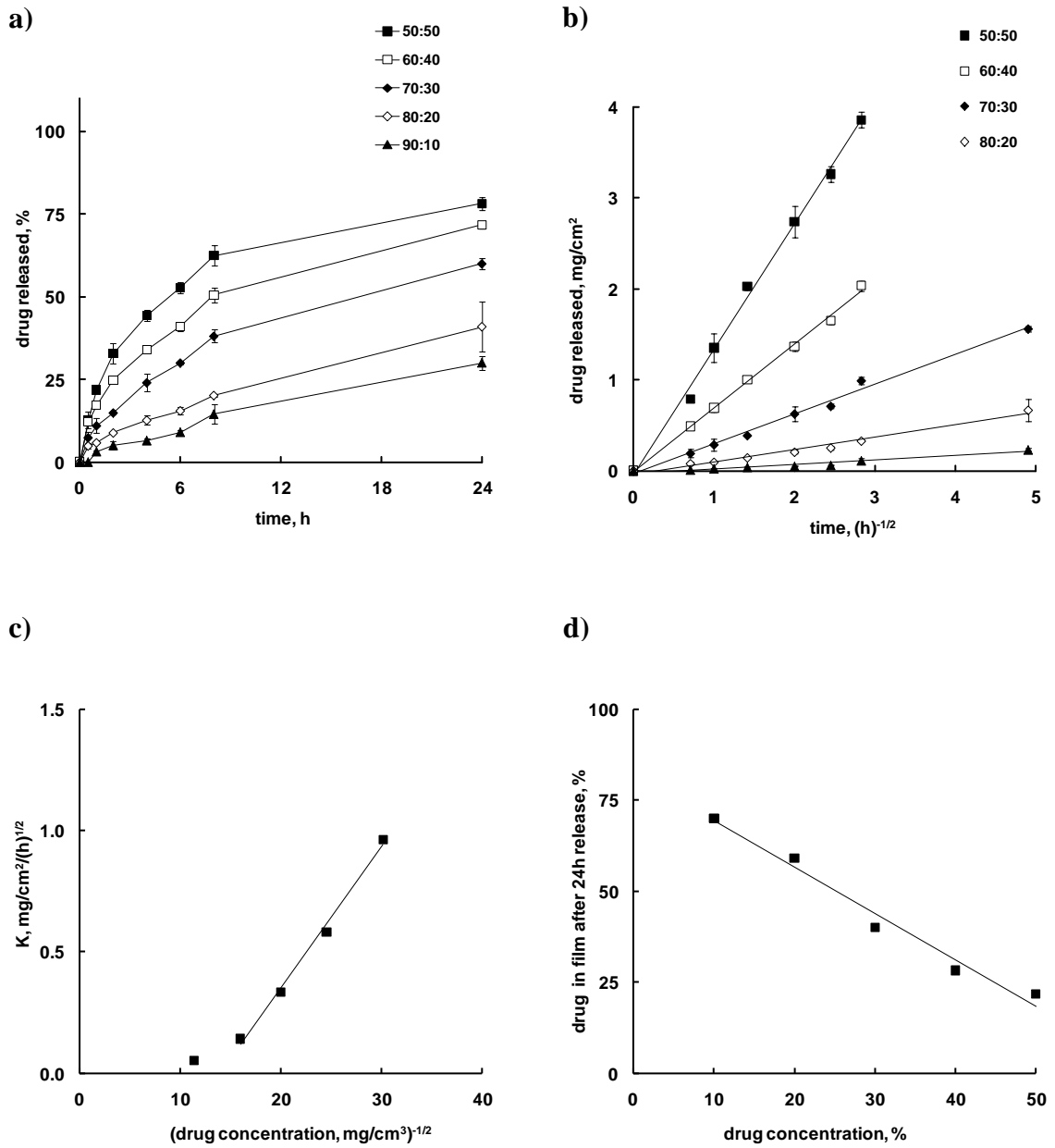


Figure 9: Effect of ibuprofen loading on ethylcellulose matrix cast films. a) drug release, %, b) drug release, mg/cm^2 vs. $(t)^{-1/2}$, c) release rate constant (K), $\text{mg}/\text{cm}^2/(\text{h})^{-1/2}$ and d) drug remaining in the matrix at 24h, %.

3.1.2.2 Solid dispersion

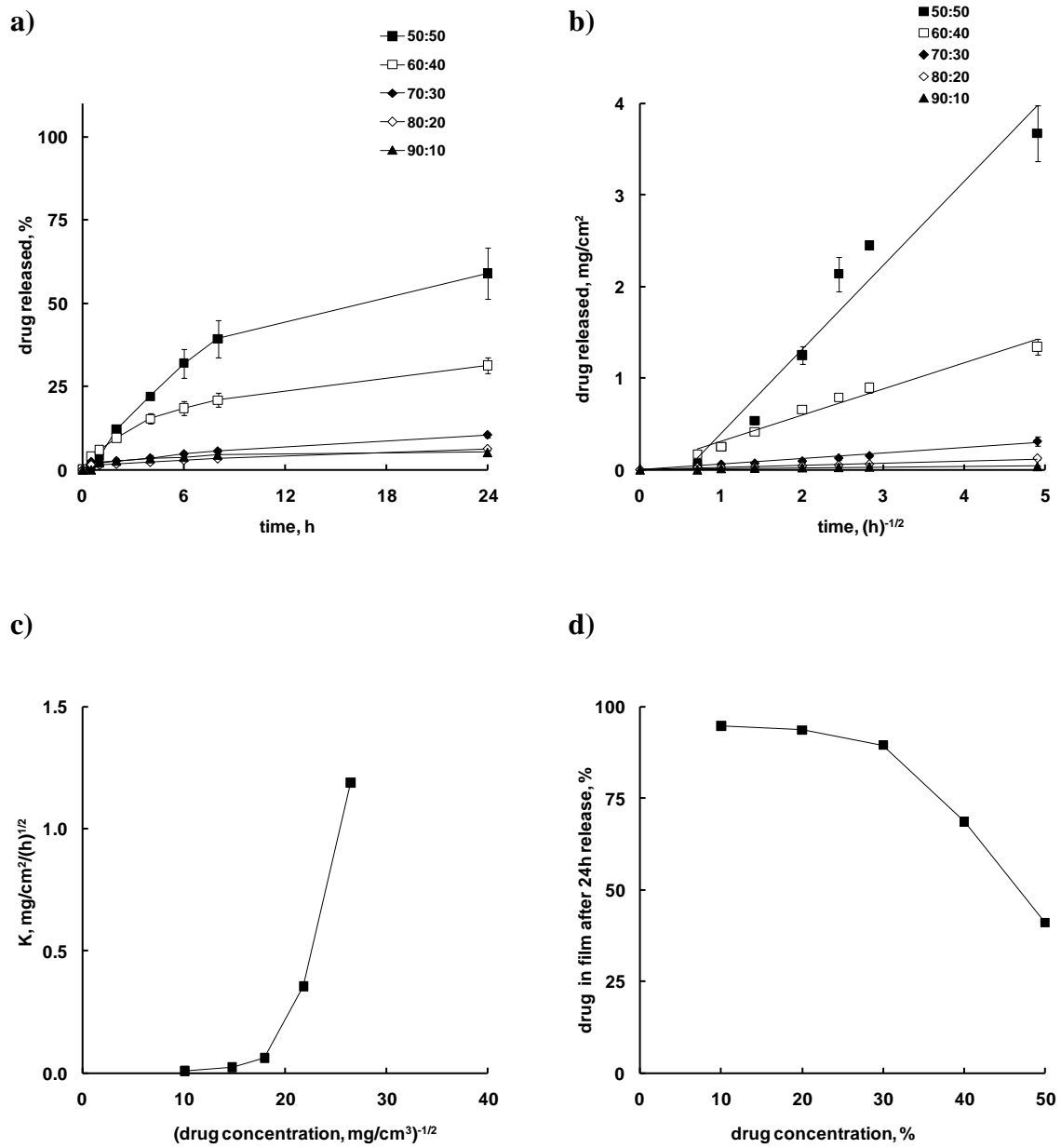


Figure 10: Effect of metoprolol tartrate loading on ethylcellulose matrix cast films. a) drug release, %, b) drug release, mg/cm² vs. (t)^{-1/2}, c) release rate constant, mg/cm²/(h)^{1/2} and d) drug remaining in the matrix at 24h, %.

Metoprolol tartrate release was very low up to 30% drug loading and then increased with increasing drug loading. However, complete release was not reached (Figure 10a).

Drug release could be described by a square root of time relationship, indicating a diffusion controlled mechanism (Figure 10b). In this case, since drug is dispersed in the matrix, diffusion occurred through water filled pores. The release rate showed a positive deviation from linearity (Figure 10c). From the plot of drug remaining in the matrix at 24h against drug loading, an inflexion point could be determined around 30% drug loading (Figure 10d). This result showed that other parameters (like porosity) are changing with drug loading and not in a proportional fashion. The release mechanism could be explained as follows: at low drug loadings (< 30% drug loading), pores randomly situated in the matrix are not interconnected and most of drug is entrapped in the matrix with no possible diffusion and release. When drug loading increases above a critical value (30% drug loading), pores start to interconnect, a wet porous network is formed and drug release occurs via diffusion through water filled pores. This critical drug loading is known as the percolation threshold (Leuenberger et al., 1995). Therefore, only the drug particles accessible to the outside medium through the porous network will contribute to diffusion in the matrix. In other words, isolated drug particles cannot contribute to the transport. When a drug cannot access the matrix surface through the wetted pore network, it will not be released and drug release is slower than it would be predictable from the simple consideration of aqueous diffusion.

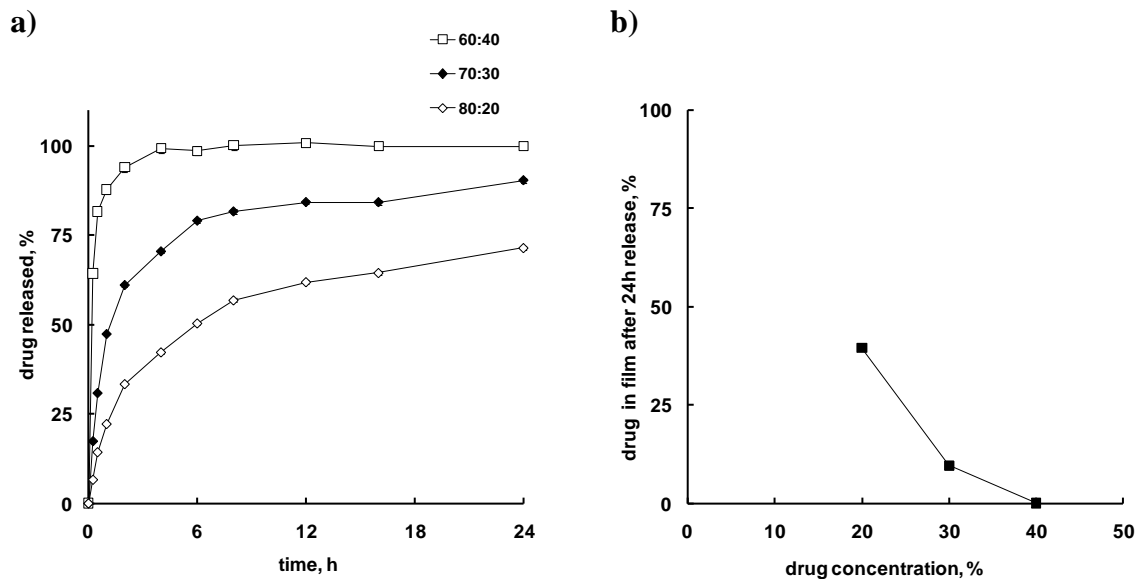


Figure 11: Effect of metoprolol tartrate loading on ethylcellulose matrix coated pellets. a) drug release, % and b) drug remaining in the matrix at 24h, % (15% coating level).

Metoprolol tartrate release from matrix coated pellets increased with increasing drug loading (Figure 11a and b). With increasing drug loading, the leached drug formed a more porous network and facilitated water penetration, increasing drug release. At 40% drug loading, metoprolol tartrate release was immediate and almost complete. At lower drug loadings, release rate was initially fast and decreased over time. In the beginning, drug release was faster due to drug crystals at matrix surface and/or very close to the surface and with increasing time, the diffusion path length for the drug increased, requiring more time to reach the surface and being released.

3.1.3 Effect of additives

3.1.3.1 Solid solution

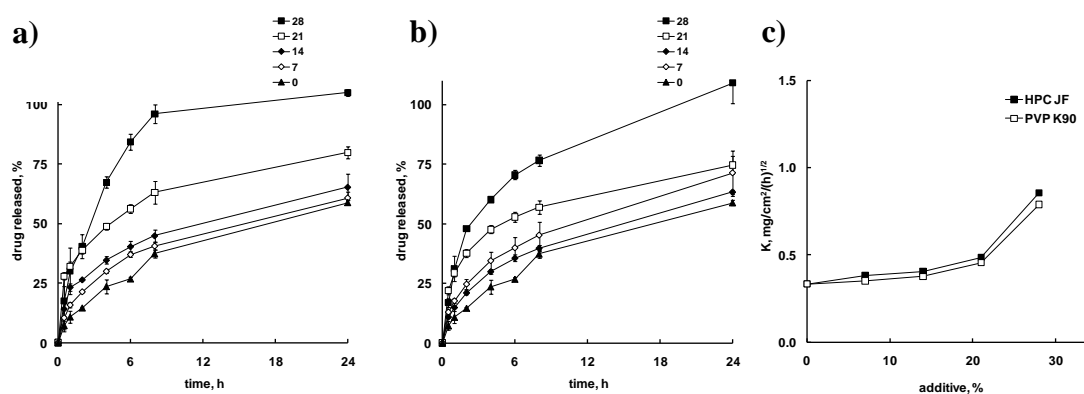


Figure 12: Effect of additive content (w/w) on ibuprofen release from ethylcellulose matrix cast films (30% drug loading). a) HPC JF, b) PVP K90 and c) release rate

In order to achieve complete drug release from matrix cast films, HPC JF and PVP K90, were used as hydrophilic additives. Increasing HPC JF and PVP K90 content, increased drug release in similar trend (Figure 12a and b). Additive content of 7% and 14% showed almost no effect on drug release rate, probably due to similar drug diffusion through the matrices (drug dissolved in the polymers). At 21% and 28% of additive, drug release rate significantly increased (Figure 12c), due to matrix erosion during drug release studies. This erosion, caused by the additive leaching, shortened the path length for the drug diffusion, increased surface area and drug release increased.

3.1.3.2 Solid dispersion

Metoprolol tartrate release was increased by increasing the HPC JF, PVP K90 and mannitol content in the matrix (Figure 13a-c). However the increase in drug release was just in the initial phase. Afterwards, a plateau was reached with all matrices. The increase in initial release was due to an increase in internal porosity, increasing drug diffusivity through water filled pores and/or channels. The plateau could be explained by entrapment of drug in the matrix. Consequently, below or at the drug percolation threshold, any optimization of drug release profiles is critical.

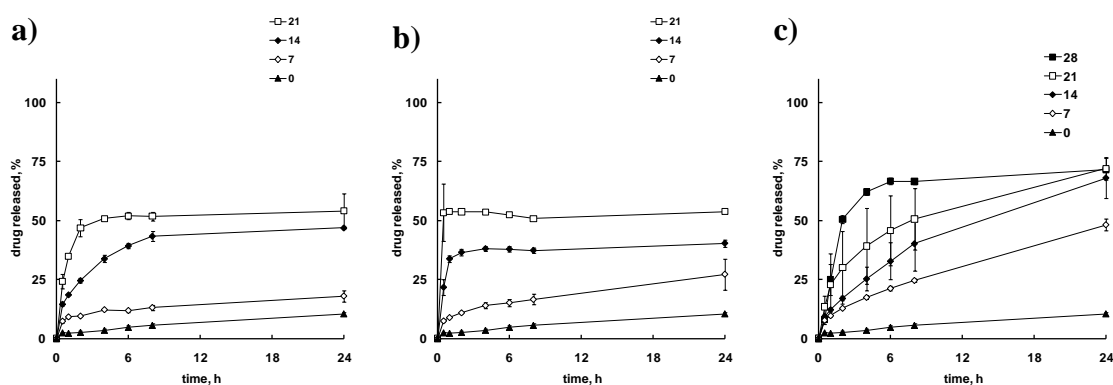


Figure 13: Effect of additive content (w/w) on metoprolol tartrate release from ethylcellulose matrix cast film (30% drug loading). a) HPC JF, b) PVP K90 and c) mannitol.

Polyethylene glycol (PEG) is widely used as an additive to increase drug release profiles. Due to its hydrophilicity, it leaches from the films, creating porosity and enhancing drug release profiles. In few cases PEG was reported to decrease drug release due its affinity to the drug and phase separation with the polymer (Kang et al., 2007; Mu et al., 2005). Therefore, it was an objective of this study to decrease diclofenac Na release from ethylcellulose matrix systems, by adding PEG 1500 to the matrix. Diclofenac Na release from ethylcellulose films was very fast, due to fast dissolution of drug crystals on the matrix surface (Figure 14a, b and 15a). Addition of 6% of PEG slightly decreased diclofenac Na release; whereas addition of 12-24% strongly decreased drug release (Figure 14a and b). In an opposite way, 30% PEG increased again drug release rate due to incomplete and discontinuous matrix (Figure 14a and

15d), which contributed to a fast drug release. The decreased diclofenac Na release when PEG was added to the matrices was attributed to a better drug entrapment into the ethylcellulose matrices (Figure 15a-c). Drug solubility, determined by the occurrence of crystals in dried films was ~ 10% in ethylcellulose film and ~ 60% in PEG. PEG itself had a low solubility in ethylcellulose films (around 10%). When PEG was added to ethylcellulose: diclofenac Na films, very small crystals well distributed over the matrix were seen (Figure 15a-c). To determine whether crystallinity was due to diclofenac Na or PEG, DSC was performed. Since diclofenac Na decomposes immediately after the melting point, interpretation of the results was not possible (data not shown). However, DSC results showed that PEG displayed an amorphous phase after incorporation in ethylcellulose: diclofenac Na matrix (Figure 16). Therefore, crystals observed in the ternary matrix were due to drug. And these crystals might be dispersed in or had crystallized out from the PEG microdomains, which acted as drug solubilizer. In the initial phase of drug release, diclofenac Na was preferential distributed in PEG domains (ring structures), with better entrapment in the matrix and this accounted for the slower dissolution / diffusion of diclofenac Na, resulting in a slower initial drug release. However, complete release was achieved due to PEG leaching, which created porosity and facilitated drug diffusion.

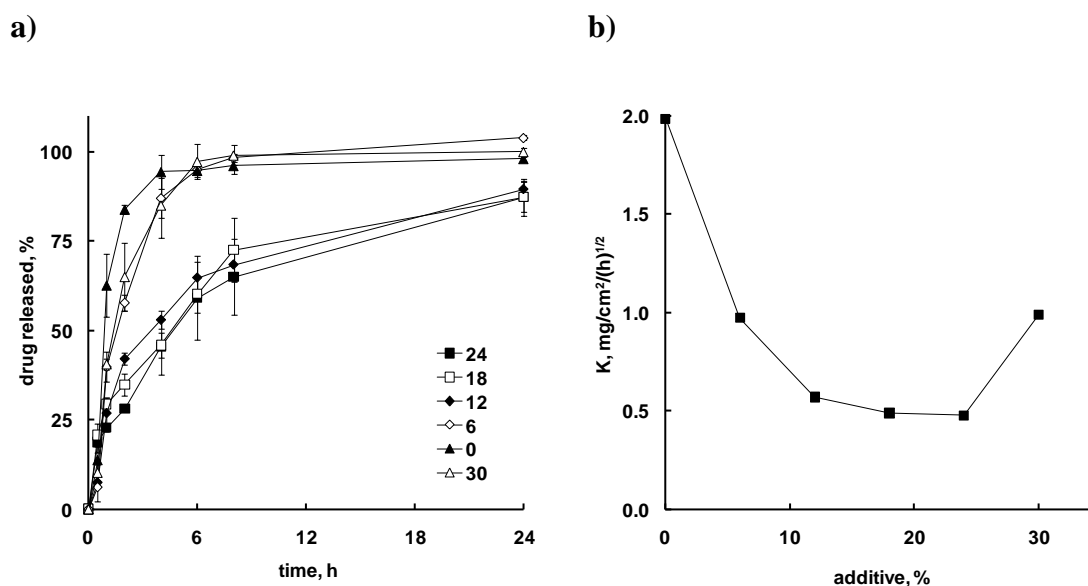


Figure 14: Effect of PEG 1500 content (w/w) on: a) diclofenac Na release and b) diclofenac Na release rate from ethylcellulose matrix cast films (40% drug loading).

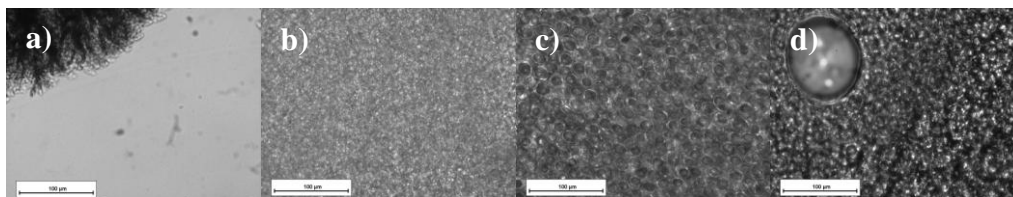


Figure 15: Polarizing light microscope images from ethylcellulose: diclofenac Na matrix cast films and different contents of PEG 1500 (w/w) (40% drug loading). a) 0, b) 12, c) 18 and d) 30.

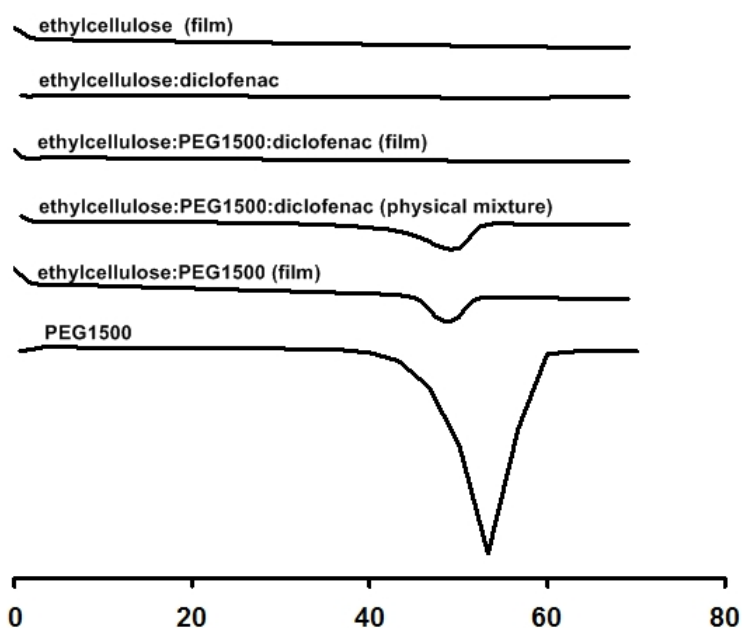


Figure 16: DSC thermograms (first cycle) of PEG 1500, ethylcellulose film, ethylcellulose: PEG 1500 70:30, ethylcellulose: PEG 1500: diclofenac Na 42:18:40 films and corresponding physical mixtures.

3.1.4 Effect of polymer type

Ibuprofen release was in the following order: Eudragit RL > ethylcellulose > Eudragit RS (Figure 17a). Drug was dissolved (clear films) in all matrix films and release mechanism occurred by diffusion through the polymer. The drug partition (%) into the

polymer was calculated to be: 73.4 ± 2.6 (Eudragit RL) $>$ 39.7 ± 2.0 (ethylcellulose) $>$ 3.8 ± 0.0 (Eudragit RS). These values can be interpreted in terms of drug solubility in the polymer. In addition, matrix permeability is a function of drug diffusivity in the matrix and drug partition into the polymer. Thus drug release order is related with ibuprofen solubility in the polymers and matrix permeability. Metoprolol tartrate release from ethylcellulose was around 10% in 24h in contrast with immediate release from Eudragit RS (Figure 17b). Drug was dispersed and entrapped in ethylcellulose matrix and dissolved in Eudragit RS matrix. Moreover, metoprolol tartrate is able to form an amorphous mixture with Eudragits (Glaessl et al., 2009), being the reason for the extremely fast drug release.

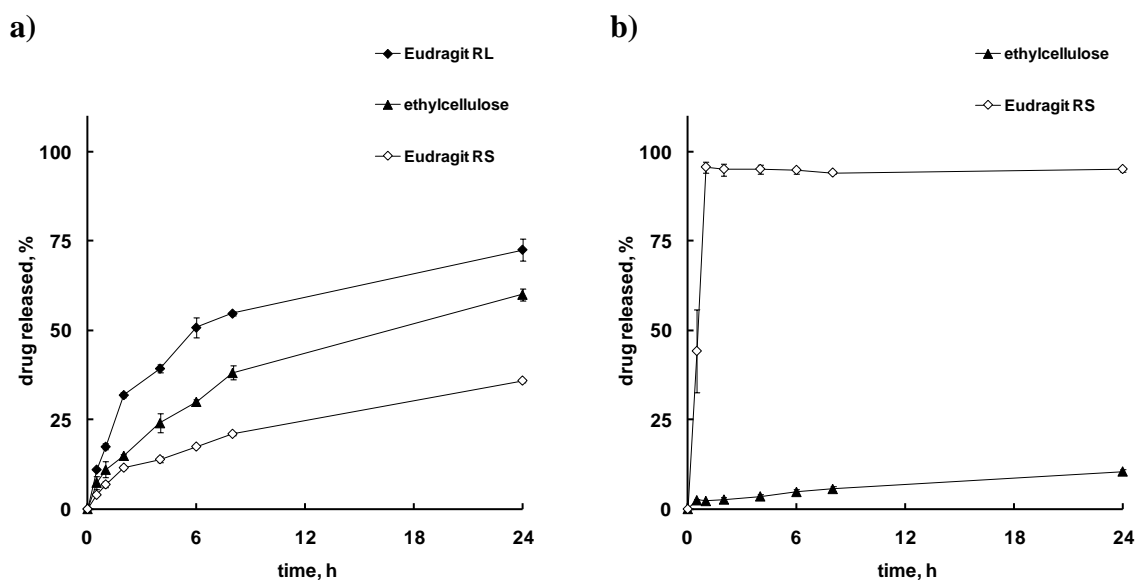


Figure 17: Effect of polymer type on release of: a) ibuprofen and b) metoprolol tartrate from matrix cast films (30 % drug loading).

3.1.5 Effect of core type and size

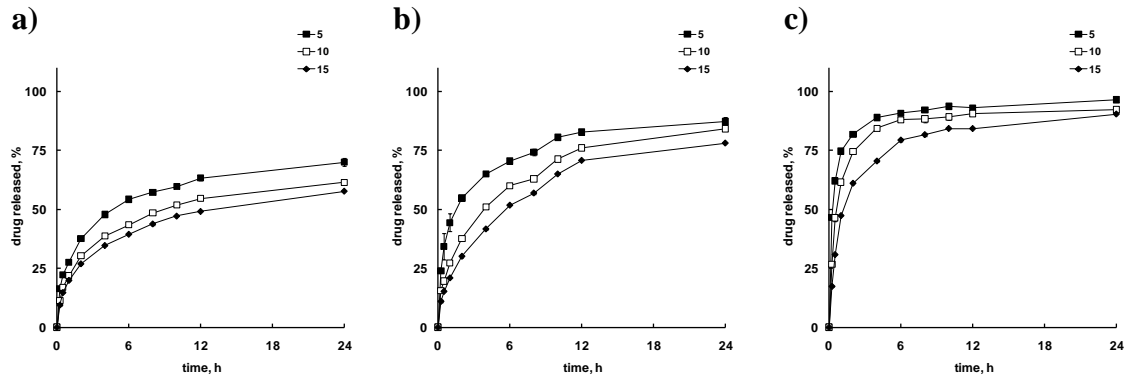
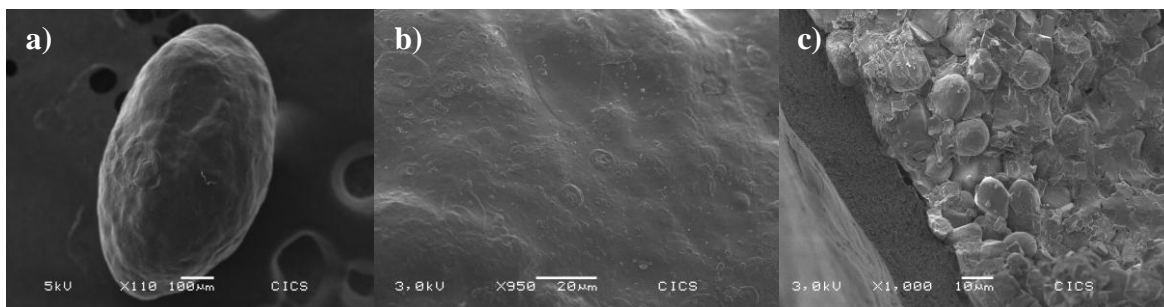


Figure 18: Effect of core size, type and coating level on metoprolol tartrate release from ethylcellulose matrix coated pellets (30% drug loading). a) NP 710-850µm, b) NP 500-600µm and c) MCC 500-630µm.

For all formulations, increasing the coating level decreased drug release rate (Figure 18a-c), due to increased diffusion length. Decreasing the core size (Figure 18a and b), increased drug release, due to an increase of surface area to volume ratio ($7.1 \text{ mm}^2/\text{mm}^3$ vs. $10.0 \text{ mm}^2/\text{mm}^3$, for the starter cores). If keeping surface area to volume ratio constant, $\sim 10.0 \text{ mm}^2/\text{mm}^3$ (Figure 18c and d), but changing the type of core (sugar vs. MCC), drug release increased in case of coated MCC cores. The difference in drug release profile could not be attributed to any coating defect in the matrix coated pellets. Both matrix coatings were free of any coating defects and the surface was smooth and uniform (Figure 19).

Sugar cores



MCC cores

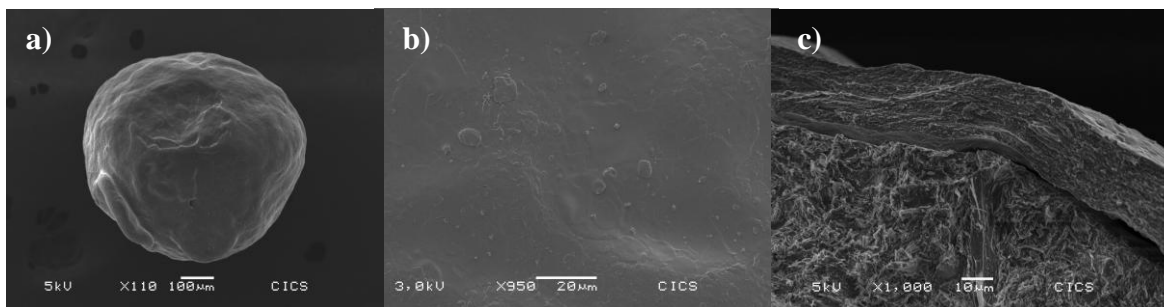


Figure 19: Scanning electron micrographs of ethylcellulose matrix coated sugar and MCC pellets. a) surface (lower magnification), b) surface (higher magnification) and c) cross section (30% metoprolol tartrate).

Metoprolol tartrate release was faster from matrix coated MCC than sugar cores. Water uptake and weight loss was higher for coated sugar cores (Figure 20a-c), due to the presence of sucrose. Water uptake was fast and complete in 1h for all formulations and MCC cores. Drug release mechanism from both matrix coated cores (sugar and MCC) was the same since the shape of release curves did not change (Figure 20a). In case of coated sugar cores, probably water uptake occurred preferential by sucrose, which dissolved and released. Metoprolol tartrate diffusion might be hindered and/or it happened towards the dissolved core and afterwards in the direction of bulk medium. This would account for the difference between metoprolol release from matrix coated sugar and MCC cores.

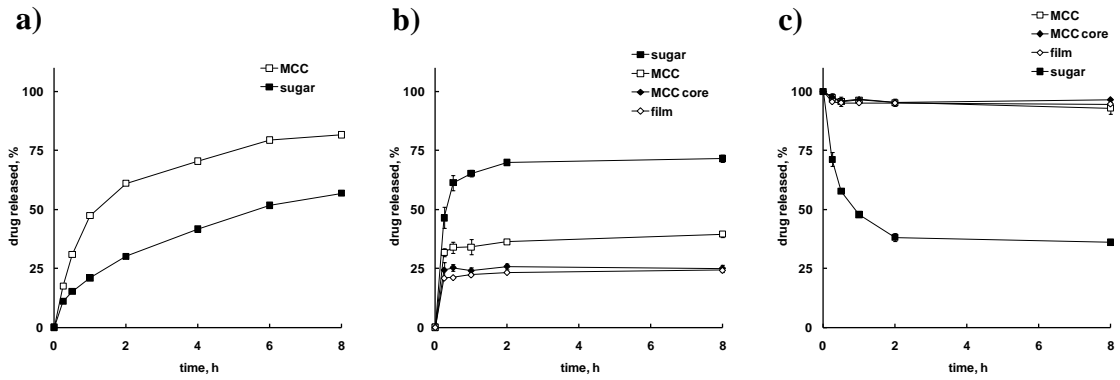


Figure 20: Effect of core type (sugar vs. MCC cores) on: a) metoprolol tartrate release, b) water uptake and c) weight loss from ethylcellulose matrix coated pellets (30% drug loading and 15% coating level). Water uptake and weight loss include matrix cast films and uncoated MCC cores.

3.1.6 Effect of medium osmolality

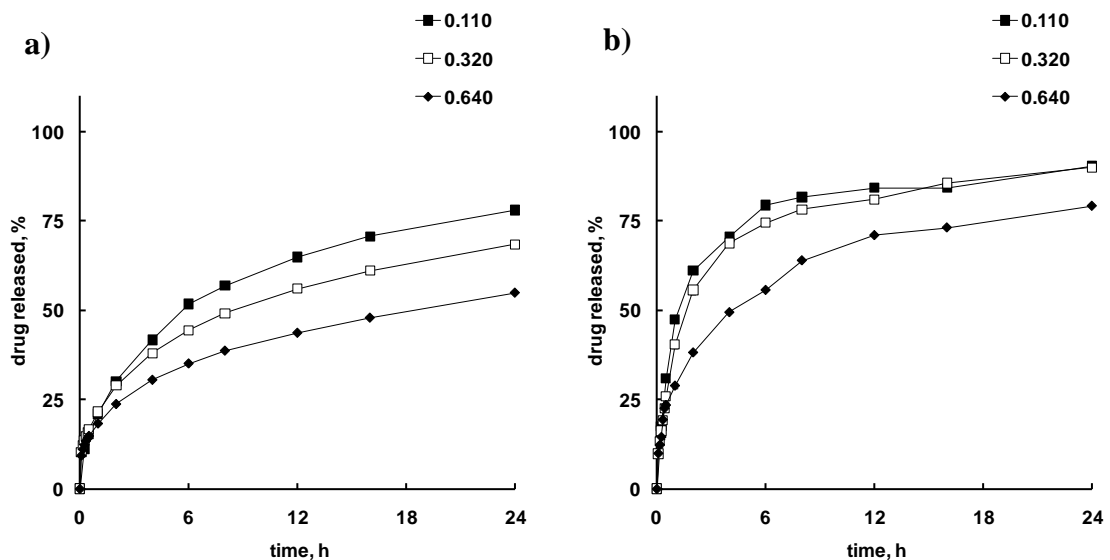


Figure 21: Effect of osmolality of release media (Osmol/Kg) on metoprolol tartrate release from ethylcellulose matrix coated pellets. a) sugar cores and b) MCC cores (30% drug loading and 15% coating level).

Metoprolol tartrate release from matrix coated pellets (sugar and MCC cores) decreased when increasing the osmolality of the medium (Figure 21). This can be explained by the decrease in the water penetration rate into the systems, with increasing osmolality, water being required for drug dissolution and only dissolve drug can diffuse. Thus potential food effects based on this mechanism are probable to decrease drug release from both matrix coated cores.

In conclusion, key parameters affecting drug release from matrix cast films and coated pellets were identified. Independent if drug is dissolved or dispersed in the matrix, drug release profiles from matrix systems were characterized by an initial fast release followed by decreased release rate.

3.2 Reservoir Systems

3.2.1 Effect of coating type and level

Drugs with different aqueous solubilities, paracetamol, 17 mg/ml (Granberg and Rasmuson, 1999); propranolol HCl, 130 mg/ml (Takka et al., 2001); metoprolol tartrate, 3630 mg/ml (Glaessl et al.) were layered on water-soluble sugar and -insoluble MCC cores, followed by coating with different aqueous polymer dispersions. The effect of polymer coating system on drug release from uncured coated pellets and cured (60°C/24h) ethylcellulose coated pellets was evaluated. The aqueous coatings differed in composition (e.g. type of polymer, plasticizer content and presence/absence of talc). Ideally, a coating level in the range of 10-20 % should be able to achieve controlled release (t_{50} , 50% drug release in 6h). This coating level is optimal in terms of reproducibility and economic aspects. The coating level to achieve t_{50} in 6h was determined by extrapolation of the plots t_{50} vs. coating level for all coatings.

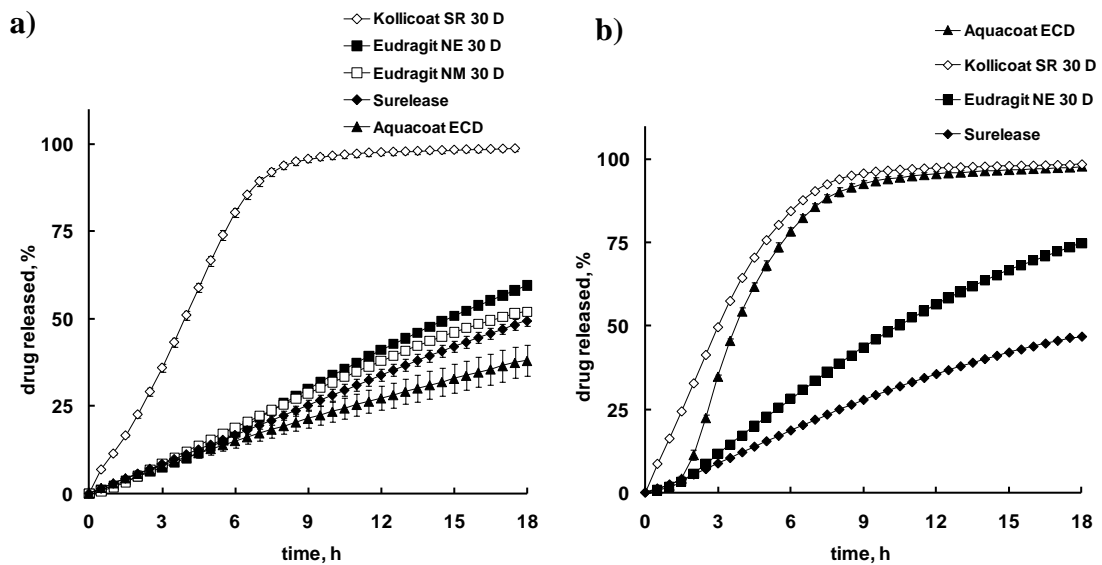


Figure 22: Effect of polymer coating system on paracetamol release from coated pellets (10% coating level). a) sugar cores and b) MCC cores.

Paracetamol release from coated sugar cores was in the following order: Kollicoat SR 30 D >> Eudragit NE 30 D ~ Eudragit NM 30 D ~ Surelease > Aquacoat ECD (Figure 22a). Paracetamol release from coated MCC cores was in the following order: Kollicoat SR 30 D ~ Aquacoat ECD > Eudragit NE 30 D > Surelease (Figure 22b). Drug release of the uncharged and sparingly soluble paracetamol occurred mainly by diffusion through the coating and resulted in profiles without lag time (except Aquacoat ECD-coated MCC cores). Drug diffusion might have occurred through intact coatings or water-filled pores. The differences in drug release profiles from the coated cores could be attributed to different drug permeabilities through the polymer coating system.

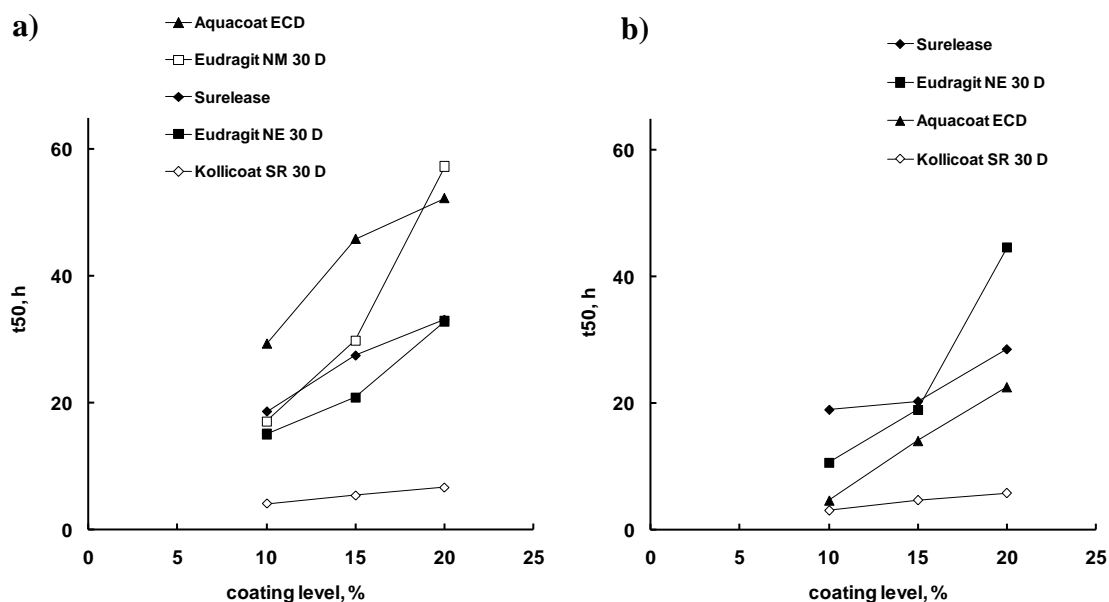


Figure 23: Effect of coating level on t_{50} from paracetamol coated pellets. a) sugar cores and b) MCC cores.

The coating level to achieve t_{50} in 6h was very low for all coated pellets (except Kollicoat SR 30 D) (Figure 23a and b). Thus, the inclusion of water-soluble pore-formers is required. The coating level to achieve t_{50} in 6h was around 20% for Kollicoat SR 30 D-coated pellets. This was probably due to presence of povidone, which leached out from the film (acting as pore former). With Aquacoat ECD-coated MCC cores, 10% coating level was enough to reach t_{50} in 6h. This was attributed to

coating rupture upon MCC core swelling. The mechanism changed from diffusion through the coating to diffusion through ruptures, resulting in a much faster drug release.

The propranolol HCl release from coated sugar cores was in the following order: Kollicoat SR 30 D > Eudragit NE 30 D ~ Eudragit NM 30 D > Aquacoat ECD ~ Surelease. With coated MCC cores, the propranolol HCl release was: Kollicoat SR 30 D > Aquacoat ECD > Eudragit NE 30 D > Surelease (Figure 24a and b).

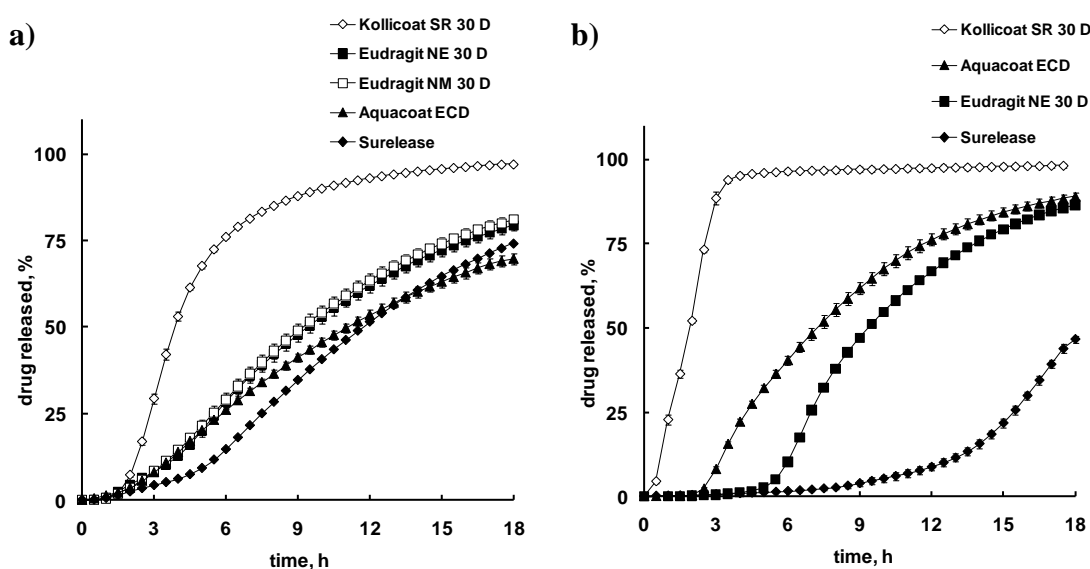


Figure 24: Effect of polymer coating system on propranolol HCl release from coated pellets (15% coating level). a) sugar cores and b) MCC cores.

Propranolol HCl (charged and freely soluble drug) release profiles were sigmoidal with a clear lag time. Independent of the coating, the drug release occurred in three steps: 1) water penetration and film hydration; 2) increasing osmotic pressure (coated sugar cores) and MCC core swelling (coated MCC cores) until film mechanical stability is not exceeded and 3) formation of ruptures in the coating and the liquid inside the coated pellets is released out (drug release). Consequently, propranolol HCl release is controlled by a combination of film coating properties (hydration and mechanical

properties) and type of starting core. Propranolol HCl release from Kollicoat SR 30 D-coated pellets (both cores) was faster compared with the other coatings. This is attributed to a higher aqueous permeability (rate and extent) from the coating. Propranolol HCl release rate from Eudragit NE 30 D-, Eudragit NM 30 D-, Surelease- and Aquacoat ECD-coated sugar cores was more uniform when compared with the corresponding coated MCC cores (Figure 24a). Despite differences in rate and extent of hydration and mechanical properties of different coatings, once osmotic pressure is generated (approximately 1.5h), ruptures in the coatings occurred followed by similar drug release. In contrast, very different lag times and release rates were observed with coated MCC cores (Figure 24b). In this case, the mechanical properties of different coatings were emphasised.

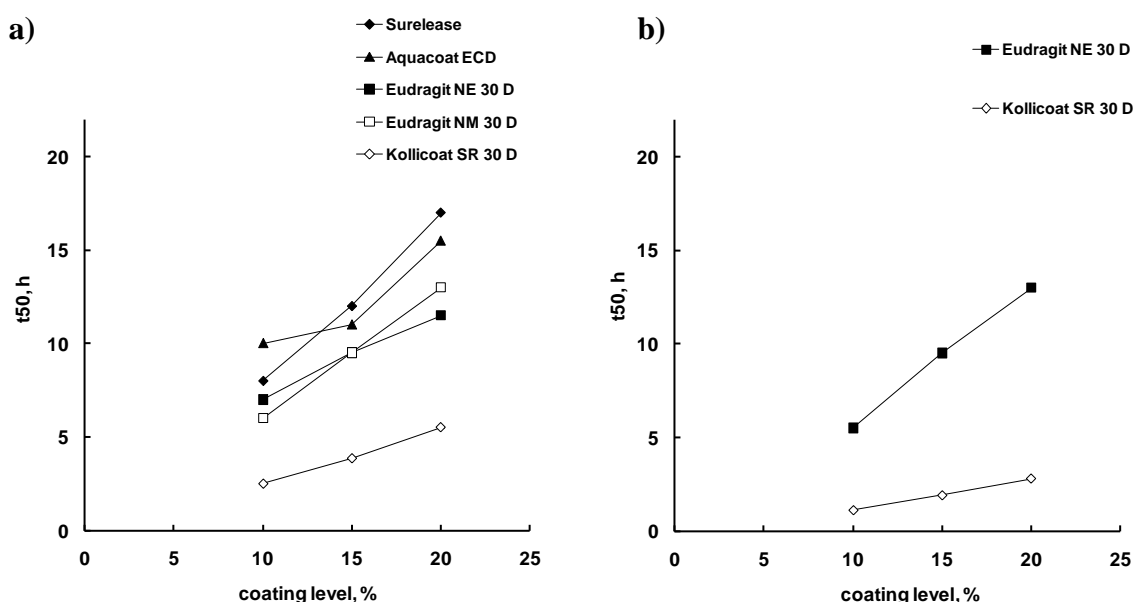


Figure 25: Effect of coating level on t_{50} from propranolol HCl coated pellets. a) sugar cores and b) MCC cores.

The coating level to achieve t_{50} in 6h was low for ethylcellulose based coated sugar cores (Surelease and Aquacoat ECD), due to high polymer impermeability. In contrast, 10-20% coating level of Kollicoat SR 30 D, Eudragit NE 30 D and Eudragit NM 30 D were sufficient to control propranolol HCl release from coated sugar cores. Eudragit NE 30 D (~ 10% coating level) coated MCC cores also reached t_{50} in 6h (Figure 25a and b)

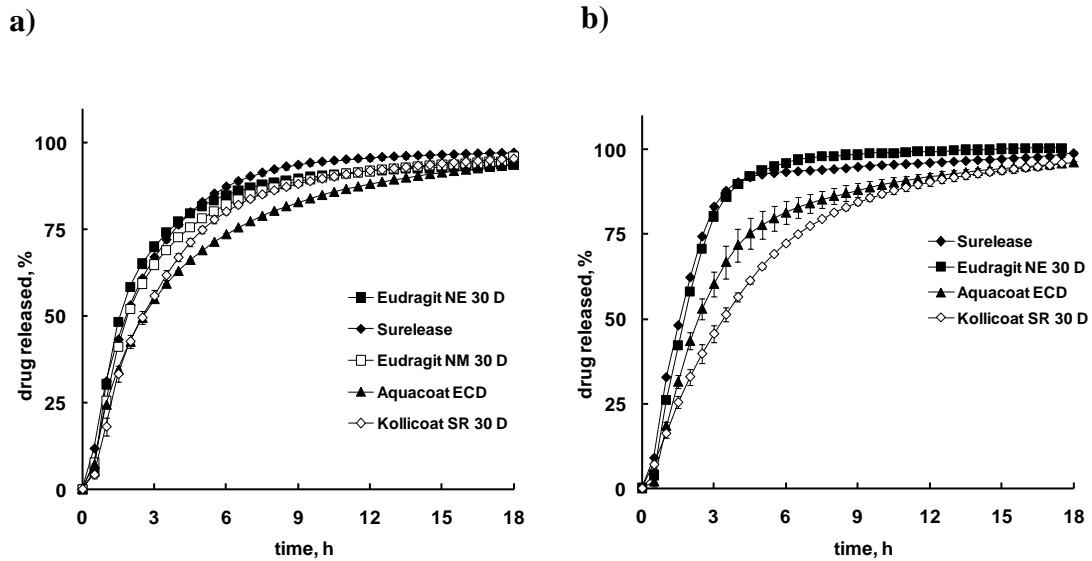


Figure 26: Effect of polymer coating system on metoprolol tartrate release from coated pellets (15% coating level). a) sugar cores and b) MCC cores.

Metoprolol tartrate release from coated sugar cores was in the following order: Eudragit NM 30 D ~ Eudragit NE 30 D ~ Surelease > Kollicoat SR 30 D ~ Aquacoat ECD. In case of coated MCC cores, drug release was in the following order: Surelease ~ Eudragit NE 30 D > Aquacoat ECD > Kollicoat SR 30 D (Figure 26a and b). The ranking order for metoprolol tartrate release from both coated cores is based in minor differences between drug releases. Drug release profiles were also sigmoidal and drug release followed the 3 steps described for coated propranolol HCl pellets. However, due to the very high drug solubility, release mechanism is less controlled by coating properties and/or core type, but by drug solubility, resulting in similar drug release profiles for all coated pellets.

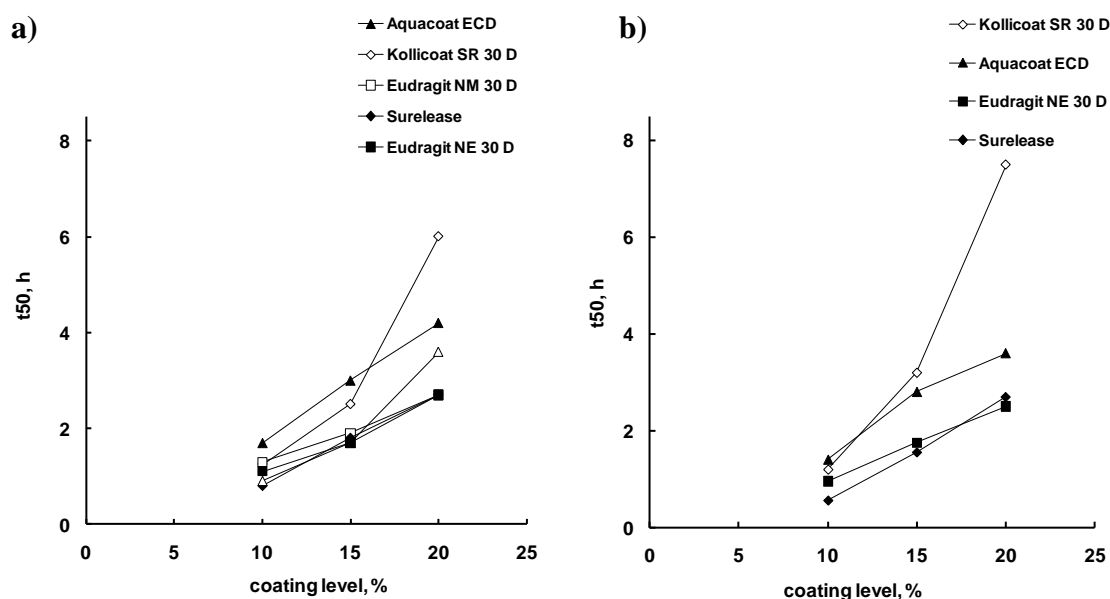


Figure 27: Effect of coating level on t_{50} from metoprolol tartrate coated pellets. a) sugar cores and b) MCC cores.

Due to high drug solubility, very high coating levels ($\geq 30\%$) are necessary to control metoprolol tartrate release (t_{50} in 6h). The exception was Kollicoat SR 30 D-coated pellets (both cores), where 20% coating level was enough to control metoprolol tartrate release (Figure 27a and b). At this coating level, Kollicoat SR 30 D-coated pellets were swollen and no cracks (Figure 28a) were visible (macroscopically), thus t_{50} could be achieved in 6h. On the contrary, Eudragit NE 30 D and Surelease-coated pellets (20% coating level) displayed ruptures at the surface (Figure 28b and c) and thus drug release was fast, requiring more than 30% coating level to get t_{50} in 6h.

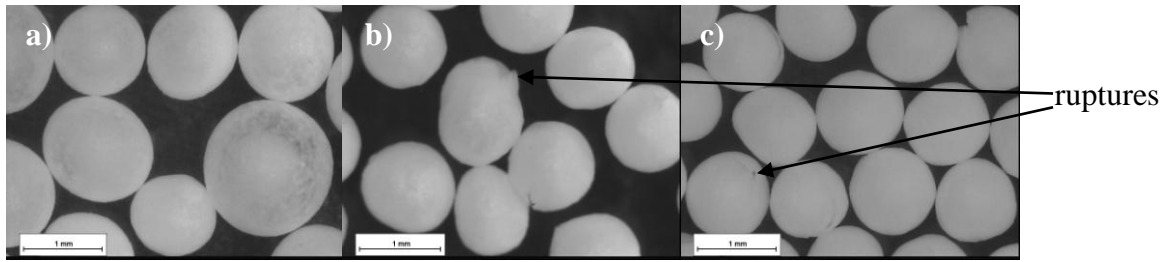


Figure 28: Macroscopic pictures from coated metoprolol tartrate MCC cores after 18h in release medium (20% coating level). a) Kollicoat SR 30 D, b) Eudragit NE 30 D and c) Surelease.

In general, varying the type of polymer coating system had less impact on metoprolol tartrate release than on paracetamol and propranolol HCl release from coated sugar pellets. This was due to the very high drug solubility, where water penetration is dictated by drug and so decreasing the effect of coating properties.

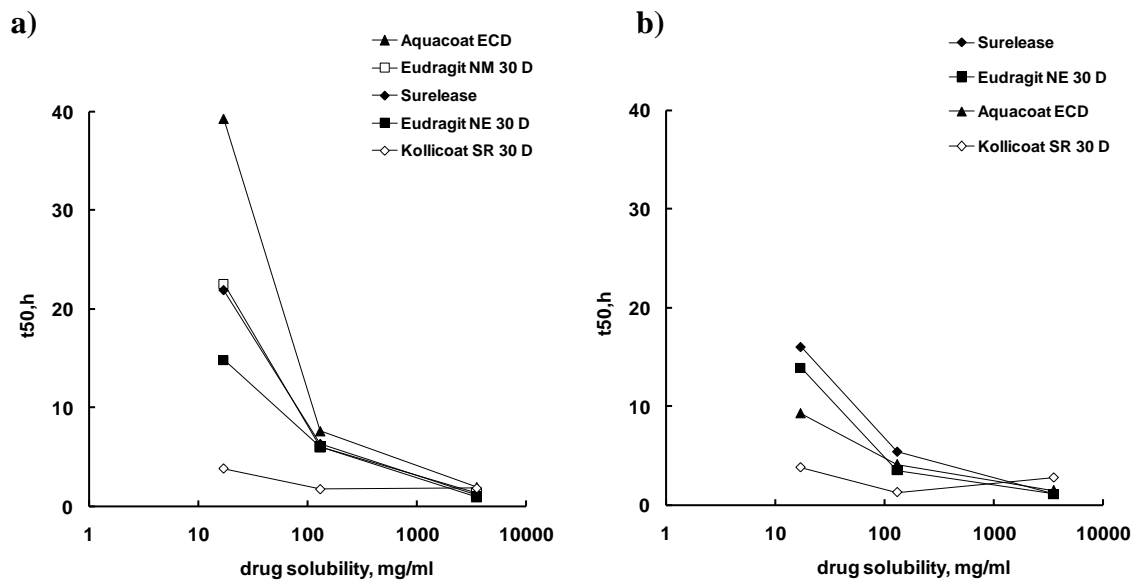


Figure 29: Effect of logarithm of drug solubility on t_{50} (h) from coated pellets (15% coating level). a) sugar cores and b) MCC cores

The effect of drug type on release rate from coated sugar and MCC cores was evaluated at the 15% coating level (Figure 29a and b). Drug release decreased with decreasing drug solubility for all coated pellets. Only the release rate from Kollicoat SR 30 D coated pellets (both cores) was relatively independent of drug solubility. Despite different release mechanisms for different drugs, polymer hydration, drug permeability in combination with mechanical properties of Kollicoat SR 30 D, overlay and compensate the effect of drug solubility.

3.2 Effect core type (sugar vs. MCC cores)

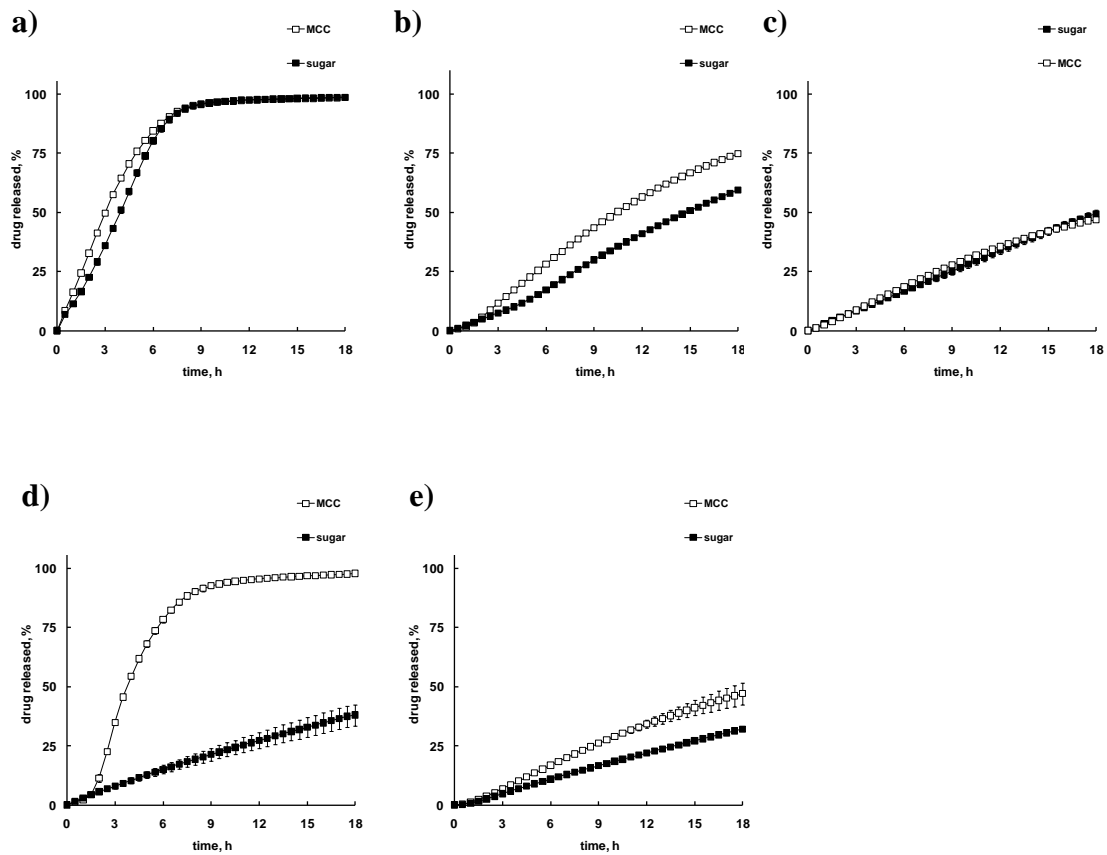


Figure 30: Effect of core type on paracetamol release from coated pellets (10% coating level). a) Kollicoat SR 30 D, b) Eudragit NE 30 D, c) Surelease, d) Aquacoat ECD and e) organic ethylcellulose solution.

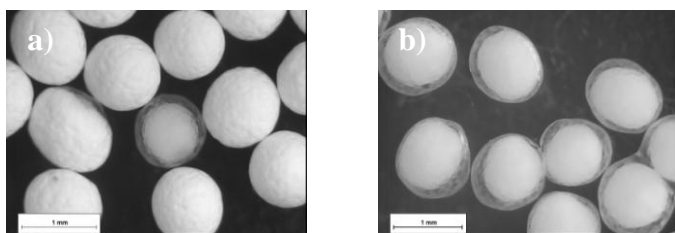


Figure 31: Macroscopic pictures from Aquacoat ECD-coated paracetamol pellets after 18h in release medium. a) sugar cores and b) MCC cores.

Minor to moderate differences were observed between drug release from coated sugar and MCC cores for all coatings (Figure 30a-e). The f_2 similarity factor was between 45 and 86. This further confirmed that paracetamol diffusion through the coatings is the controlling mechanism of release with minor contribution from the starting core. Only, drug release from Aquacoat ECD-coated pellets was significantly faster from coated MCC cores than sugar cores (Figure 30d), with $f_2 = 18$. With Aquacoat ECD-coated MCC cores, the coating ruptured during drug release (Figure 31b) and thus the release mechanism changed from diffusion through the polymer to diffusion through water-filled ruptures, resulting in a faster release from coated MCC cores. Ruptures in the Aquacoat ECD coating were probably due to MCC core swelling. In fact, upon contact with medium, uncoated MCC cores adsorb high amounts of water (45%, w/w) and swell (30% v/v). The core swelling created a high mechanical stress and the Aquacoat ECD coating did not resist and ruptured (Figure 31b).

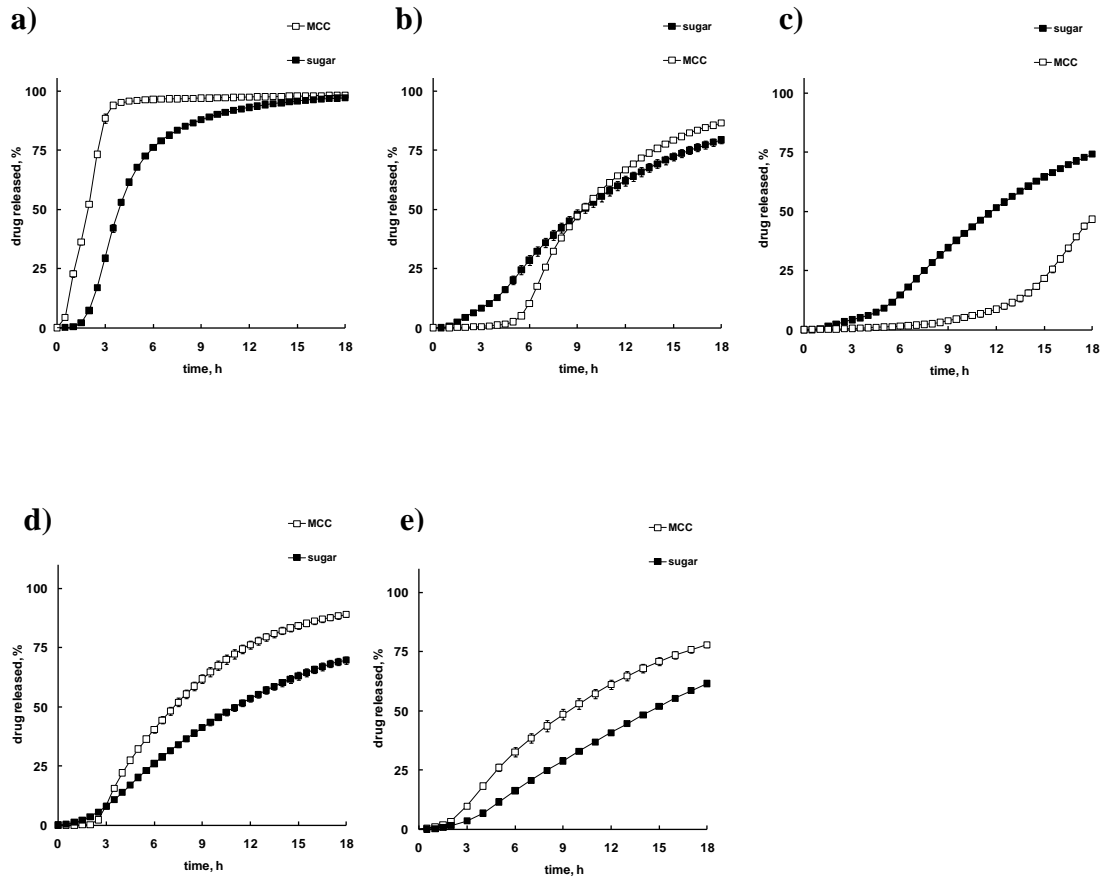


Figure 32: Effect of core type on propranolol HCl release from coated pellets (15% coating level). a) Kollicoat SR 30 D, b) Eudragit NE 30 D, c) Surelease, d) Aquacoat ECD and e) organic ethylcellulose solution.

Significant differences in propranolol HCl release from coated sugar and MCC cores were observed for all coatings (Figure 32a-e), with f_2 , similarity factor between 19 and 38. The release (lag time and rate) could be summarized as follows:

coatings	lag time	release rate
Kollicoat SR 30 D	NP < MCC	NP=MCC
Eudragit NE 30 D and Surelease	NP > MCC	NP<MCC
Aquacoat ECD	NP < MCC	NP<MCC
organic ethylcellulose	NP = MCC	NP<MCC

The propranolol HCl release mechanism from Kollicoat SR 30 D-, Eudragit NE 30 D- and organic ethylcellulose-coated pellets was investigated further.

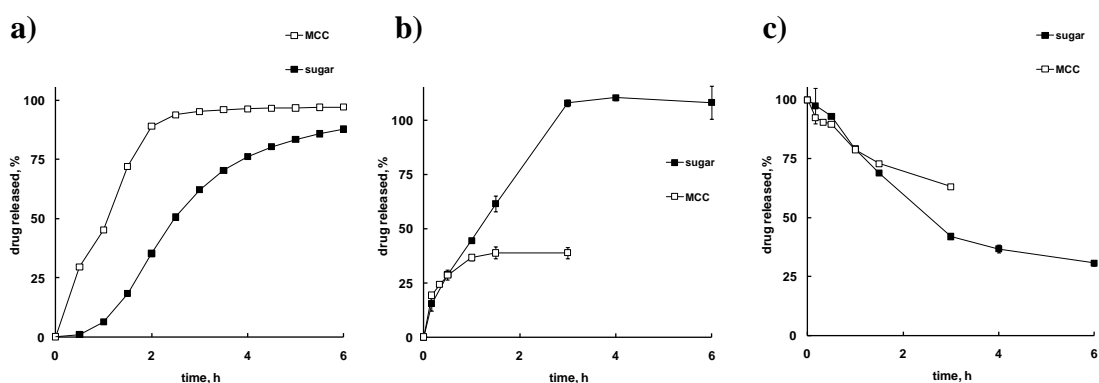


Figure 33: Effect of core type (sugar vs. MCC cores) on: a) drug release, b) water uptake and c) weight loss from Kollicoat SR 30D-coated propranolol HCl pellets (10% coating level).

Propranolol HCl release from Kollicoat SR 30 D-coated MCC cores showed no lag time. This is in contrast with the clear lag time from coated sugar cores (Figure 33a). The lag time from coated sugar cores reflects the influx of water, leading to development of hydrostatic/osmotic pressure until the mechanical stability of the coating is not exceeded. Beyond the coating mechanical stability, ruptures are formed and drug release occurs. Despite similar initial water uptake from both coated cores (Figure 33b), coated MCC cores ruptured much earlier. This was a result of strong local water uptake/swelling from MCC cores (water penetrates into the amorphous parts of

MCC) (Chambin et al., 2004) and local water uptake/swelling from the coating itself (probably due to hydrophilic parts of the polymer) (Figure 34d). This generated a high localized stress in the coating, leading to ruptures confined to a small area (Figure 34e). Coated sugar cores showed local swelling as well (Figure 34b), but required more time to build up osmotic pressure to cause ruptures in the coating. After coating rupturing and due to large cracks in the coating, coated MCC cores were pushed out from the coating (coating shell and MCC core separated from each other) (Figure 34f). Coated sugar cores swelled to a greater extent until the critical threshold value was reached and crack formation was induced in the coating, followed by drug release. With propranolol HCl, the critical threshold of mechanical stability of Kollicoat SR 30 D coatings was reached earlier from coated MCC cores than sugar cores, consequently overall drug release was faster from coated MCC cores.

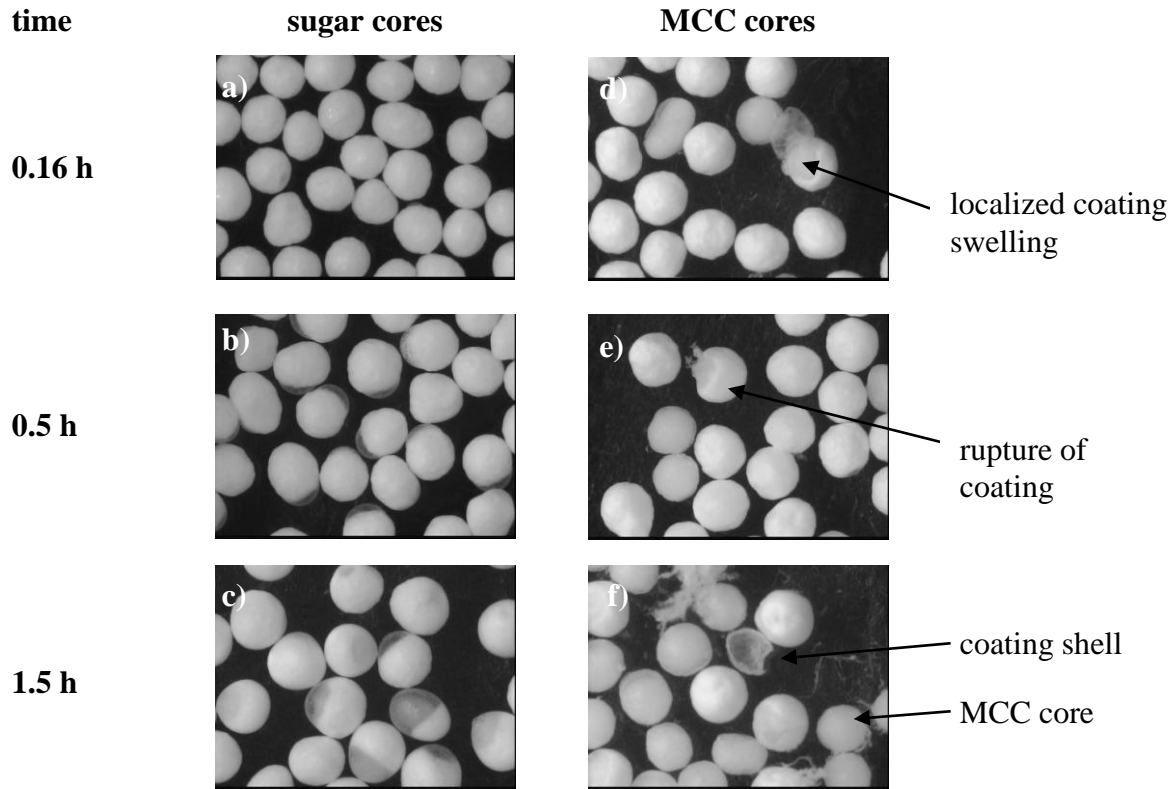


Figure 34: Macroscopic pictures from Kollicoat SR 30 D-coated propranolol HCl pellets after 0.16, 0.5 and 1.5h in release medium (10% coating level). a-c) sugar cores and d-f) MCC cores.

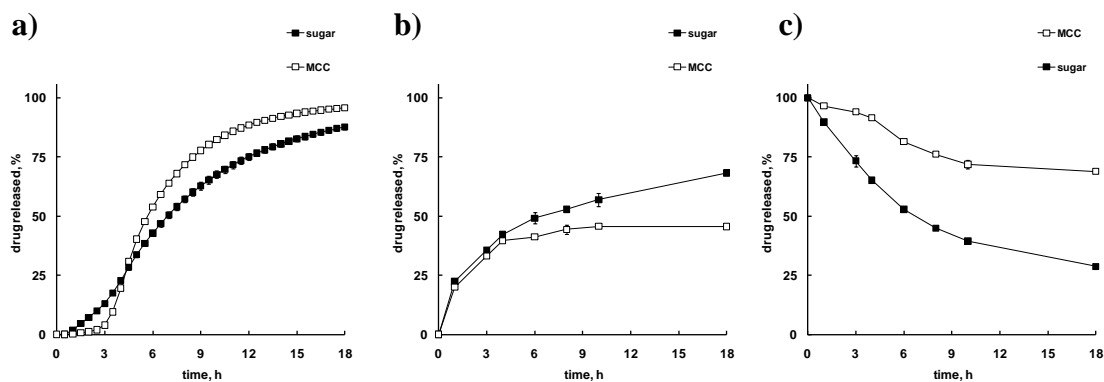


Figure 35: Effect of core type (sugar vs. MCC cores) on: a) drug release, b) water uptake and c) weight loss from Eudragit NE 30D-coated propranolol HCl pellets (10% coating level).

Eudragit NE 30 D-coated sugar cores showed a smaller lag time when compared with coated MCC cores, despite similar initial water uptake rate (Figure 35a and b). During

water penetration in coated sugar cores, sucrose and drug dissolved and osmotic pressure was build up until coating's mechanical stability was not exceed. Coating ruptures were formed and drug release occurred through these cracks (Figure 36b). In case of coated MCC cores, after water penetration, water distributed first within in the amorphous parts of MCC cores and afterwards swelling occurred. In case of coated sugar cores, drug release was a function of the osmotic pressure gradient and the slowing nature of the dissolution curve indicated that the osmotic pressure inside the core was equalized and there was no driver for the drug release. In contrast coated MCC cores resulted in a stepper curve due to greater internal stress generated in the coating (Figure 35a). The weight loss was higher from coated sugar cores than MCC cores due to sucrose release.

In conclusion, Eudragit NE 30 D coating could withstand longer and/or better to MCC swelling in comparison with osmotic pressure developed by sucrose dissolution, consequently lag time is shorter for coated sugar cores. On the other hand, drug release rate was faster and more complete from coated MCC cores than coated sugar cores (release curve from coated MCC cores was more sigmoidal –steeper, than coated sugar cores – smoother). This was due to a decrease in osmotic pressure difference between the coating (inside of coated pellets) and bulk solution and the swelling force generated by MCC that compensated for the loss of osmotic pressure.

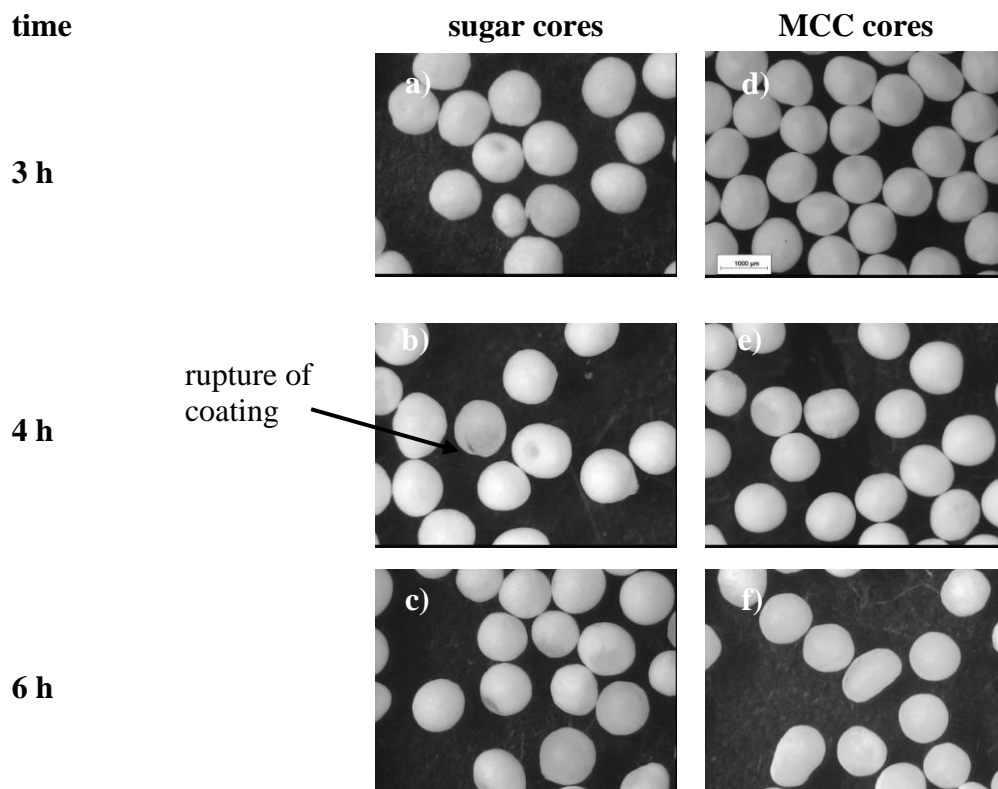


Figure 36: Macroscopic pictures from Eudragit NE 30 D-coated propranolol HCl pellets after 3, 4 and 6h in release medium (10% coating level). a-c) sugar cores and d-f) MCC cores.

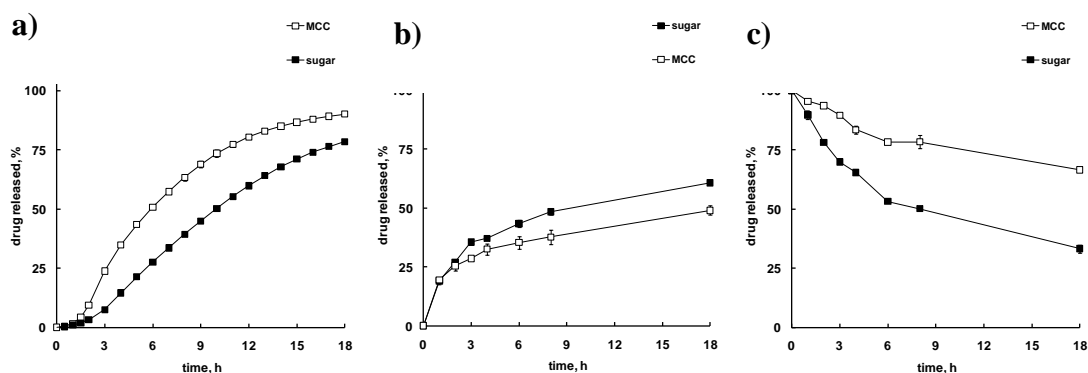


Figure 37: Effect of core type (sugar vs. MCC cores) on: a) drug release, b) water uptake and c) weight loss from organic ethylcellulose solution-coated propranolol HCl pellets (10% coating level).

Organic ethylcellulose coated pellets showed a similar lag time for both coated cores and similar water penetration rate and extent (Figure 37a and b). Coating films from

organic ethylcellulose solution are brittle in nature, but strong and could resist to osmotic pressure and MCC swelling in the same manner. The weight loss was higher from coated sugar cores than MCC cores due to sucrose release (Figure 37c). On the other hand, the release rate from coated MCC cores was faster than coated sugar cores (swelling force of MCC cores compensated for the loss of osmotic pressure with time).

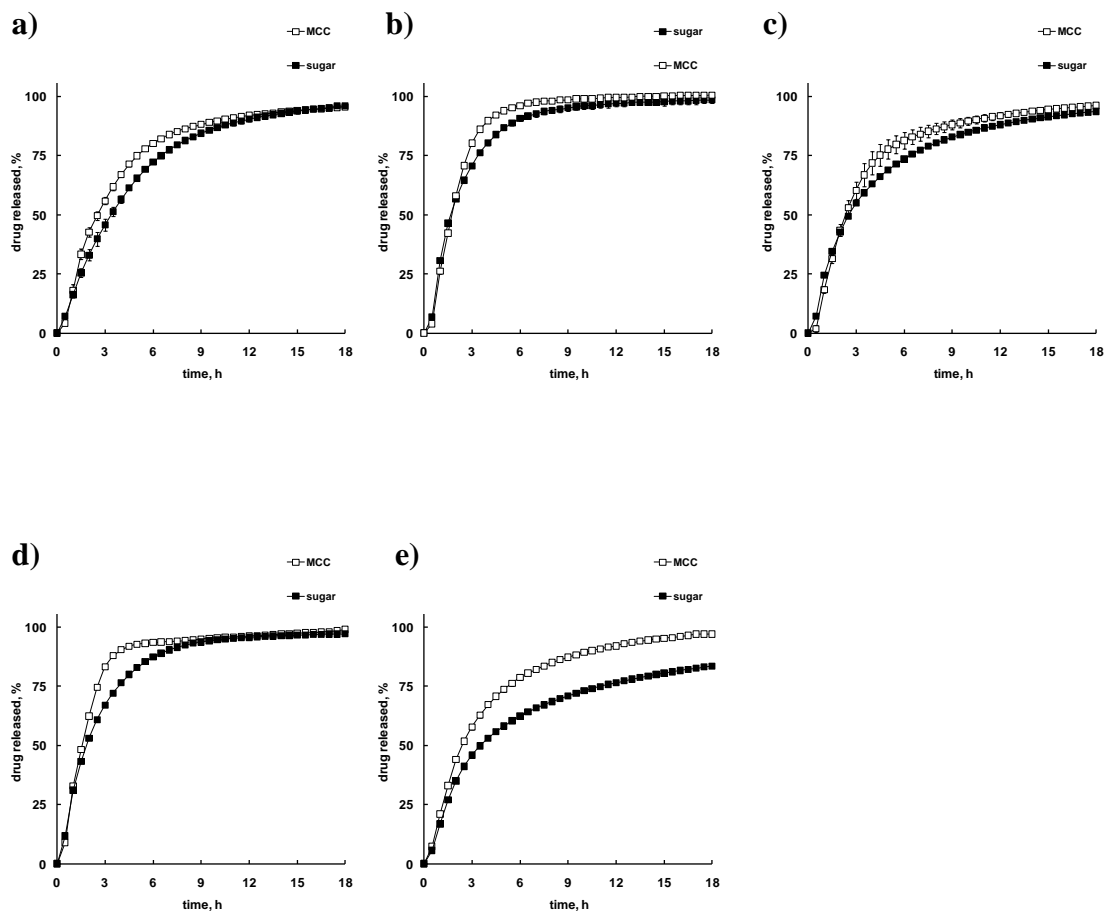


Figure 38: Effect of core type on metoprolol tartrate release from coated pellets (15% coating level). a) Kollicoat SR 30 D, b) Eudragit NE 30 D, c) Surelease, d) Aquacoat ECD and e) organic ethylcellulose solution.

Metoprolol tartrate release was very similar for both coated sugar and MCC cores (Figure 38a-e) with $47 < f_2 < 60$. In case of coated sugar cores, water penetration and osmotic pressure is controlled mainly by drug dissolution, since metoprolol tartrate solubility (~ 3.6 g/ml), is comparable to the solubility of sucrose (~ 2.3 g/ml). On the

other hand, with coated MCC cores, the contribution of water penetration/swelling of the MCC cores is probably reduced compared to drug layer hydration since drug is highly water soluble. Consequently, with both coated cores, drug solubility is driving force for release mechanism and core effect was reduced.

3.3 Curing effect

The effect of thermal curing (40°C and 60°C for 24h) and thermal/humidity curing (60°C/75% RH for 24h) was investigated for all coated pellets.

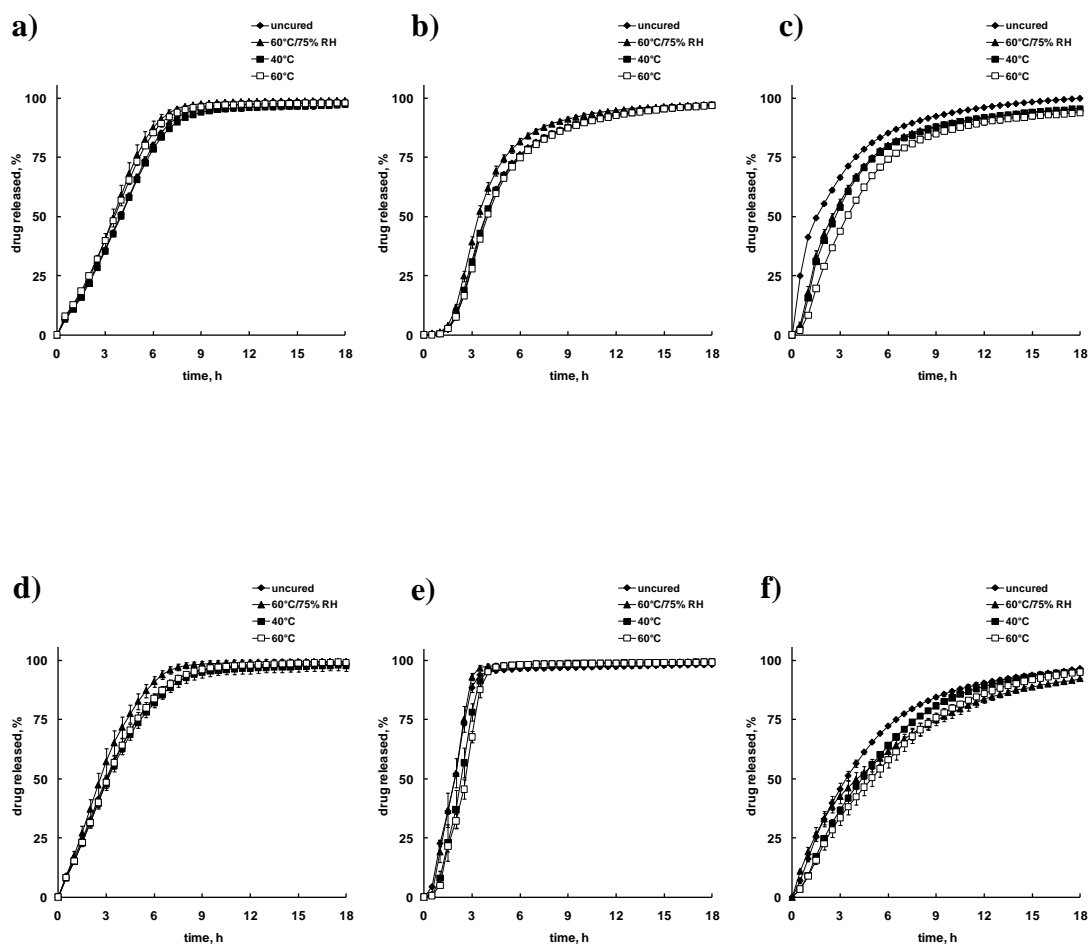


Figure 39: Curing effect (40°C, 60°C and 60°C/75% RH, for 24h) on drug release from Kollicoat SR 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

Drug release from Kollicoat SR 30 D-coated pellets showed minor changes upon curing at all conditions (Figure 39a-f). This was probably due to no further film formation

during curing. Kollicoat SR 30 D is an aqueous dispersion with low MFT ($\sim 5^{\circ}\text{C}$), when plasticized with 10% TEC. Thus, complete polymer particle coalescence is expected during coating process. In case of coated metoprolol pellets, drug release increased upon thermal/humidity curing due to drug dissolution and migration through the coating (Figure 39c and f). Metoprolol tartrate is hygroscopic in nature and could dissolve in the absorbed moisture, diffuse and resulting in a burst release. Metoprolol tartrate migration was common to all coatings (discussed in detail in section 3.4).

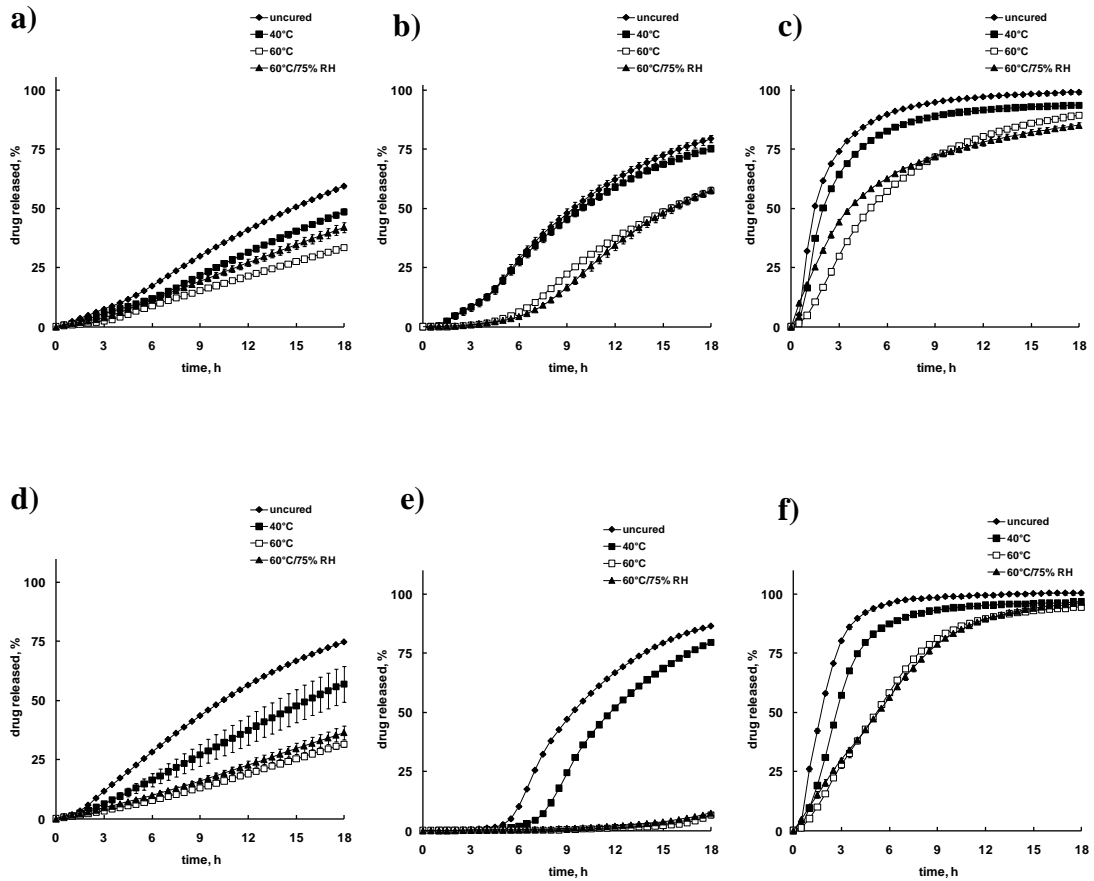


Figure 40: Curing effect (40°C, 60°C and 60°C/75% RH, for 24h) on drug release from Eudragit NE 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

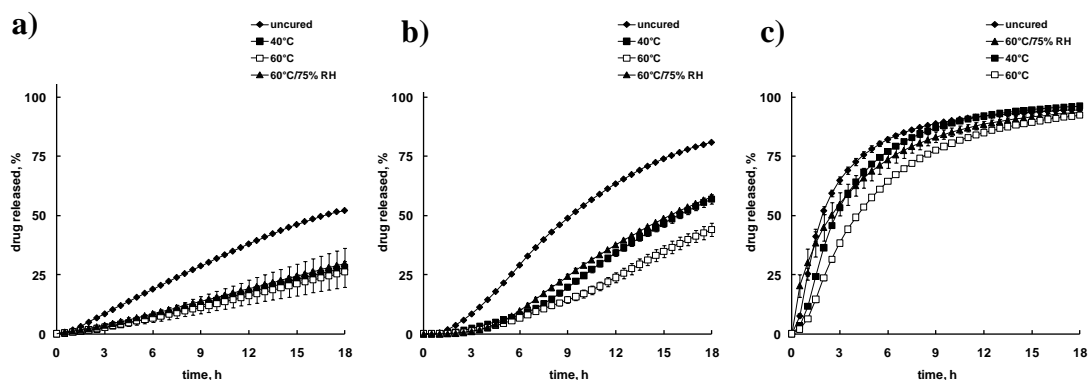


Figure 41: Curing effect (40°C, 60°C and 60°C/75% RH, for 24h) on drug release from Eudragit NM 30 D-coated sugar cores. a) paracetamol (10% coating level), b) propranolol HCl (15% coating level) and c) metoprolol tartrate (15% coating level).

Drug release from Eudragit NE 30 D- and Eudragit NM 30 D-coated pellets was extremely affected by curing temperature (Figure 40 and 41), although MFT of both aqueous dispersions is low as 5°C. Drug release from Eudragit NE 30 D- and Eudragit NM 30 D- coated pellets gradually decreased upon thermal curing at 40°C and 60°C. This was attributed to an increase in polymer particle coalescence with increasing curing temperature. Complete film formation was not achieved during coating process, probably due to low product temperature (19-20°C). On the other hand, thermal/humidity curing had no additional effect on drug release when compared with thermal curing. Consequently, it can be concluded that the presence of humidity did not enhance film formation in comparison with only heat.

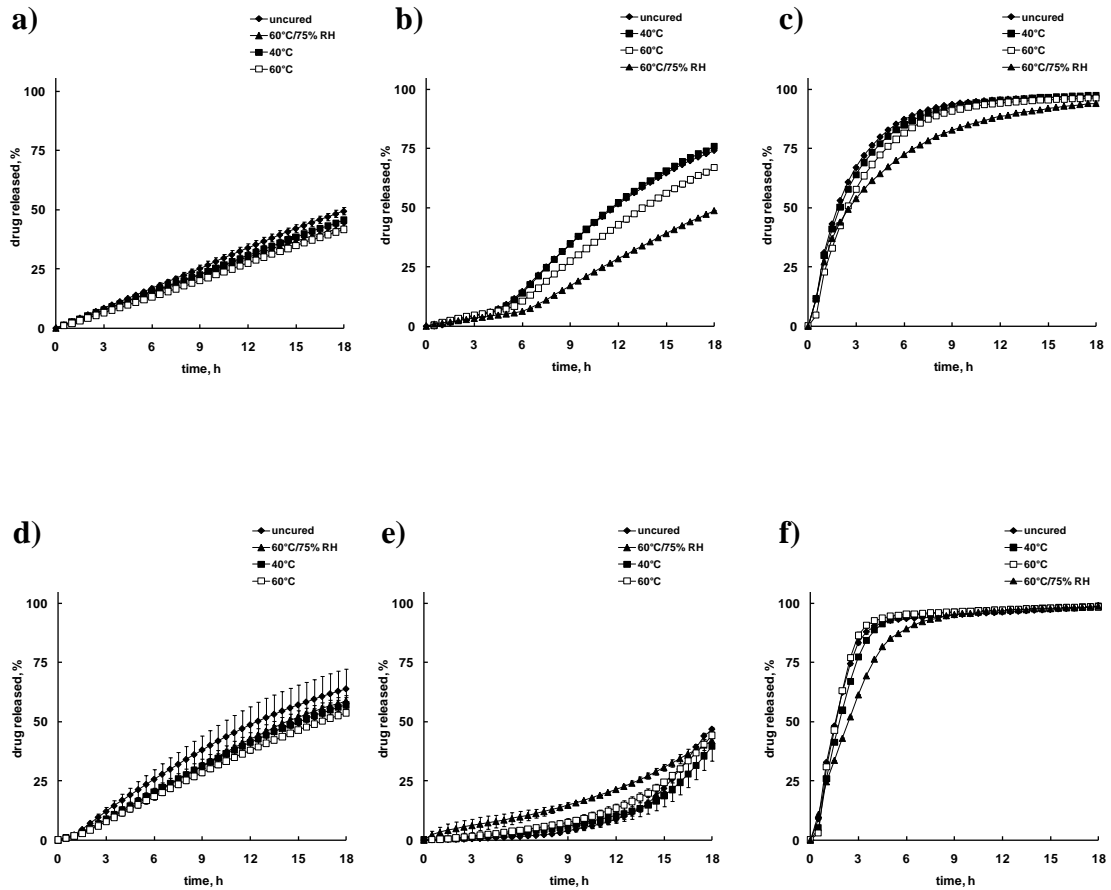


Figure 42: Curing effect (40°C, 60°C and 60°C/75% RH, for 24h) on drug release from Surelease-coated pellets a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

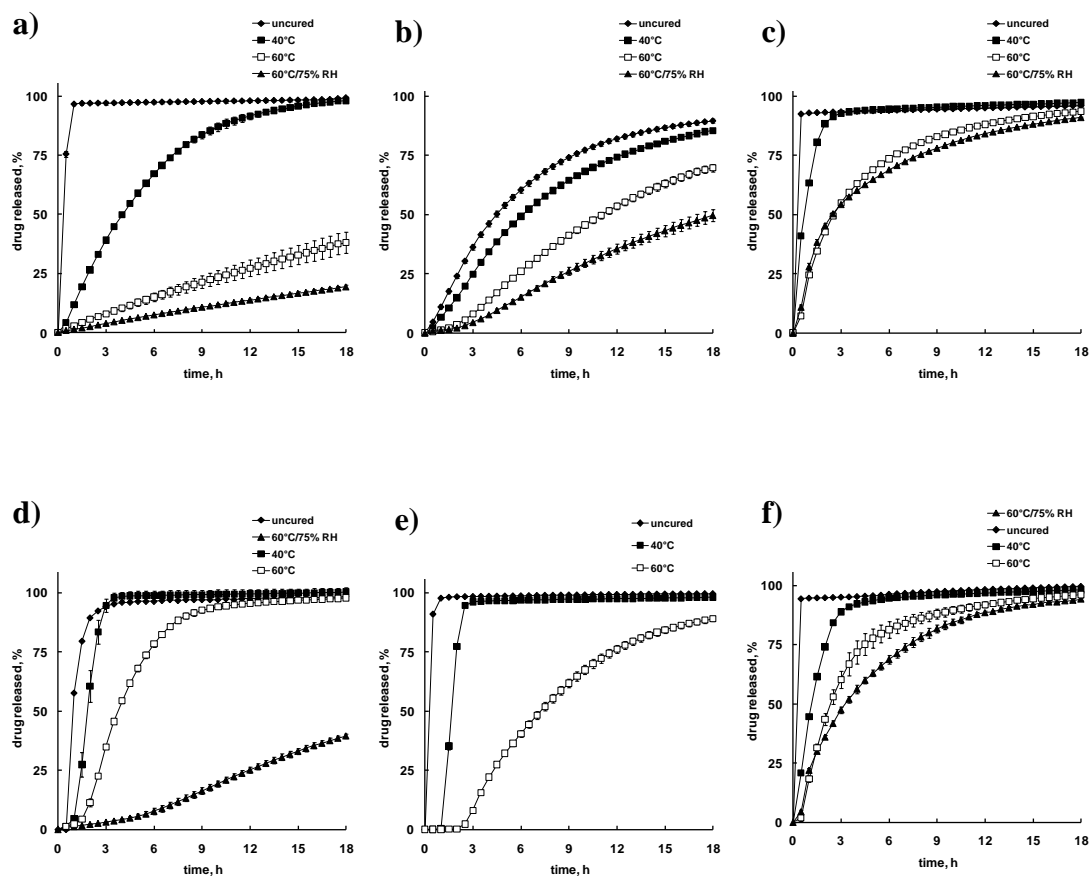


Figure 43: Curing effect (40°C, 60°C and 60°C/75% RH, for 24h) on drug release from Aquacoat ECD-coated pellets a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

Drug release from Surelease- and Aquacoat ECD-coated pellets (Figure 42 and 43) gradually decreased upon curing at 40°C, 60°C and 60°C/75% RH. Increasing temperature, increased polymer particle coalescence, the film became denser and drug release decreased. The presence of humidity further decreased drug release, since water within the film functions as plasticizer and increases ethylcellulose chain mobility, leading to a denser film and thus less permeable for water and drug.

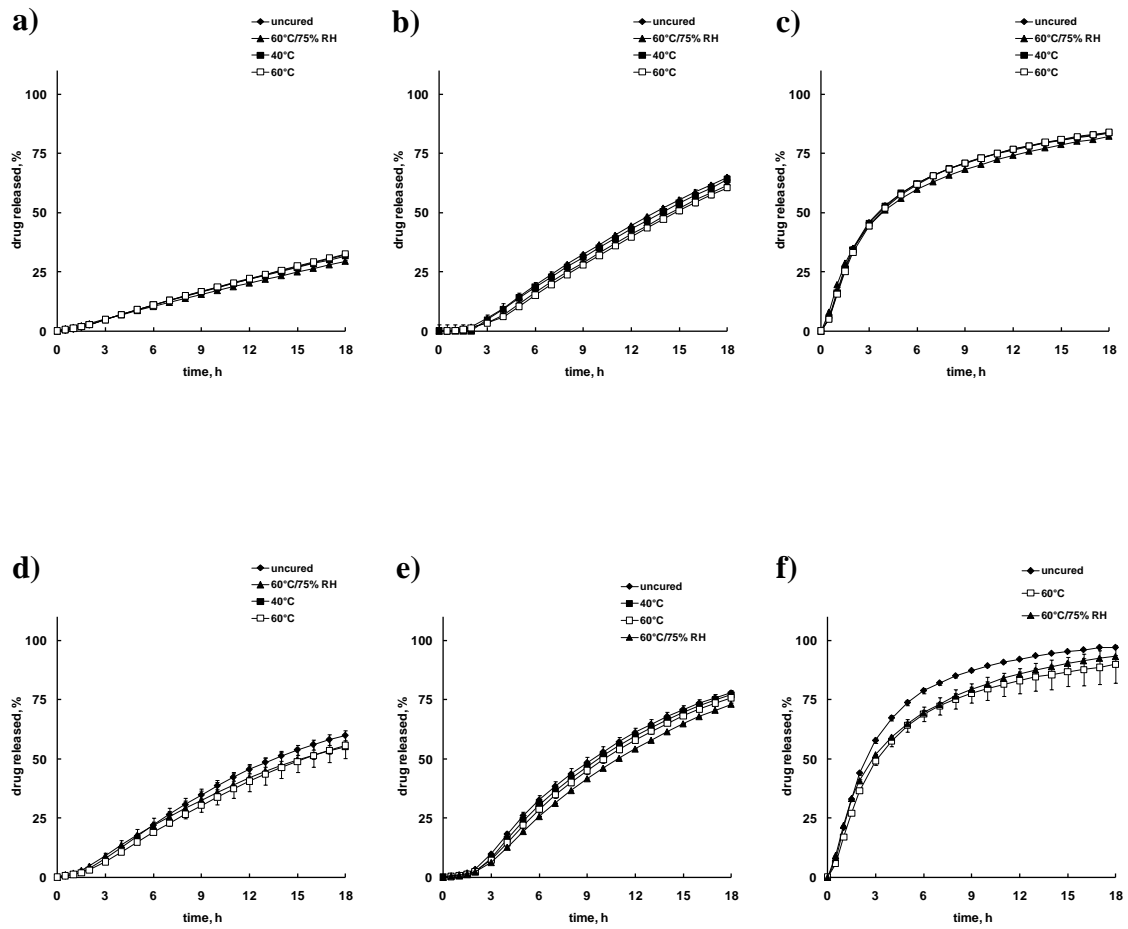


Figure 44: Curing effect (40°C, 60°C and 60°C/75% RH, for 24h) on drug release from organic ethylcellulose solution-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

As expected, curing had negligible effect on drug release from organic ethylcellulose solution-coated pellets (Figure 44a-f).

Table 4: Effect of curing conditions (60°C/75% RH, 60°C and 40°C for 24h) on f_2 similarity factor for coated sugar and MCC cores.

coatings	similarity factor, f_2																	
	60°C/75% RH				60°C				40°C									
	paracetamol	propranolol HCl	metoprolol tartrate	MCC	sugar	paracetamol	propranolol HCl	metoprolol tartrate	MCC	sugar	paracetamol	propranolol HCl	metoprolol tartrate	MCC	sugar			
Kollicoat SR 30D	61	62	56	80	47	54	67	94	91	37	51	46	95	86	95	44	86	56
Eudragit NE 30D	50	28	34	15	34	21	39	26	34	15	21	20	55	41	78	44	49	34
Eudragit NM 30D	37	n.d.	34	n.d.	53	n.d.	37	n.d.	26	n.d.	33	n.d.	38	n.d.	31	n.d.	50	n.d.
Surelease	63	63	38	53	45	40	63	53	59	75	53	74	77	60	95	74	78	59
Aquacoat ECD	3	6	19	n.d.	8	6	30	7	27	1	7	5	5	9	51	4	23	13
Organic ethylcellulose	87	77	75	62	81	52	99	71	94	78	94	99	99	n.d.	83	87	99	n.d.

n.d. not determined

In conclusion:

- The extent of the thermal curing, calculated based on f_2 similarity factor (Table 4), was in the following order: Aquacoat ECD >> Eudragit NE 30 D = Eudragit NM 30 D > Surelease > Kollicoat SR 30 D > organic ethylcellulose solution.
- Curing effect:
 - Negligible on drug release from Kollicoat SR 30 D- and organic ethylcellulose-coated pellets, similar f_2 similarity factors were obtained at 40°C, 60°C and 60°C/75% RH for 24h (Table 4).
 - Decrease drug release from Eudragit NE 30 D- and Eudragit NM 30 D-coated pellets upon thermal curing, however thermal/humidity curing had not additional effect compared to thermal curing ($f_2, 40^\circ\text{C} > f_2, 60^\circ\text{C} \sim f_2, 60^\circ\text{C}/75\% \text{ RH}$) (Table 4).
 - Decrease drug release from Surelease- and Aquacoat ECD- coated pellets upon thermal curing and further decrease upon thermal/humidity curing ($f_2, 40^\circ\text{C} > f_2, 60^\circ\text{C} > f_2, 60^\circ\text{C}/75\% \text{ RH}$) (Table 4).
- Kollicoat SR 30 D-coated pellets showed no curing effect in contrast with Eudragit NE 30 D- and Eudragit NM 30 D-coated pellets which demonstrated strong curing effect, although all aqueous dispersion have low MFT (5°C). This could be attributed to different coating temperatures for Kollicoat SR 30 D (28-30°C) and Eudragit NE 30 D and Eudragit NM 30 D (19-20°C) coated pellets. With Kollicoat SR 30 D, film formation occurred in the coating chamber, whereas Eudragit NE 30 D and Eudragit NM 30 D required the curing step in order to further continue film formation.
- The curing mechanism was independent of drug and core type. When a curing step is applied after the coating process, continuous film formation is the predominant mechanism, in which the type of drug and core contribute to a less extent. The only deviation was the metoprolol tartrate migration through the coating upon curing at 60°C/75% RH, resulting in a burst release. The burst was more pronounced with coated sugar cores than MCC cores, due to higher moisture uptake from coated sugar cores after thermal/humidity curing (Table 5) (discussed in detail in section 3.4)

Table 5: Moisture uptake (based on total weight) upon 60°C/75%RH during 24h for uncoated and coated paracetamol and metoprolol tartrate sugar and MCC cores (\pm , standard deviation)

core	drug	coating	moisture uptake, %	
			60°C/75% RH	
sugar	unloaded	-	0.4 \pm 0.0	
	paracetamol	uncoated	0.4 \pm 0.1	
		Kollicoat SR 30 D	< 1	
		Eudragit NE 30 D		
		Surelease		
		uncoated	8.9 \pm 0.2	
		metoprolol tartrate	Kollicoat SR 30 D	~ 8.0
	Eudragit NE 30 D			
	Surelease			
	MCC	unloaded	-	1.9 \pm 0.0
		paracetamol	uncoated	1.3 \pm 0.0
			Kollicoat SR 30 D	< 1
Eudragit NE 30 D				
Surelease				
uncoated			4.8 \pm 0.0	
metoprolol tartrate			Kollicoat SR 30 D	5-6
		Eudragit NE 30 D		
		Surelease		

3.4 Storage stability

Cured (Kollicoat SR 30 D, Eudragit NE 30 D, Eudragit NM 30 D, Surelease and Aquacoat ECD) and uncured (Kollicoat SR 30 D, Eudragit NE 30 D, Eudragit NM 30 D and organic ethylcellulose) coated pellets were stored 40°C/75% RH, RT/60% RH and 40°C for 1 and 3 months. Storage of uncured aqueous coated pellets was also studied in order to investigate whether a curing step is required for low MFT aqueous dispersions.

3.4.1 Uncured Kollicoat SR 30 D

40°C/75% RH

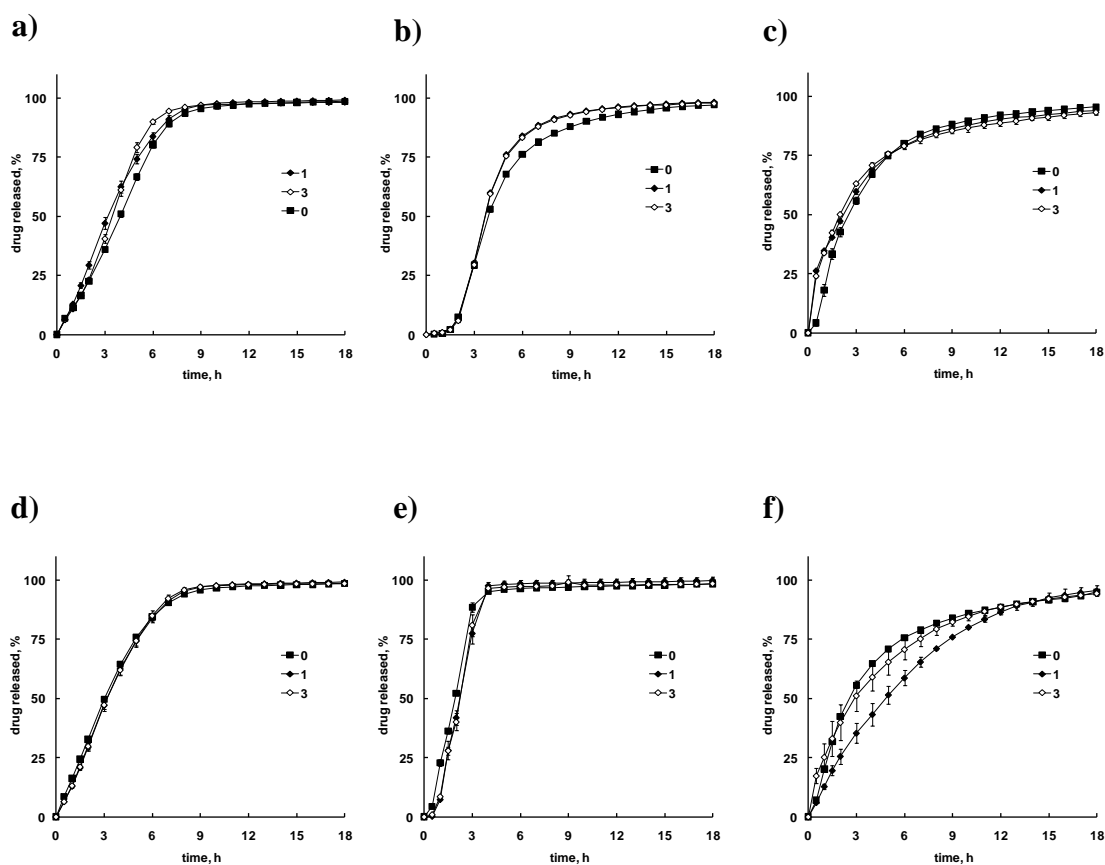


Figure 45: Effect of storage (40°C/75% RH, 1 and 3 months) on drug release from uncured Kollicoat SR 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

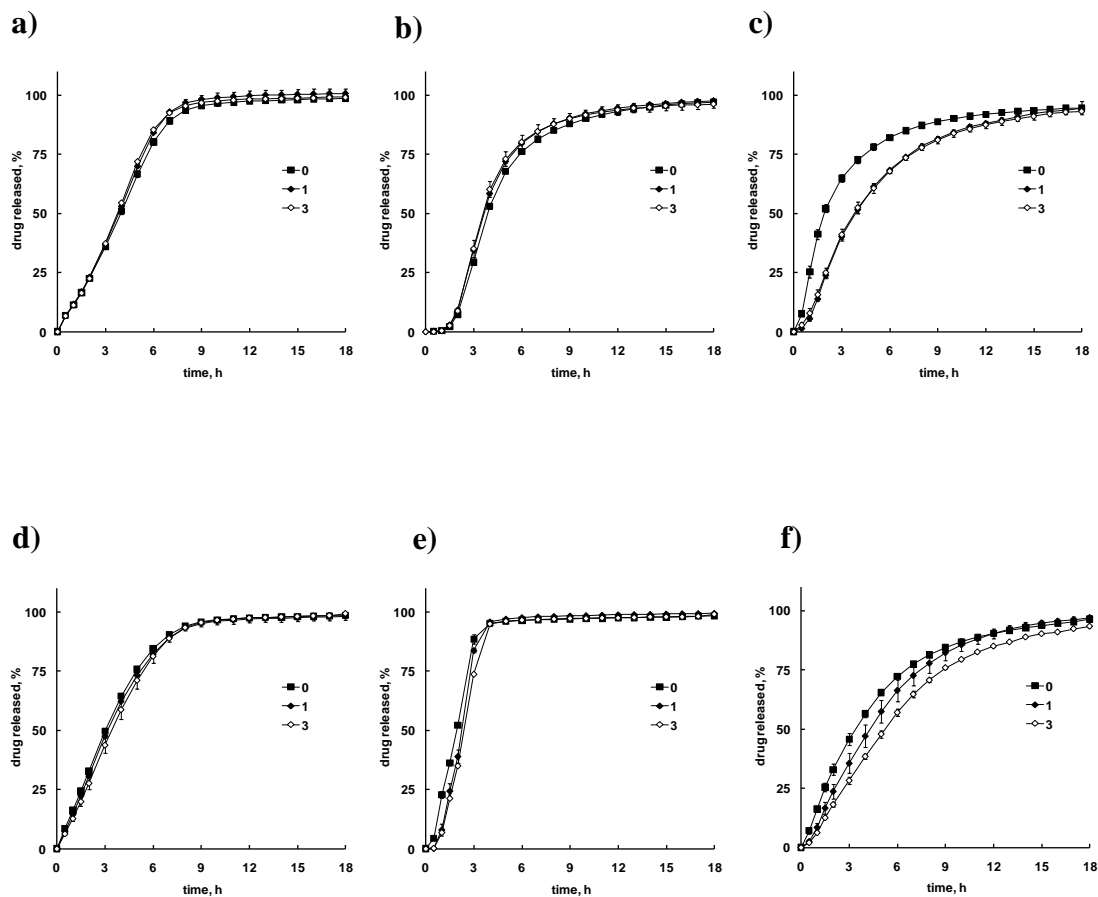
RT/60% RH

Figure 46: Effect of storage (RT/60% RH, 1 and 3 months) on drug release from uncured Kollicoat SR 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

40°C

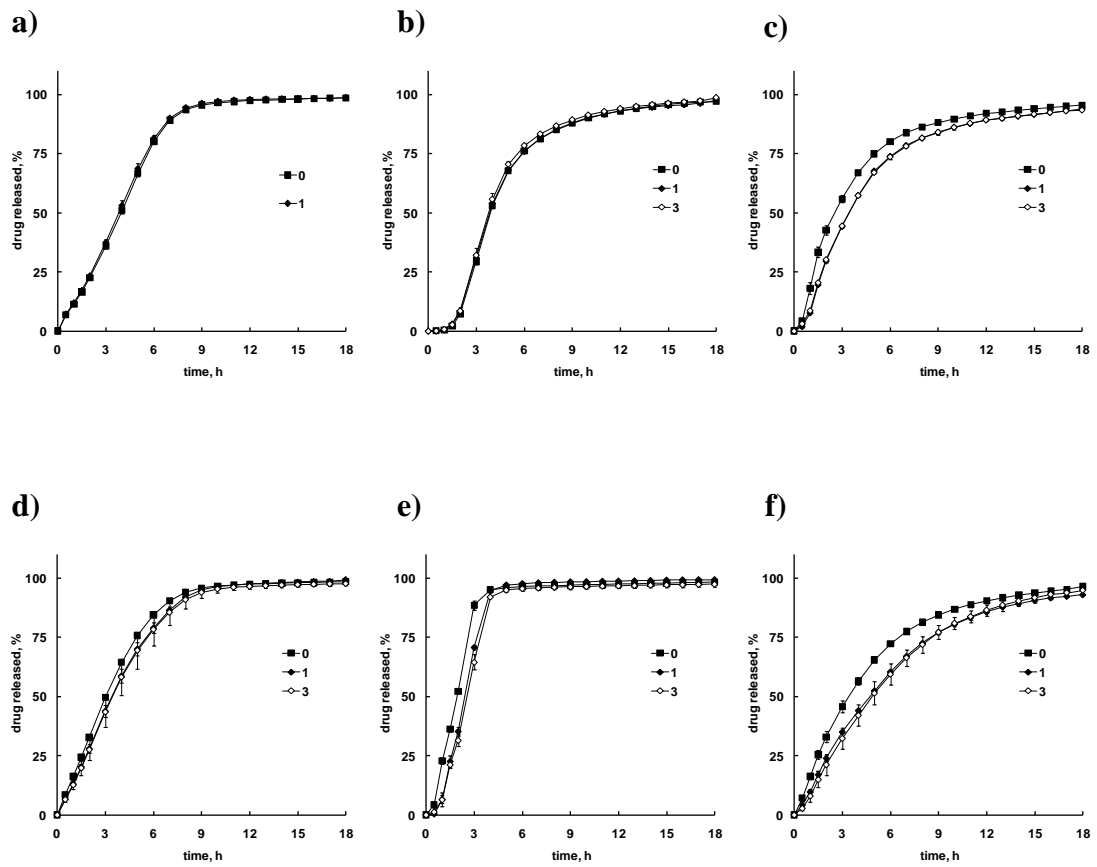


Figure 47: Effect of storage (40°C, 1 and 3 months) on drug release from uncured Kollicoat SR 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

3.4.2 Cured Kollicoat SR 30 D

40°C/75%RH

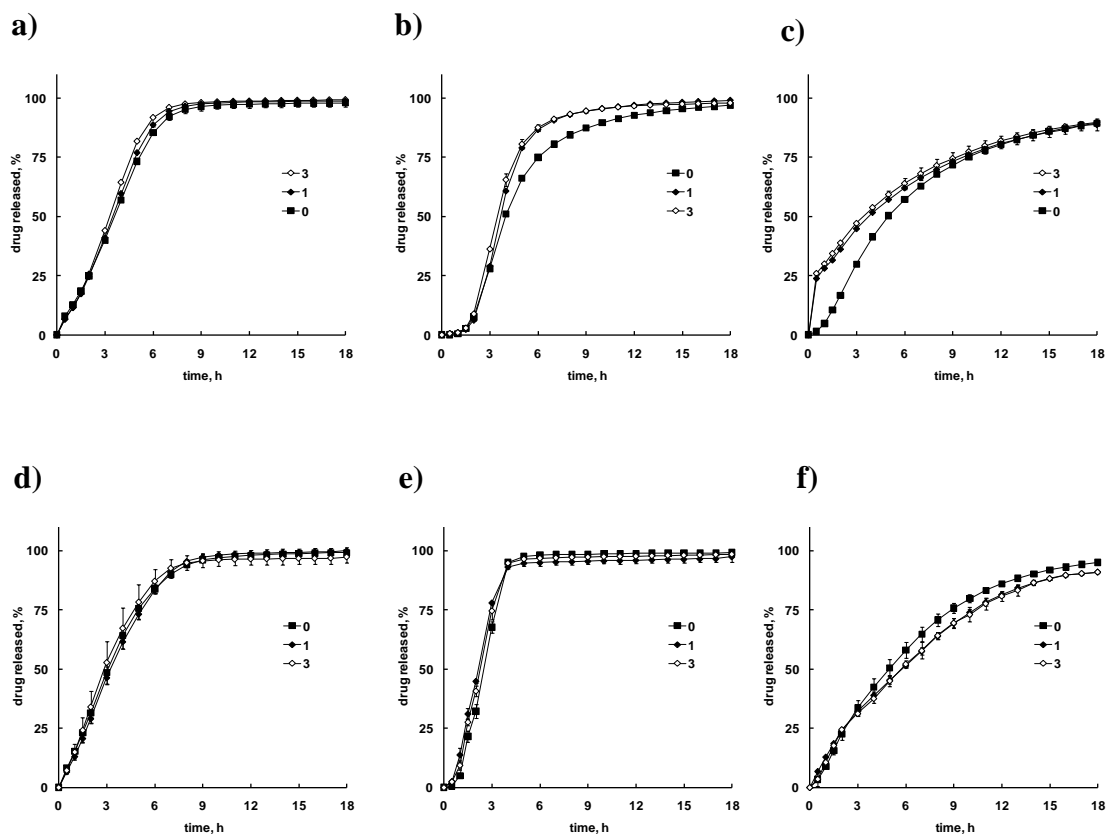


Figure 48: Effect of storage (40°C/75% RH, 1 and 3 months) on drug release from cured Kollicoat SR 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

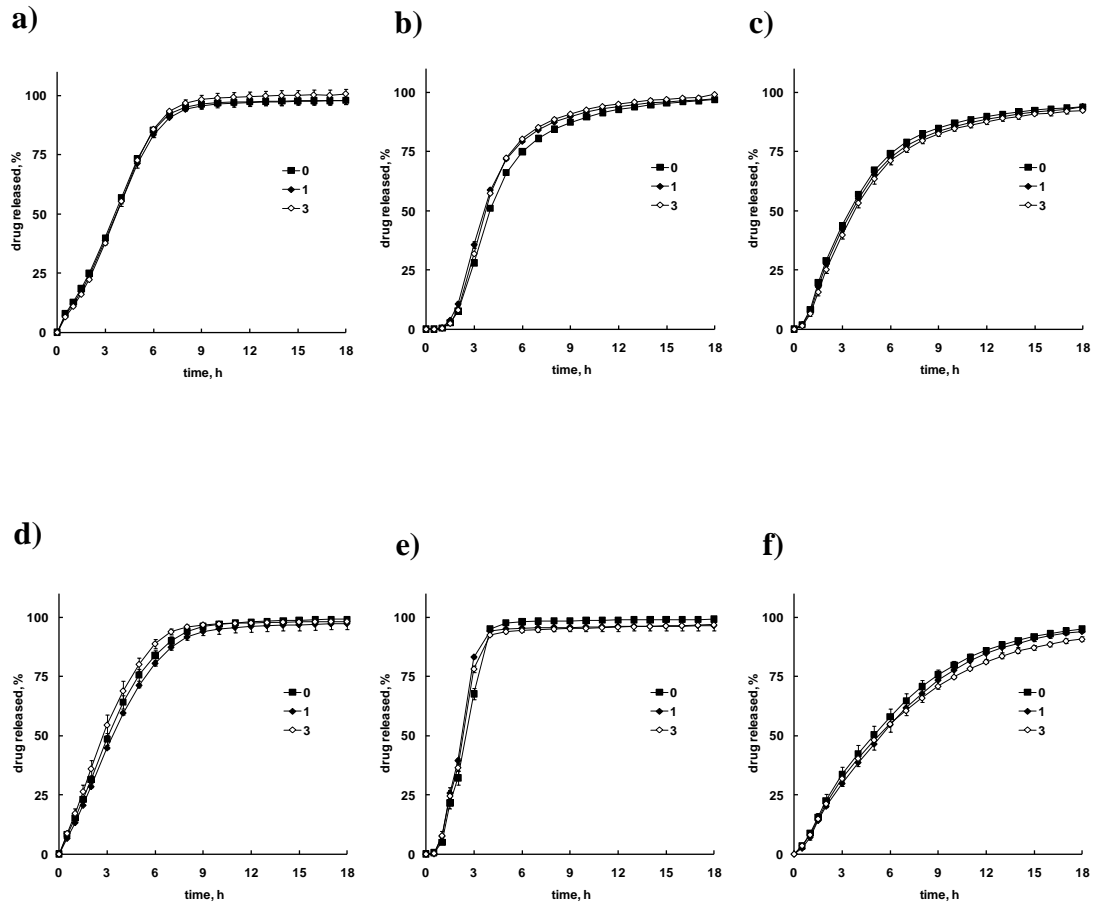
RT/60%RH

Figure 49: Effect of storage (RT/60% RH, 1 and 3 months) on drug release from cured Kollicoat SR 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

40°C

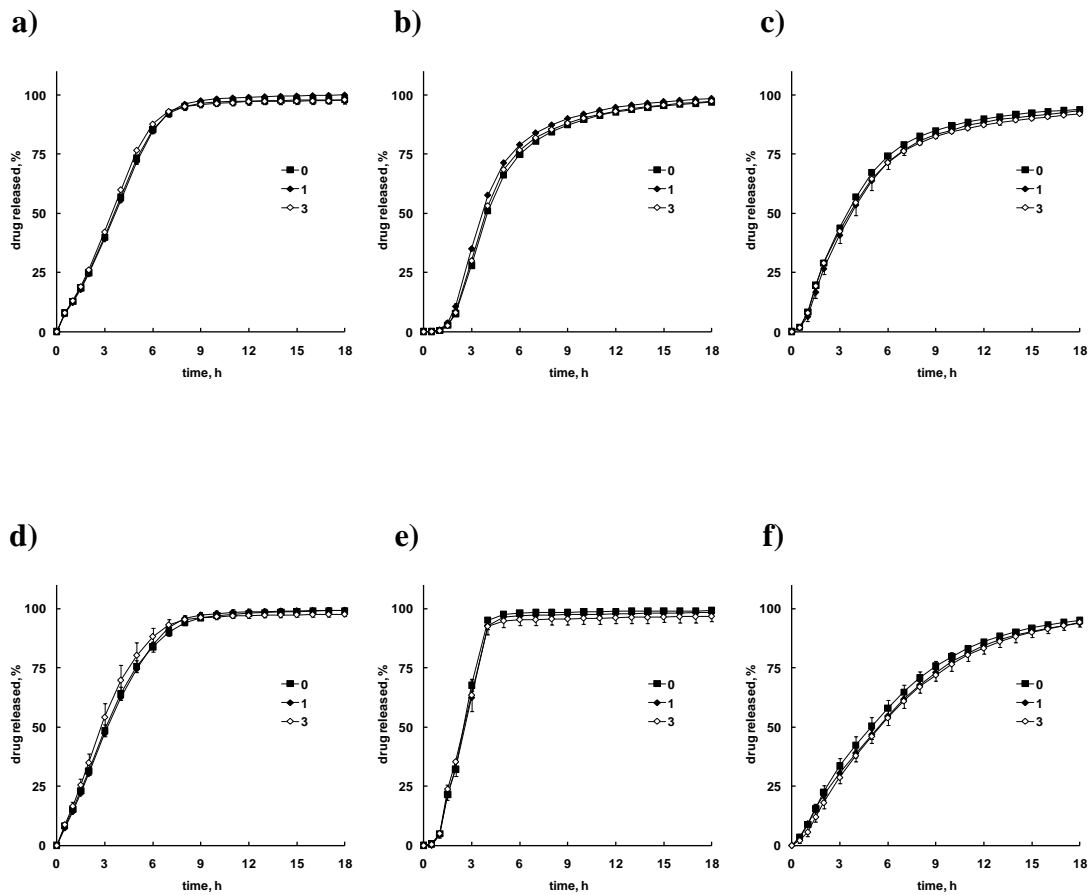


Figure 50: Effect of storage (40°C, 1 and 3 months) on drug release from cured Kollicoat SR 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

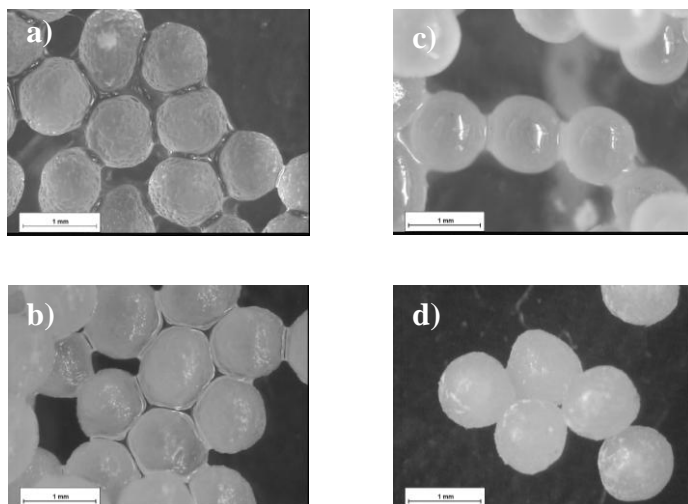


Figure 51: Macroscopic pictures from metoprolol tartrate loaded cores. a) uncoated sugar cores, b) uncoated MCC cores, c) uncured Kollicoat SR 30 D-coated sugar cores and d) uncured Kollicoat SR 30 D-coated MCC cores after 1 month storage at 40°C/75% RH.

Uncured and cured Kollicoat SR 30 D coated pellets showed minor changes upon storage at all conditions (Figures 45-50). This indicated that film formation was completed during the coating process, with no further changes upon storage (as expected from curing studies). The exceptions were uncured and cured Kollicoat SR 30 D-coated-metoprolol tartrate pellets showing a burst release upon storage at 40°C/75% RH (Figure 45 and 48, c and f). This was due to drug dissolution and migration through the coating (Figure 51a-d). The burst was more pronounced with sugar cores than MCC cores due to the higher moisture uptake from coated sugar cores than from coated MCC cores (15% and 5% for uncured coated pellets, respectively). The moisture uptake from metoprolol tartrate-layered sugar cores (uncoated) was extremely high (~31%), resulting in dissolution of drug and sucrose. This was due to a lowering of critical relative humidity for deliquescence to occur of sugar and/or metoprolol tartrate. When two hygroscopic substances are in contact, the relative humidity at which deliquescence occurs is lower than for any of the individual components (Mauer and Taylor). This lowering in the critical relative humidity is even more critical when temperature is increased. Probably the critical relative humidity for both substances decreased,

resulting in a very high moisture uptake and drug dissolution / migration through the coatings. On the other hand, moisture uptake from metoprolol tartrate-layered MCC cores was around 4.7%. With less moisture, less amount of drug dissolved and diffused through the coating resulting in less changes in drug release profile. The difference between moisture uptake from metoprolol tartrate-layered sugar and MCC cores was related with the enhanced dissolution of metoprolol tartrate in presence of sugar. In addition, the drug dissolution and migration was just evident upon storage at 40°C/75% RH and not at RT/60% RH (Figure 45, 46, 48 and 49, c and f). These results correlate very well with the difference in moisture uptake from metoprolol tartrate cores at both conditions. Moisture uptake from metoprolol tartrate sugar cores was 31.1% and 0.7% at 40°C/75% RH and RT/60% RH, respectively. It can be concluded that metoprolol tartrate migration was enhanced in the presence of heat and humidity. Moreover, metoprolol tartrate dissolution and migration was also enhanced if the sugar core was used. Metoprolol tartrate migrated through all coatings during storage at 40°C/75% RH. The extent of drug migration through the coatings varied with core and coating type and uncured/cured coated pellets.

3.4.3 Uncured Eudragit NE 30 D

40°C/75%RH

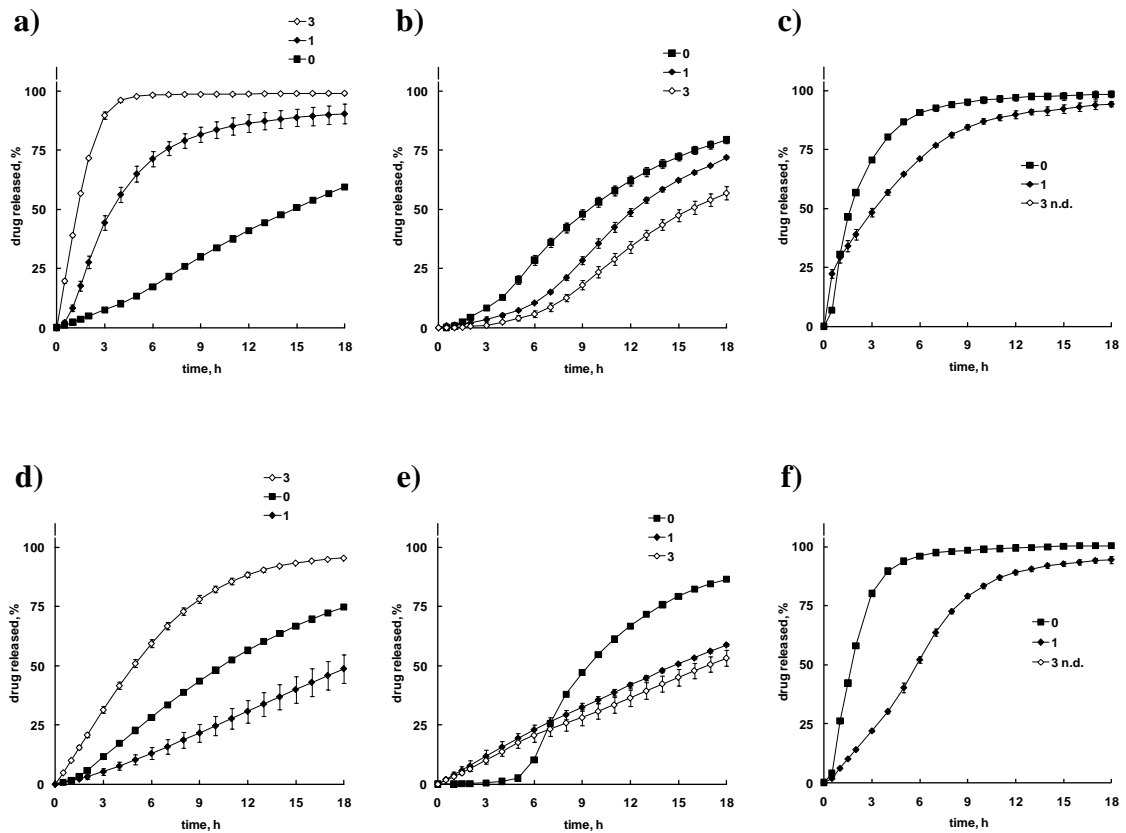


Figure 52: Effect of storage (40°C/75% RH, 1 and 3 months) on drug release from uncured Eudragit NE 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

RT/60%RH

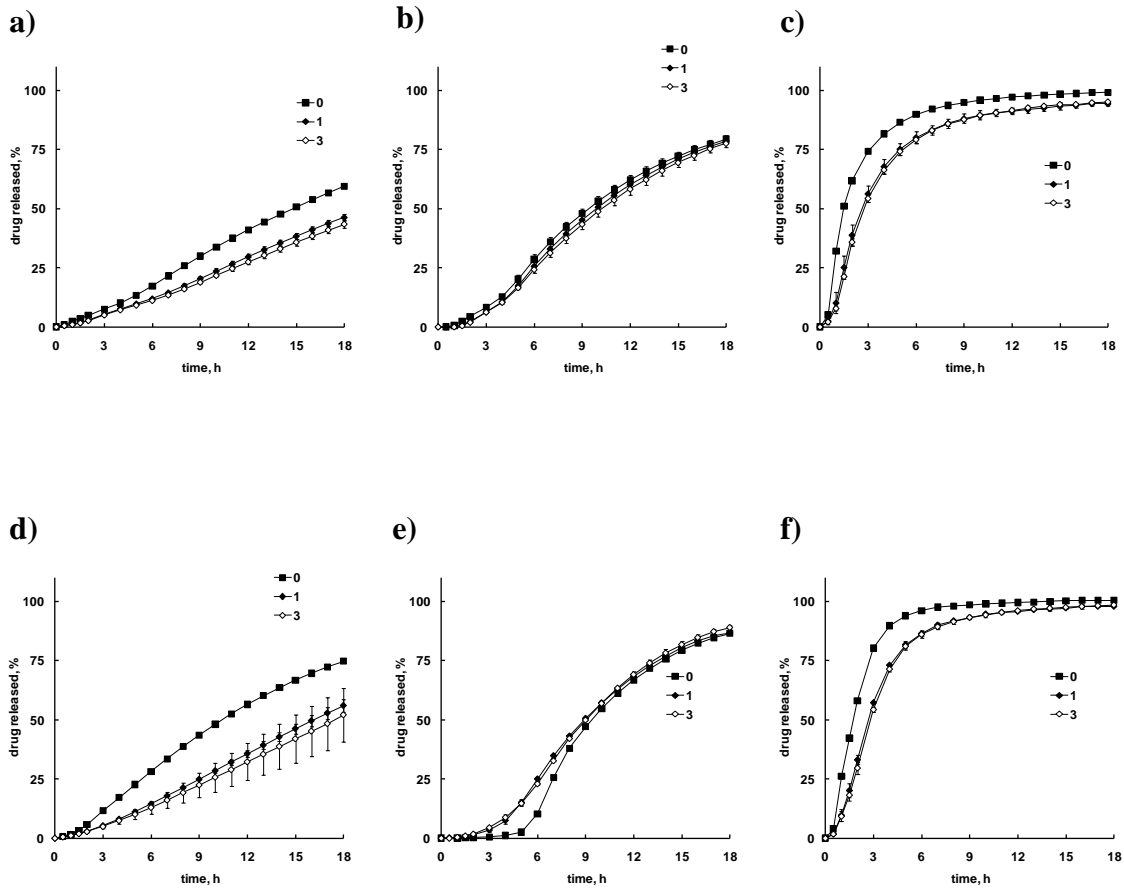


Figure 53: Effect of storage (RT/60 RH, 1 and 3 months) on drug release from uncured Eudragit NE 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

40°C

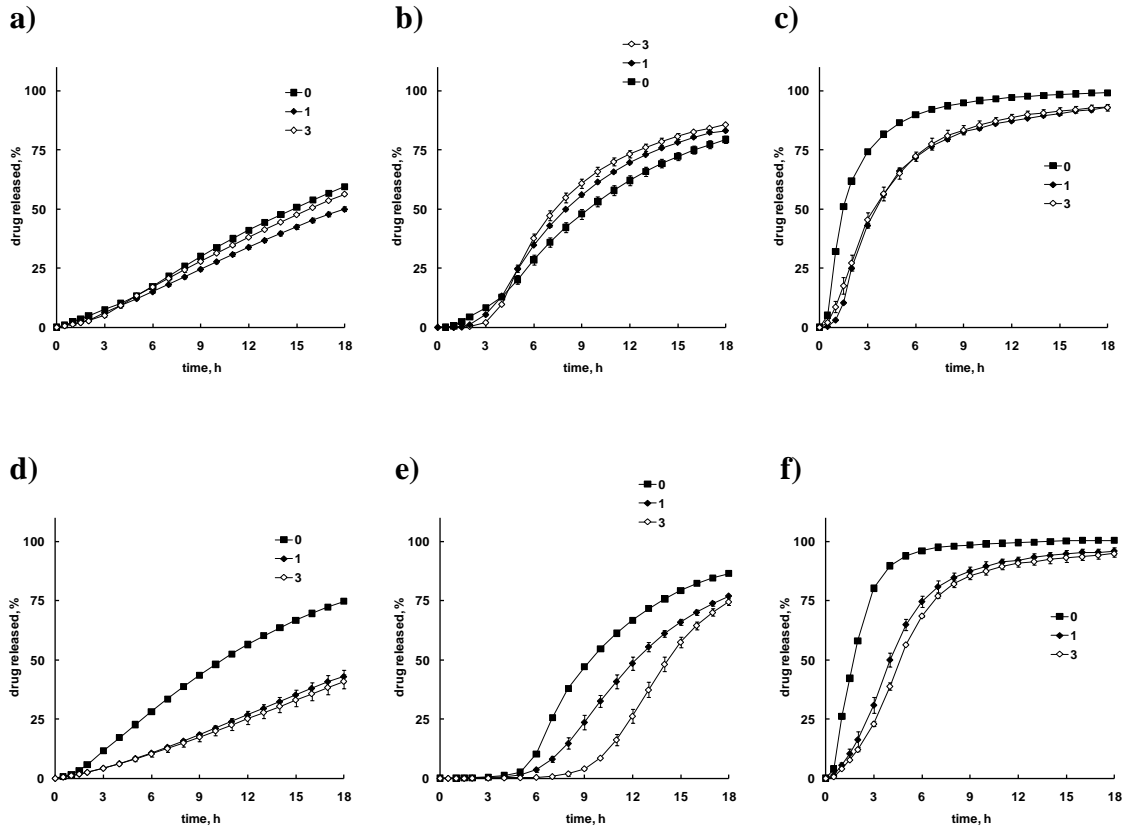


Figure 54: Effect of storage (40°C, 1 and 3 months) on drug release from uncured Eudragit NE 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

3.4.4 Cured Eudragit NE 30 D

40°C/75 RH

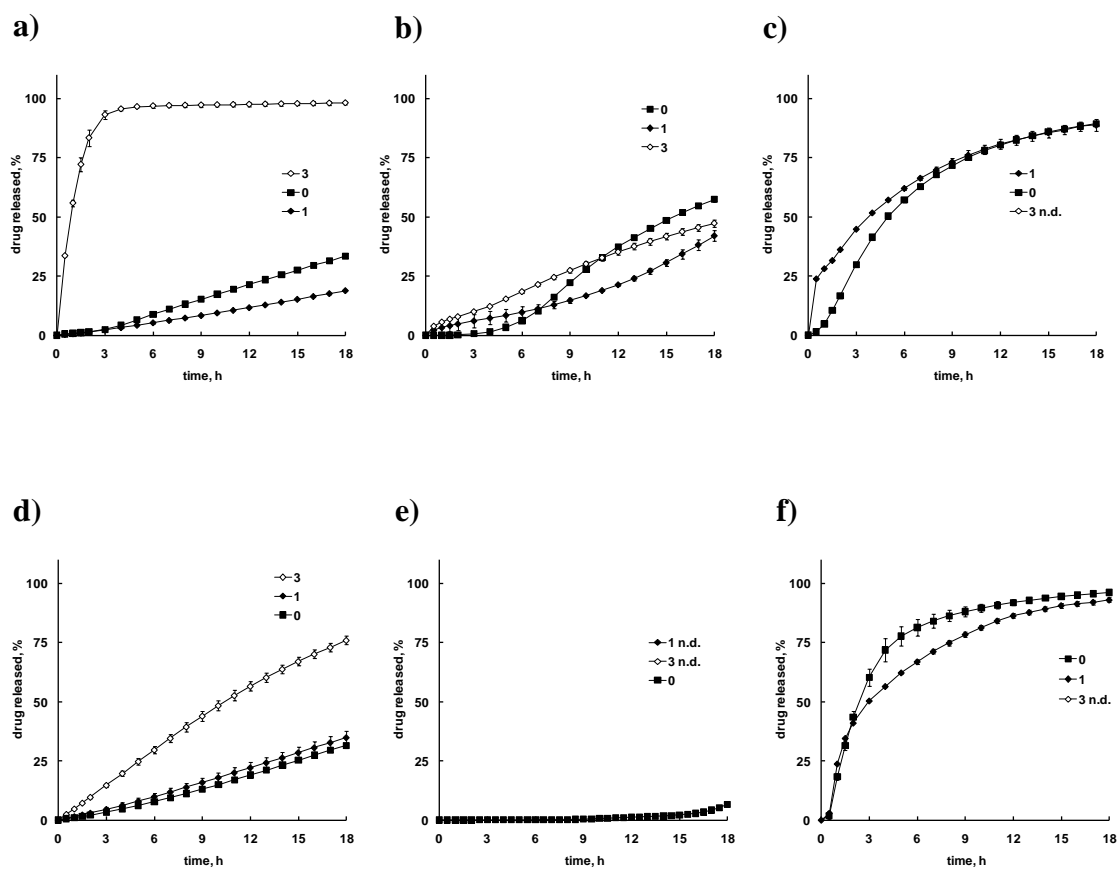


Figure 55: Effect of storage (40°C/75% RH, 1 and 3 months) on drug release from cured Eudragit NE 30 D-coated pellets a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

RT/60% RH

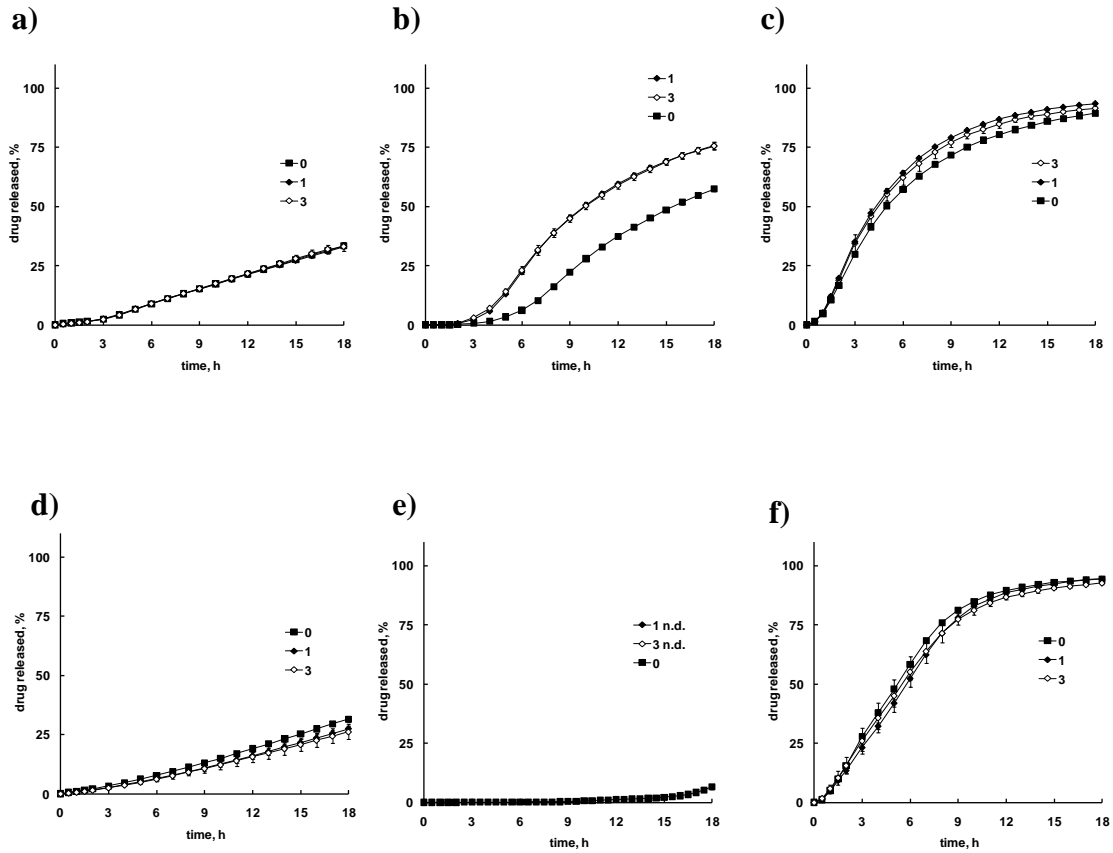


Figure 56: Effect of storage (RT/60% RH, 1 and 3 months) on drug release from cured Eudragit NE 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

40°C

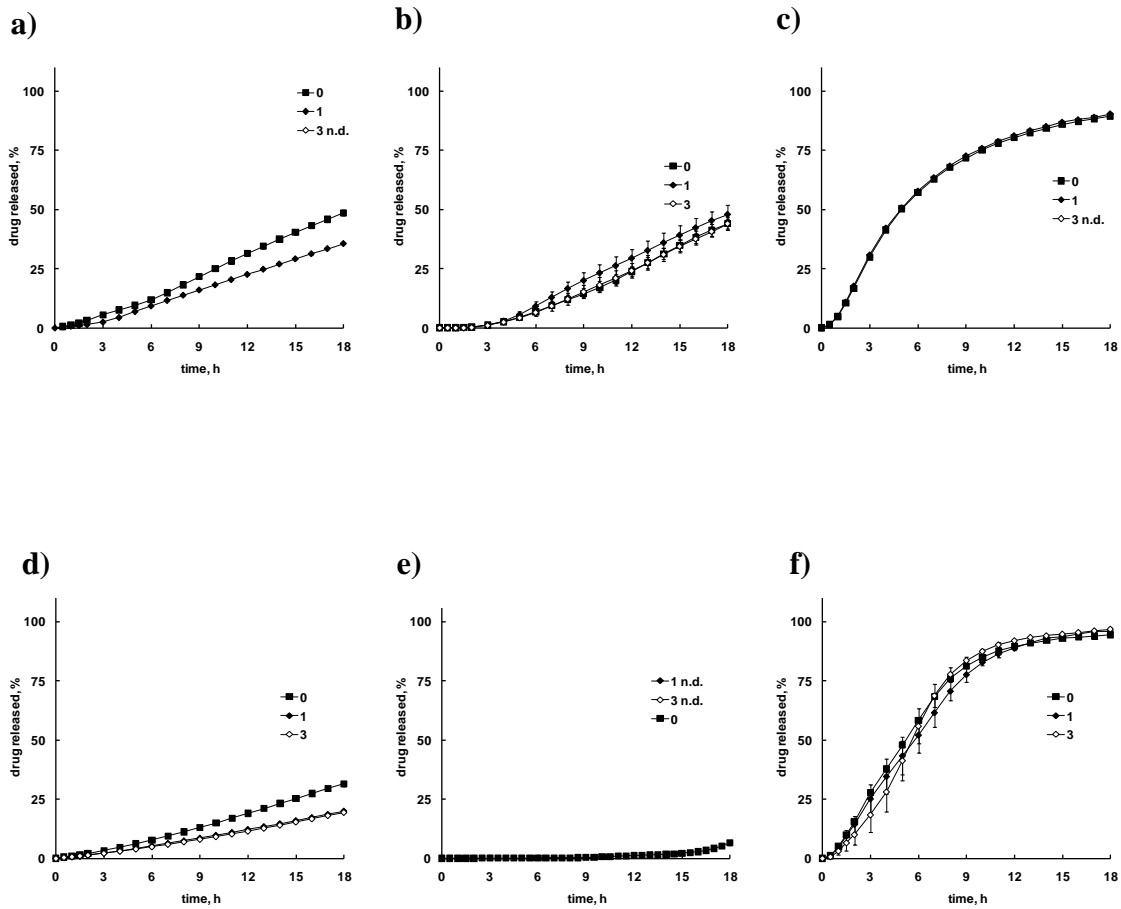


Figure 57: Effect of storage (40°C, 1 and 3 months) on drug release from cured Eudragit NE 30 D-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

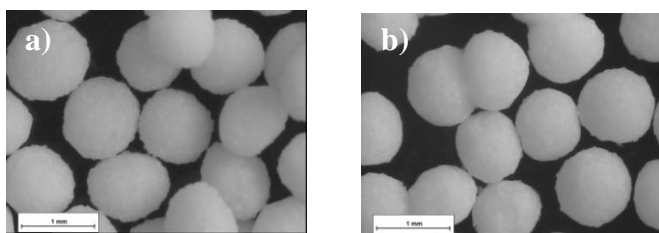


Figure 58: Macroscopic pictures from uncured Eudragit NE 30 D-coated paracetamol pellets after storage at 40°C/75% RH, for 3 months. a) sugar cores and b) MCC cores.

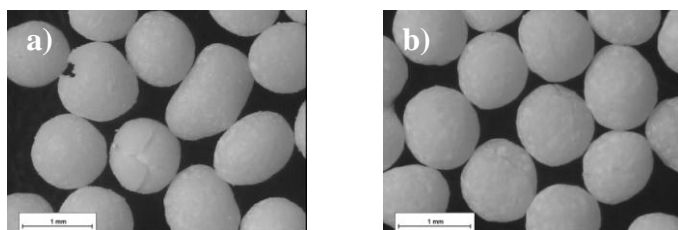


Figure 59: Macroscopic pictures from Eudragit NE 30 D-coated propranolol HCl pellets after storage at 40°C/75% RH, for 3 months. a) cured coated sugar cores and b) uncured coated MCC cores.

Storage stability of uncured and cured Eudragit NE 30 D-coated pellets was highly dependent on storage conditions, drug and core type. Upon storage at 40°C/75% RH, migration of the surfactant (Nonoxynol-100) resulted in an increase in paracetamol release from uncured and cured coated pellets with time (Figures 52 and 55, a and d). Macroscopic pictures from coated paracetamol sugar and MCC cores, after 3 months storage showed an irregular surface appearance due to surfactant deposition at the pellet surface (Figure 58). The surfactant's migration and its influence on drug release are well described in literature (Lin et al., 2001; Lin et al., 2003). The rate and extent of surfactant's migration was different for uncured/cured coated pellets and coated sugar/MCC cores. These differences are probably attributed to different moisture uptake and moisture distribution in the coated systems and the occurrence of further gradual polymer particle coalescence. Propranolol HCl release from uncured coated sugar cores decreased gradually after 1 and 3 month storage (Figure 52b). This suggested

continuous film formation with further densification of coating film. On the other hand, a change in drug release mechanism (sigmoidal vs. zero order) upon storage was observed with uncured coated propranolol HCl MCC cores (Figure 52e). This was due to coating ruptures (Figure 59b) resulting from core swelling after storage with high humidity. In addition, propranolol HCl release from cured coated sugar cores also changed upon storage (Figure 55b) and this change was attributed, as well, to coating ruptures (Figure 59a). In contrast to 40°C/75% RH, storage of uncured and cured Eudragit NE 30 D-coated pellets at RT/60% RH and 40°C, resulted in less dramatic changes in drug release for all drugs and cores (Figures 53, 54, 56 and 57). In addition, cured coated pellets were more stable than uncured coated pellets and thus curing step is required. In general, upon storage at RT/60% RH and 40°C, drug release from uncured coated pellets decreased due to continuous film formation. In case of cured coated pellets, after storage at RT/60% RH and 40°C, stable release profiles were observed. Only propranolol HCl release from coated sugar cores increased after RT/60% RH and 40°C (Figure 56b and 57b).

3.4.5 Uncured Eudragit NM 30D

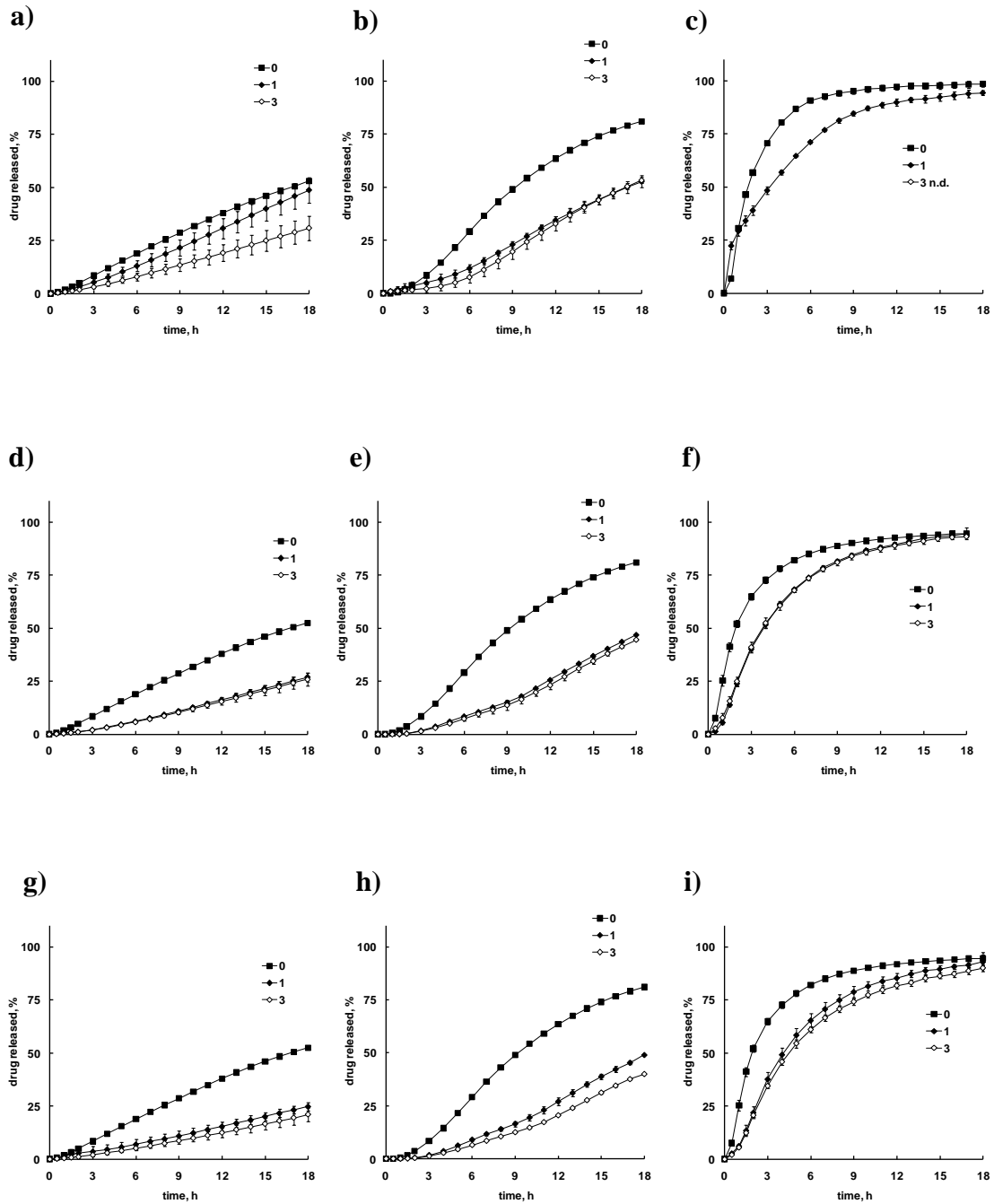


Figure 60: Effect of storage (1 and 3 months) on drug release from uncured Eudragit NM 30 D-coated sugar cores. a-c) 40°C/75% RH, d-f) RT/60% RH cores and g-i) 40°C. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

3.4.6 Cured Eudragit NM 30D

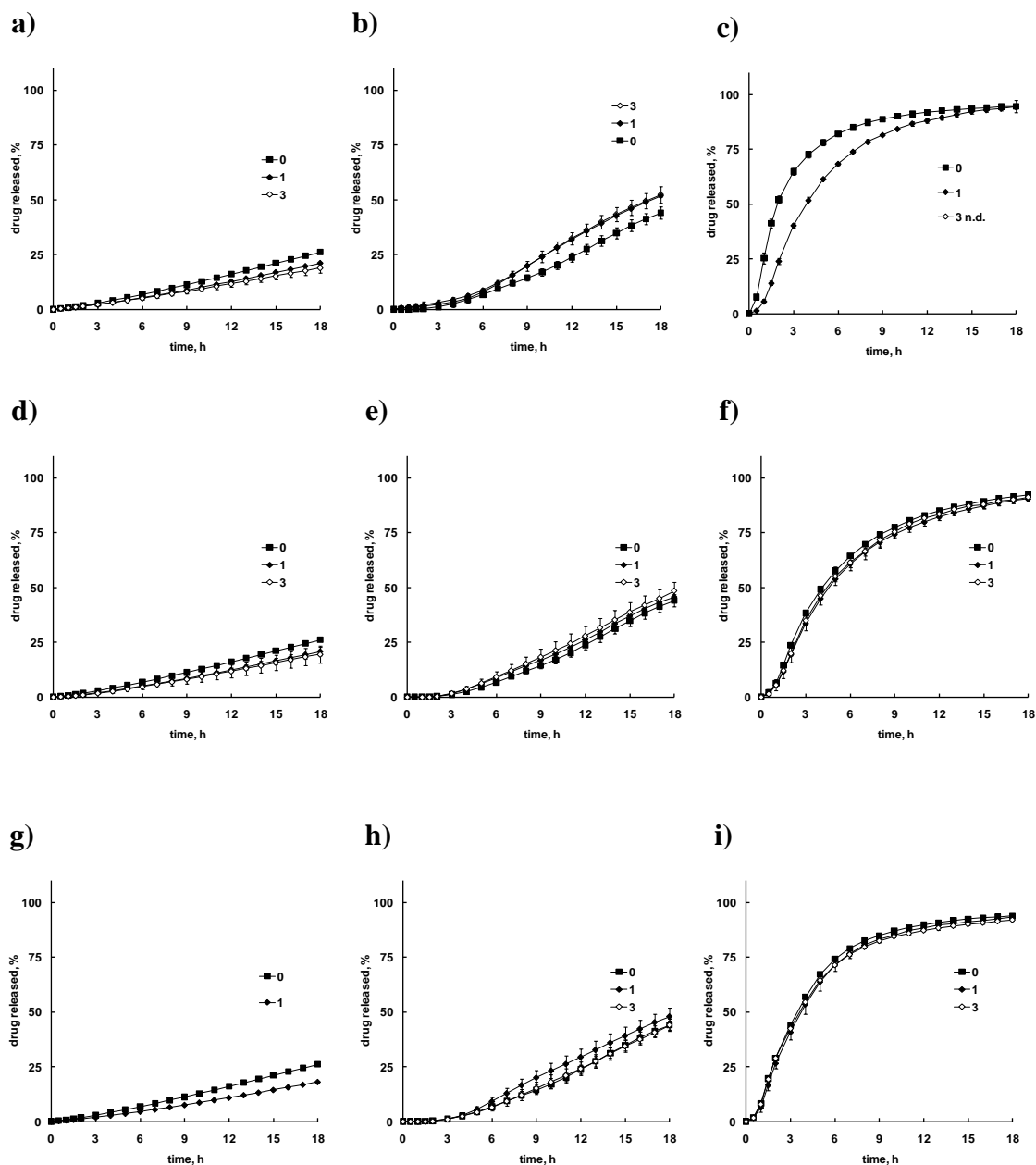


Figure 61: Effect of storage (1 and 3 months) on drug release from cured Eudragit NM 30 D-coated sugar cores. a-c) 40°C/75% RH, d-f) RT/60% RH cores and g-i) 40°C. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

Drug release from uncured Eudragit NM 30D-coated pellets (all drugs) decreased upon storage at all conditions (Figure 60a-i). In contrast, relatively stable release profiles were observed for all cured coated pellets (Figure 61a-i). This was a clear indication that Eudragit NM 30 D-coated pellets require curing prior to stability, albeit the fact that it is an aqueous dispersion with a low MFT. Film formation was not complete during coating process (as demonstrated by curing studies) and the curing step was necessary to complete film formation and achieve stable release profiles independent on drug type. Furthermore, Eudragit NM 30 D-coated pellets were much more stable than Eudragit NE 30 D coated pellets. Both aqueous dispersion are ethylacrylate methylmethacrylate (2:1), varying just in type and amount of surfactant, polyethylene glycol stearyl ether (0.7%) and nonoxynol 100 (1.5%) for Eudragit NM 30 D and Eudragit NE 30 D, respectively. Consequently the unstable release profiles from Eudragit NE 30 D-coated pellets could be to some extent attributed to the presence of nonoxynol 100.

3.4.7 Cured Surelease

40°C/75% RH

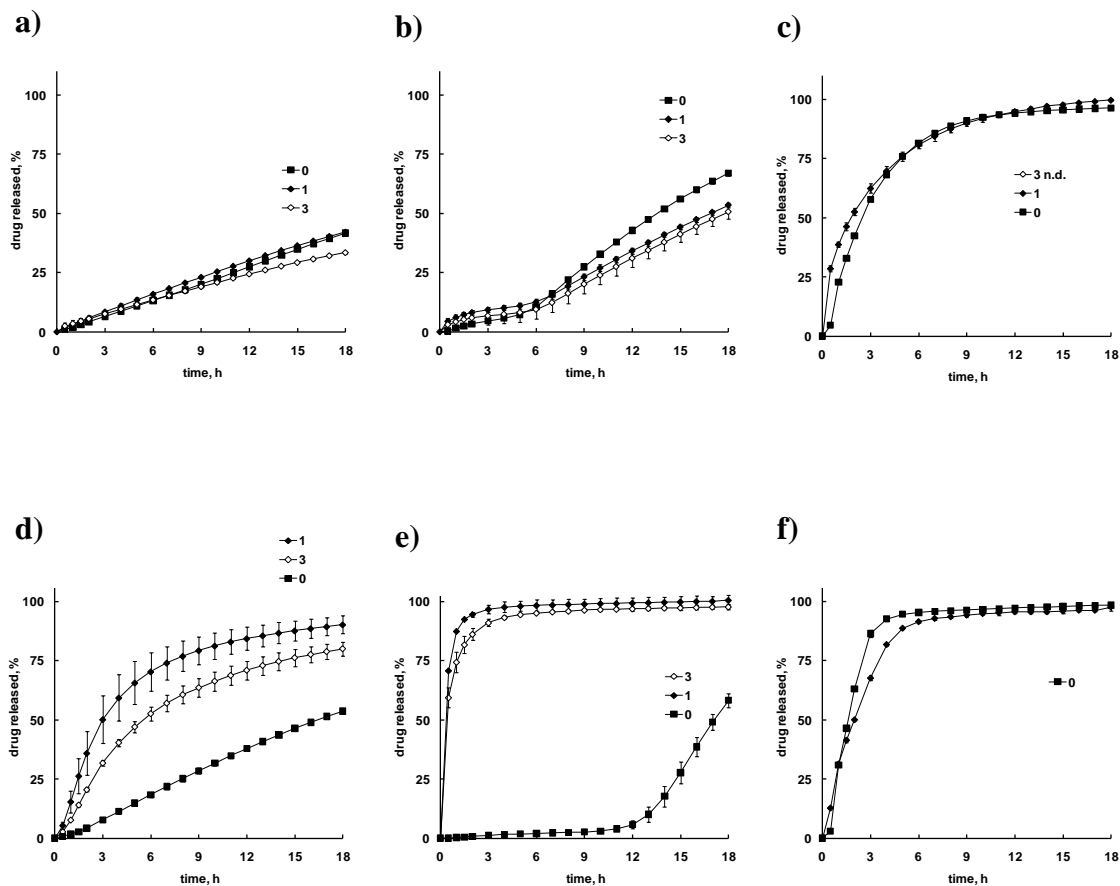


Figure 62: Effect of storage (40°C/75% RH, 1 and 3 months) on drug release from cured Surelease-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

RT/60% RH

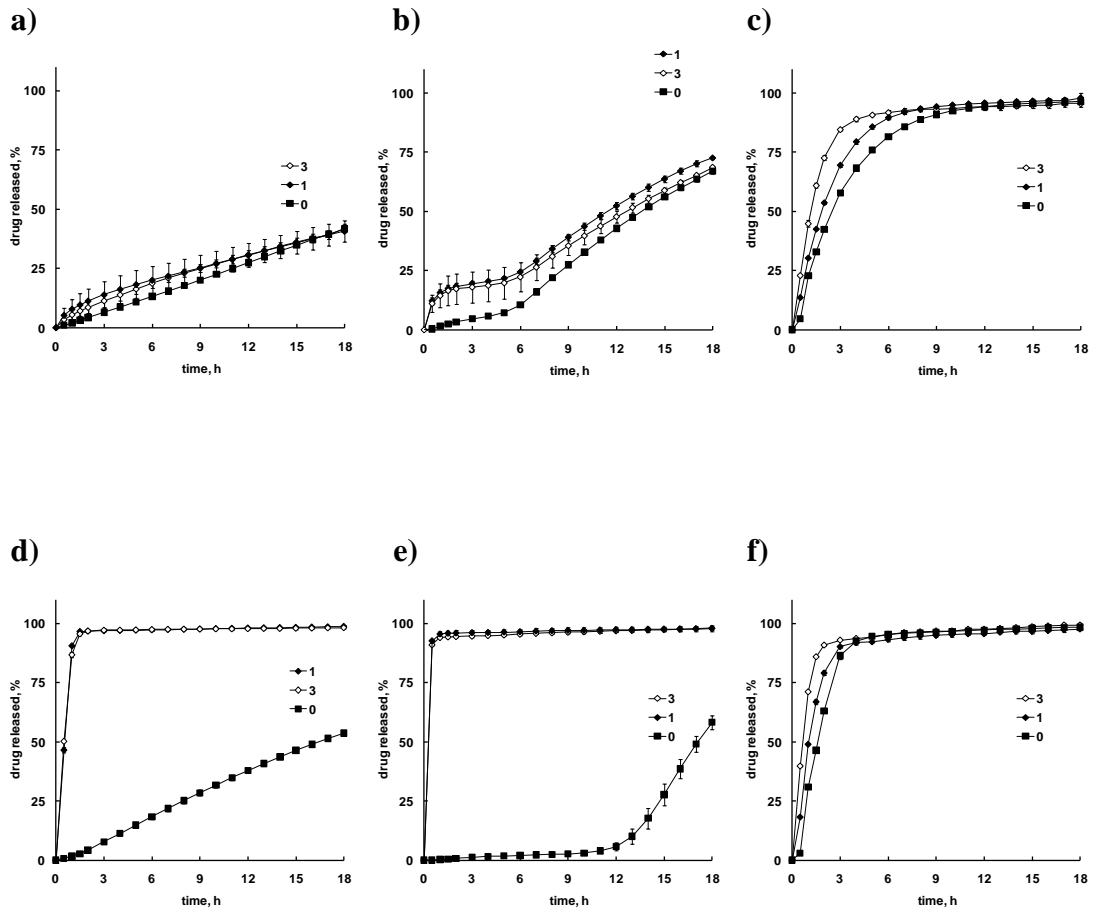


Figure 63: Effect of storage (RT/60% RH, 1 and 3 months) on drug release from cured Surelease-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

40°C

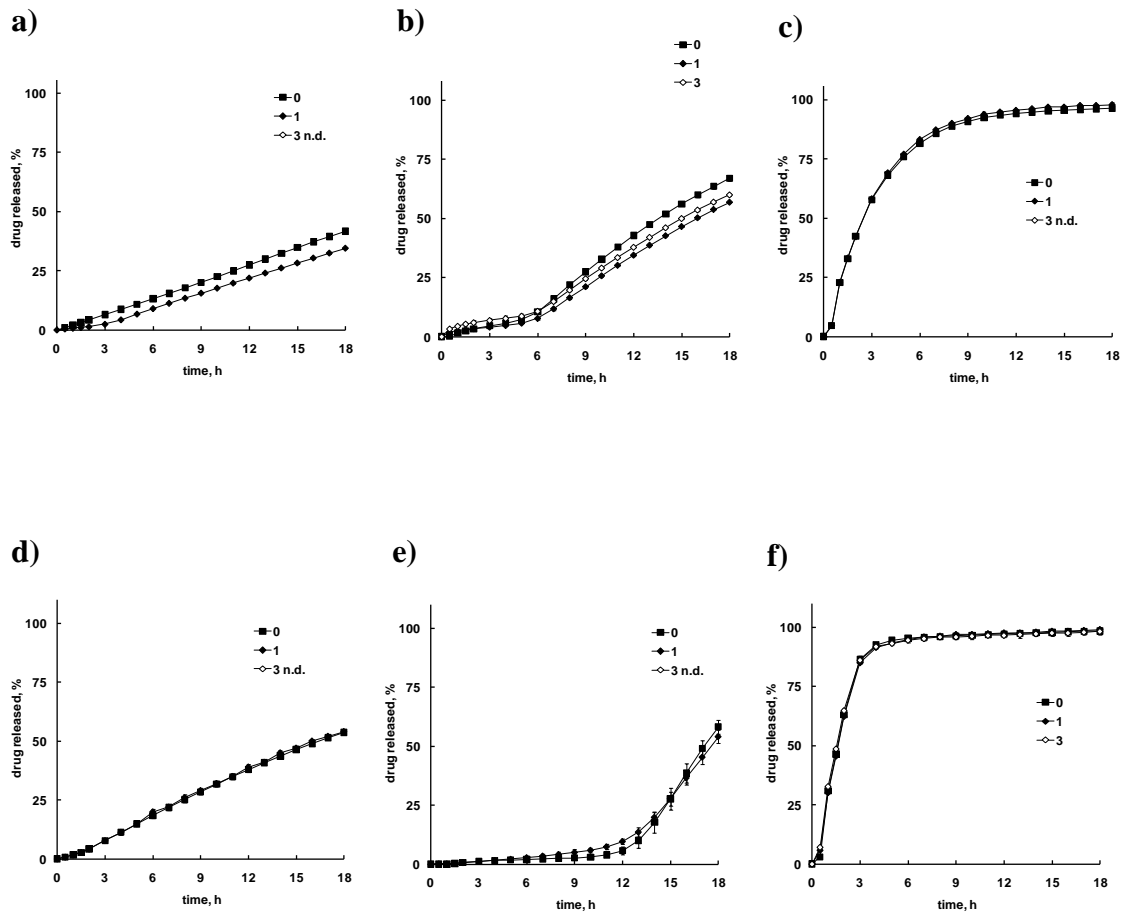


Figure 64: Effect of storage (40°C, 1 and 3 months) on drug release from cured Surelease-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

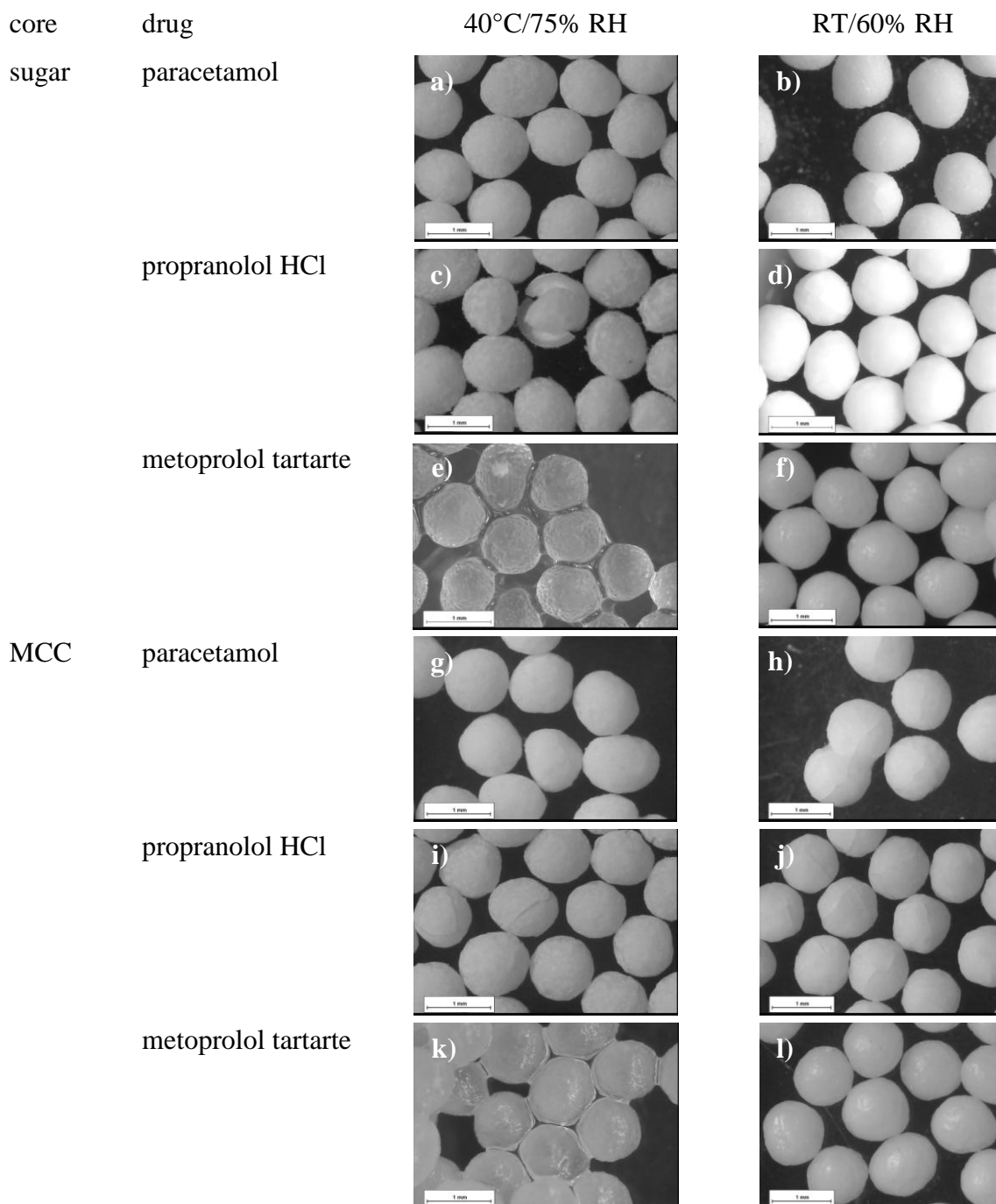


Figure 65: Macroscopic pictures from cured Surelease coated pellets after 1 month storage at 40°C/75% RH and RT/60% RH. a-b) paracetamol-layered sugar cores, c-d) propranolol HCl-layered sugar cores, e-f) metoprolol tartrate-layered sugar cores g-h) paracetamol-layered MCC cores, i-j) propranolol HCl-layered MCC cores and k-l) metoprolol tartrate-layered MCC cores.

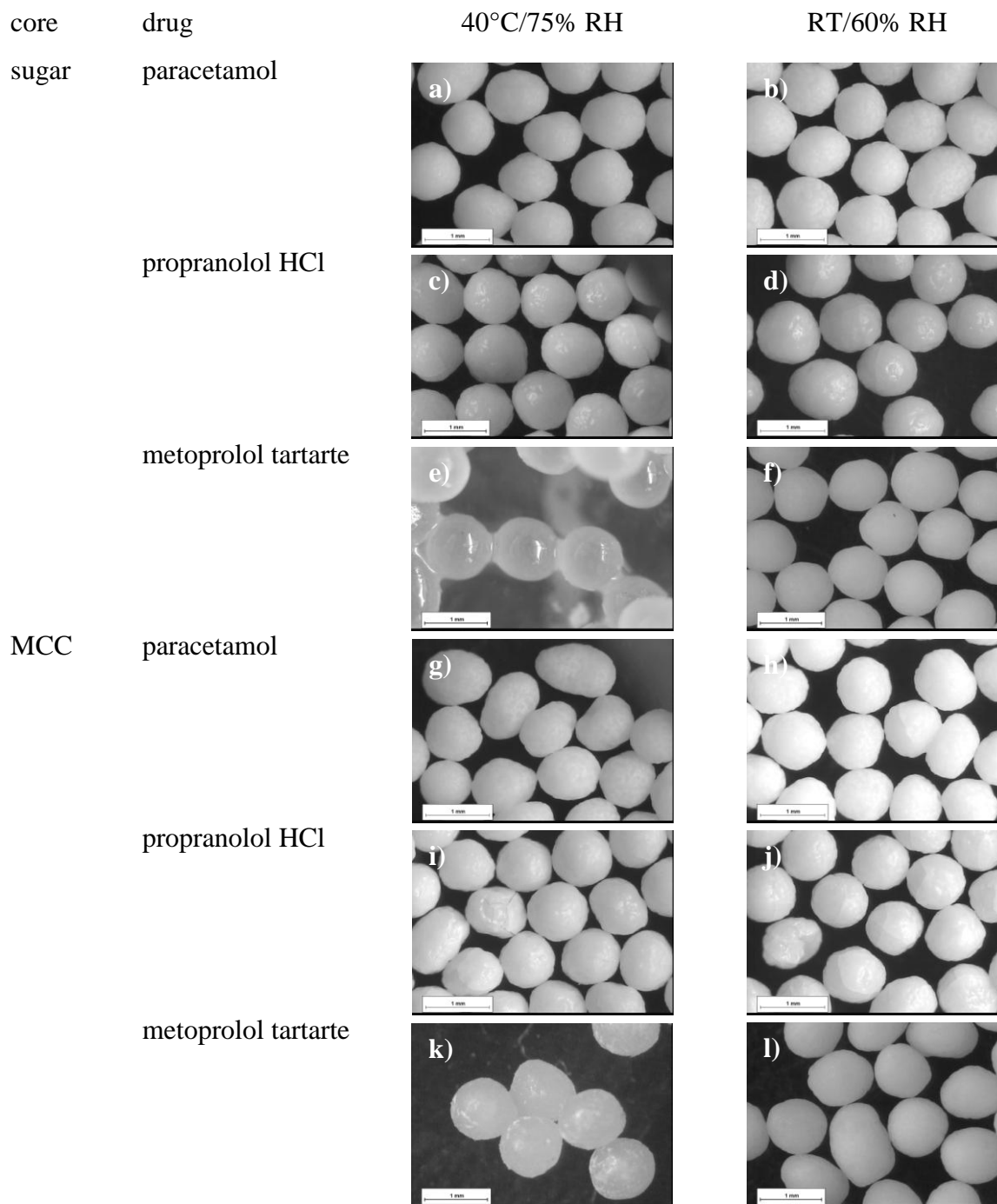


Figure 66: Macroscopic pictures from drug-loaded cores after 1 month storage at 40°C/75% RH and RT/60% RH. a-b) paracetamol-layered sugar cores, c-d) propranolol HCl-layered sugar cores, e-f) metoprolol tartrate-layered sugar cores g-h) paracetamol-layered MCC core, i-j) propranolol HCl-layered MCC cores and j-l) metoprolol tartrate-layered MCC cores.

Paracetamol and propranolol HCl release from cured Surelease-coated sugar cores was almost unchanged or slightly decreased upon storage at 40°C/75% RH (Figure 62a and b). In contrast, paracetamol and propranolol HCl release from coated MCC cores significantly increased upon storage at 40°C/75% RH (Figure 62d and e). After storage at RT/60% RH, paracetamol and propranolol HCl release from coated MCC increased in a similar way (Figure 63d and e). On the other hand, paracetamol and propranolol HCl release from coated sugar cores showed a small initial burst in comparison with unstored coated pellets, but with similar release rates (Figure 63a and b). In case of metoprolol tartrate, drug release slightly increased from coated sugar and MCC cores with time (Figure 63c and d). At 40°C, drug release profiles were stable or decreased, suggesting that the curing conditions were not optimized for each formulation (Figure 64). Moreover, it was clear that the main changes in drug release upon storage were humidity related. After storage at elevated humidity, ruptures were clearly visible in Surelease-coated paracetamol and propranolol HCl MCC cores (Figure 65). The moisture uptake after 1 month for coated paracetamol and propranolol HCl MCC cores was around 4.5% and 3-3.5% after 40°C/75% RH and RT/60% RH, respectively. To better understand the rupturing behaviour, moisture uptake of unloaded and drug-loaded cores was recorded after storage at the same conditions. Unloaded MCC cores had a moisture uptake of 4.2% and 1.9% after 1 month storage at 40°C/75% and RT/60%, respectively. The moisture uptake was accompanied by a swelling of 4.6% and 2.1%, correspondingly (Table 6). When MCC cores were loaded with paracetamol and propranolol HCl, moisture uptake decreased (Table 6), but this was due to the ability of MCC to prevent and/or decrease the rate of hydration of other substances (Angberg et al., 1991; Sari et al., 2003). In fact, most of the moisture was preferentially taken by MCC due to its hygroscopic nature. Upon moisture uptake, core swelling occurred and paracetamol and propranolol HCl layer ruptured altogether with Surelease coating (Figures 65 and 66). Core swelling exerted a high internal stress in the brittle drug layer and polymer layer, leading to ruptures. On the other hand, at RT/60% RH, when MCC cores were loaded with metoprolol tartrate layer, no coating or drug layer ruptured (Figure 65 and 66). The drug layer expanded and deformed along with core swelling indicating that the internal stress generated in the film was lower than the mechanical strength of the film (high flexibility). As a result, metoprolol tartrate release was not immediate, but rather increased due to an increase in surface area (Figure 63f). Therefore, besides MCC core swelling, mechanical properties of drug layer have an

important role in promoting or shielding the coating from rupturing. In case of unloaded sugar cores, the moisture uptake was considerably less than unloaded MCC cores and no sugar core swelling could be detected at 40°C/75% RH and RT/60% RH (Table 6). However, propranolol HCl layer ruptured and consequently coating ruptured after storage at elevated humidity. These ruptures were responsible for the small burst observed from coated propranolol HCl sugar cores at RT/60% RH (Figure 63b). Interestingly, the ruptures on uncoated and coated propranolol HCl sugar cores were visible just in a number of pellets (~15%), correlating very well to the burst in drug release. It is speculated that the mechanism of these ruptures is as well, core swelling (although not measurable). The swelling could be due to starch (25% w/w of sugar core), which is known to swell in presence of humidity. A further indication of this mechanism was that metoprolol tartrate release from Surelease-coated sugar cores also increased in the same way as the corresponding coated MCC cores (Figure 63c). Nevertheless the rupturing of uncoated/coated sugar cores was not as homogeneous as uncoated/coated MCC cores. This could be due to the different axial and radial swelling of starch, causing ruptures only directed to some areas. Another possible reason is that upon swelling, films ruptured in some weak points of core/film interface. In addition, the burst observed from coated propranolol HCl sugar cores was smaller after storage at 40°C/75% RH, than after RT/60% RH. The process of film formation is stronger at high temperature and high humidity, resulting in a film able to better resist to volumetric changes in the core.

Table 6: Moisture uptake (based on total weight) and swelling of uncoated pellets upon 1 month storage (\pm , standard deviation)

core	drug	40°C/75% RH		RT/60% RH	
		moisture uptake (%)	swelling (%)	moisture uptake (%)	swelling (%)
sugar	unloaded	1.4 \pm 0.0	not noticeable	0.4 \pm 0.0	not noticeable
	paracetamol	1.8 \pm 0.2		0.9 \pm 0.3	
	propranolol HCl	2.2 \pm 0.0	n.d.	1.0 \pm 0.1	n.d.
	metoprolol tartrate	31.1 \pm 0.3		0.7 \pm 0.1	
MCC	unloaded	4.2 \pm 1.1	4.6 \pm 1.1	1.9 \pm 0.1	2.1 \pm 0.1
	paracetamol	2.9 \pm 0.1		1.9 \pm 0.0	
	propranolol HCl	2.8 \pm 0.1	n.d.	1.4 \pm 0.2	n.d.
	metoprolol tartrate	4.7 \pm 0.1		1.9 \pm 0.1	

n.d.: not determined

3.4.8 Cured Aquacoat ECD

40°C/75% RH

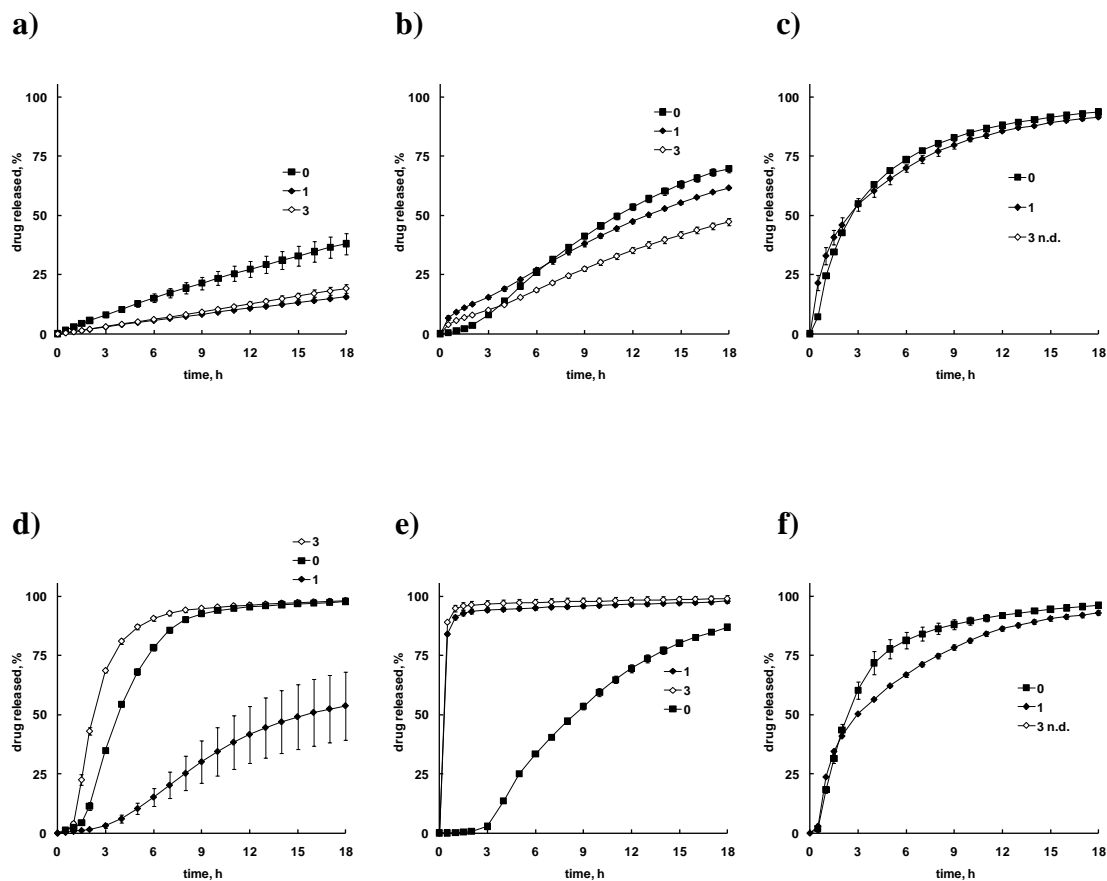


Figure 67: Effect of storage (40°C/75% RH, 1 and 3 months) on drug release from cured Aquacoat ECD-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

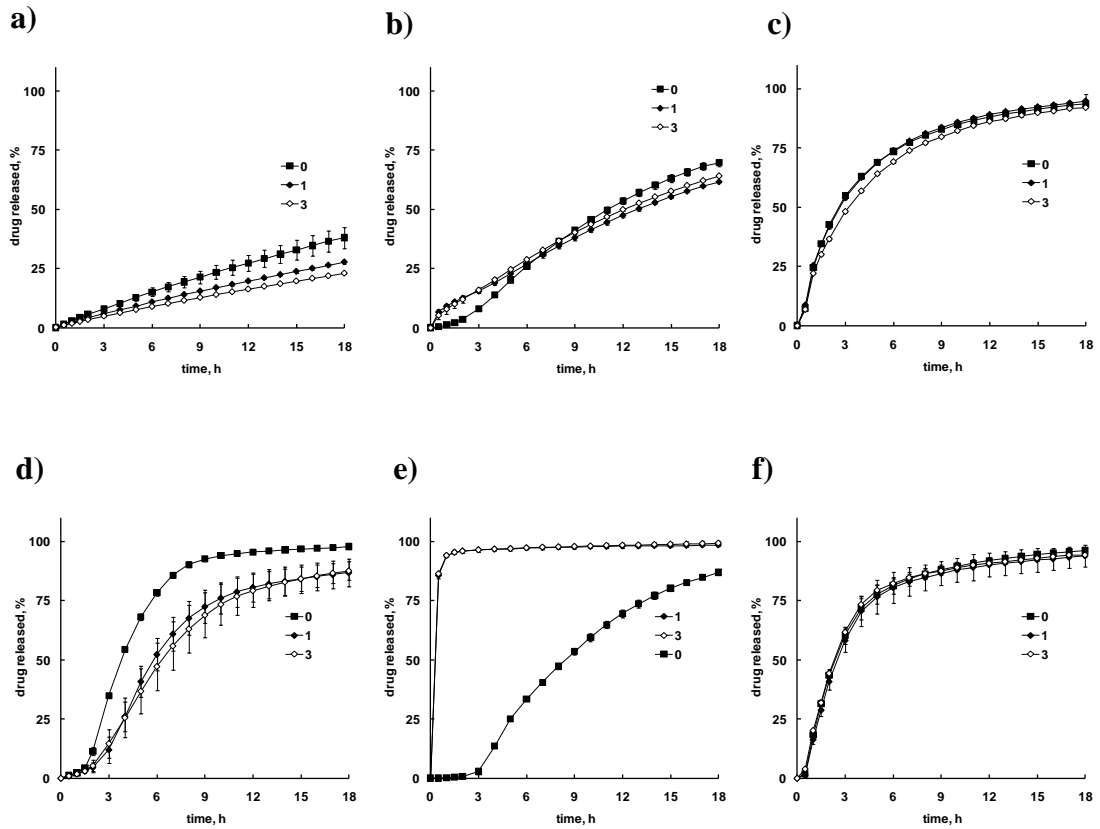
RT/60% RH

Figure 68: Effect of storage (RT/60% RH, 1 and 3 months) on drug release from cured Aquacoat ECD-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

40°C

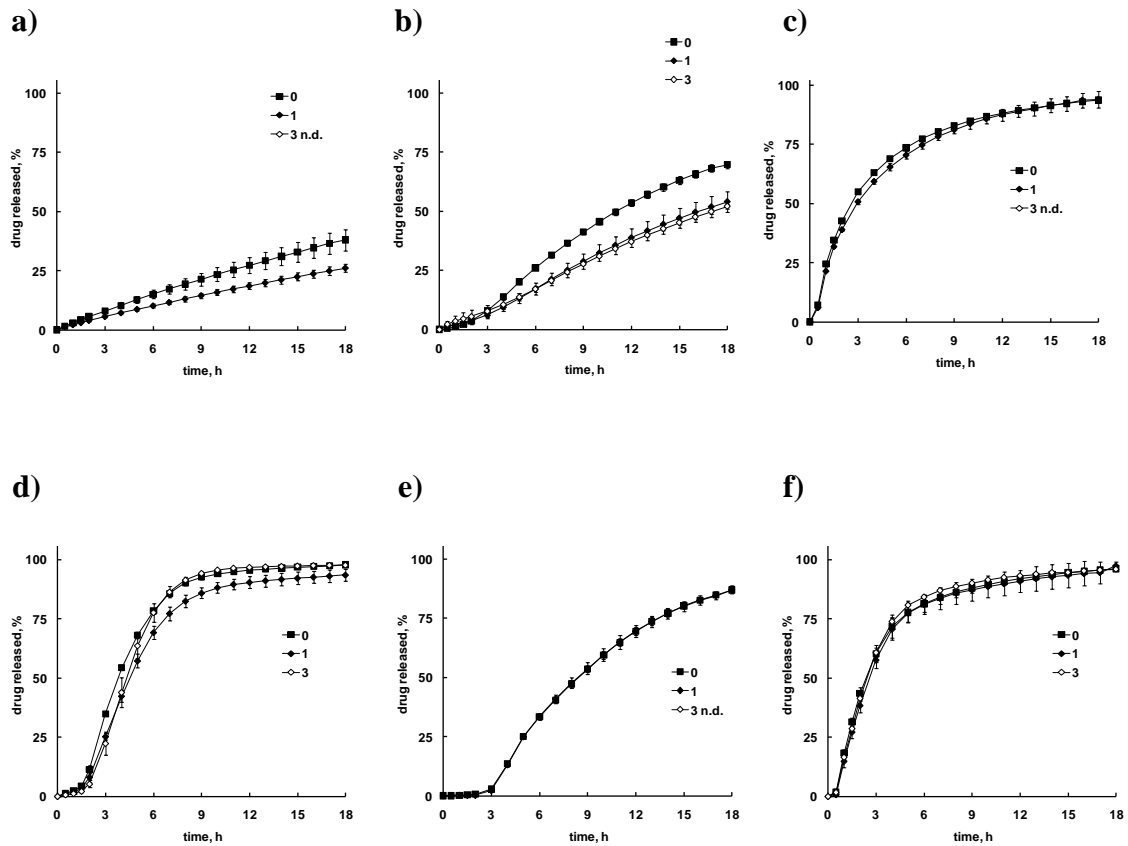


Figure 69: Effect of storage (40°C, 1 and 3 months) on drug release from cured Aquacoat ECD-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

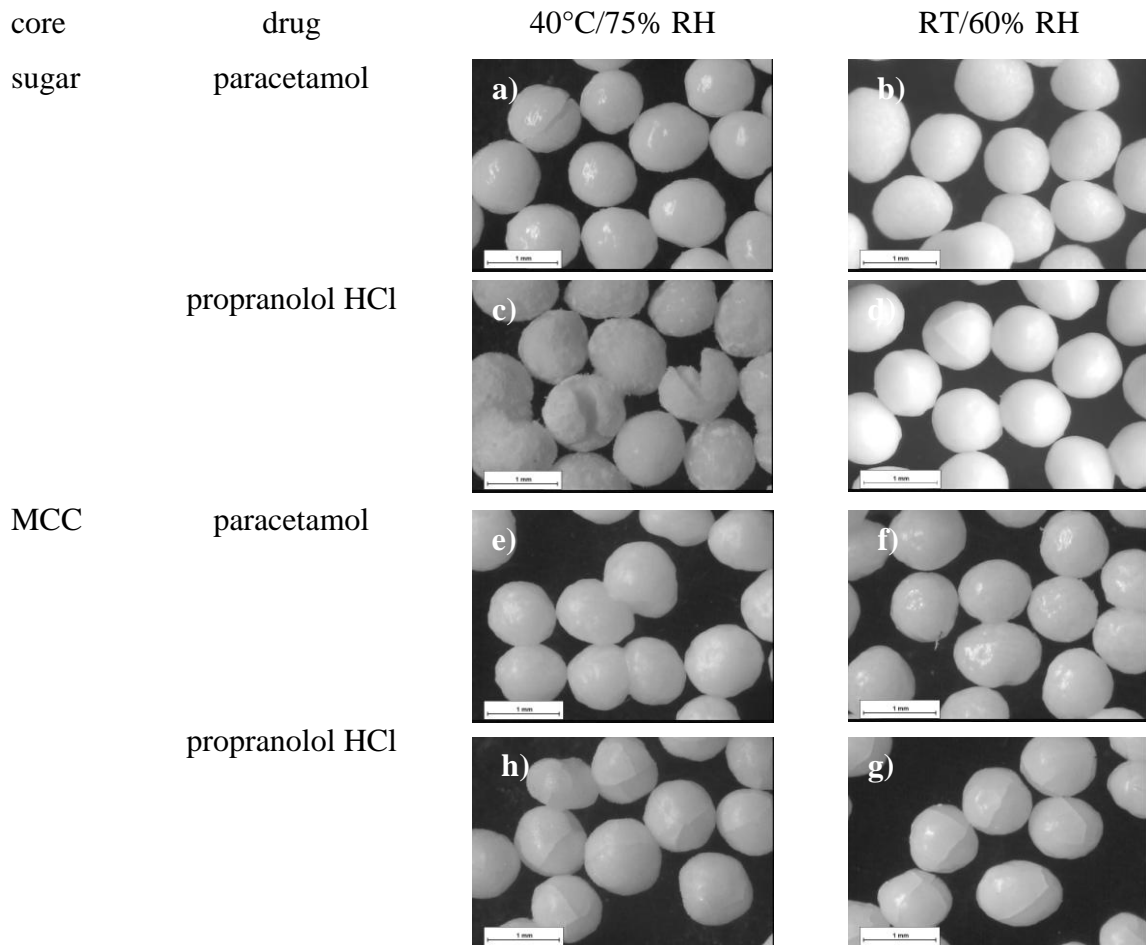


Figure 70: Macroscopic pictures from cured Aquacoat ECD-coated pellets after 1 month storage at 40°C/75% RH and RT/60% RH. a-b) paracetamol-layered sugar cores, c-d) propranolol HCl-layered sugar cores, e-f) paracetamol-layered MCC cores and g-h) propranolol HCl-layered MCC cores.

Upon storage at 40°C/75% RH and RT/60% RH, paracetamol release from Aquacoat ECD-coated sugar cores decreased due to continuous film formation (Figure 67a). In case of coated MCC cores, paracetamol release decreased after 1 month and increased after 3 months (Figure 67d). These opposite trends were related with continuous film formation (1 month) and rupturing of drug layer and coating (3 months). During the first month, film formation was the predominant mechanism and afterwards the coating rupture overlaid the film formation mechanism. The absence of visible ruptures in the coated pellets (Figure 70f) was related with the lag time on drug release. In fact, the ruptures did not reach the surface of the coated pellets. On the other hand, after RT/60% RH, paracetamol release decreased from coated MCC cores (Figure 68d). At this

condition, only continuous film formation took place and/or the coating could resist to core swelling. Storage of coated propranolol HCl sugar cores at 40°C/75% RH and RT/60% RH resulted in a small burst followed by decrease in release rate (Figure 67 and 68b). The burst was due to ruptures in the coating (Figure 70), which contributed to the fast initial release and the further decrease in release rate corresponded to continuous film formation. Propranolol HCl release from coated MCC cores was immediate after storage at 40°C/75% RH and RT/60% RH (Figure 67 and 68) and coating ruptures were clearly visible (Figure 70). The mechanism involved in formation of these ruptures was identical to Surelease coatings (*section 3.4.7*). On the other hand, metoprolol tartrate release from coated sugar and MCC cores did not change upon 3 months at RT/60% RH (Figure 68). After storage at 40°C, drug release from coated pellets was either unchanged or further decreased (Figure 69). This indicated that the curing conditions used in this study (60°C/24h) were adequate to complete film formation in case of coated MCC cores (all drugs) and coated metoprolol tartrate sugar cores, but insufficient for coated paracetamol and propranolol HCl sugar cores.

3.4.9 Uncured organic ethylcellulose solution

40°C/ 75% RH

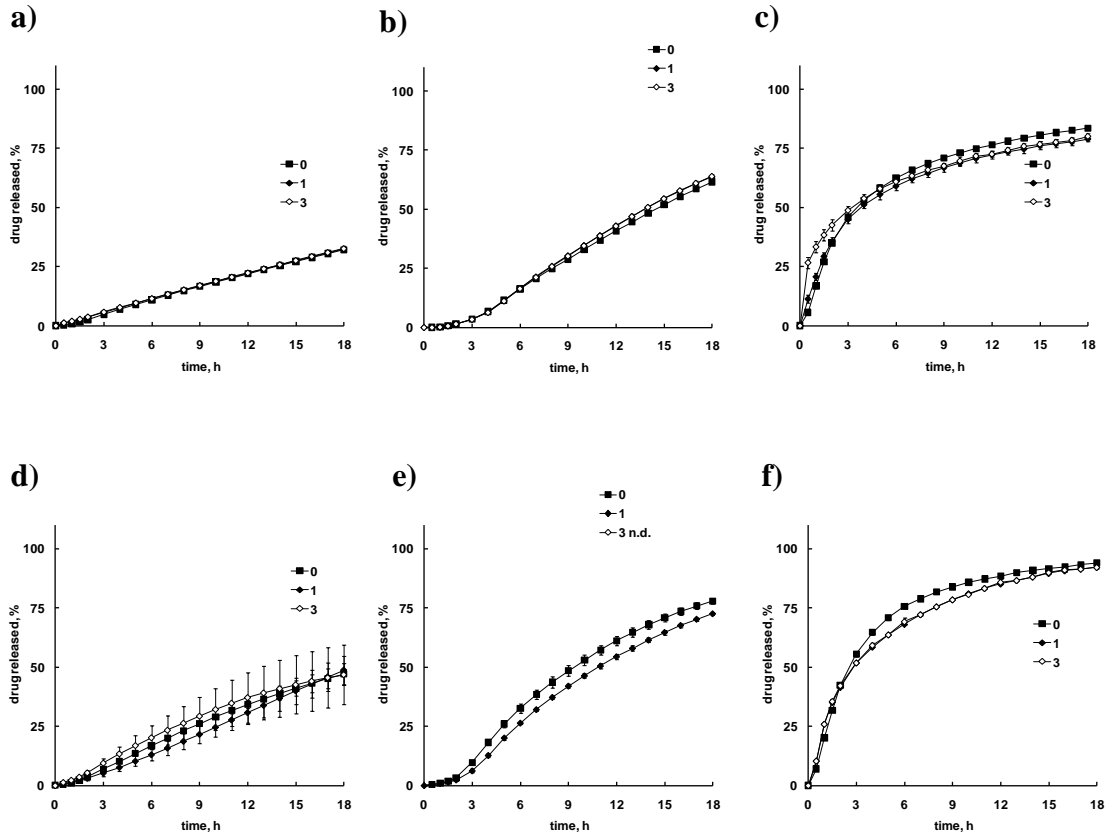


Figure 71: Effect of storage (40°C/75% RH, 1 and 3 months) on drug release from uncured organic ethylcellulose solution-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

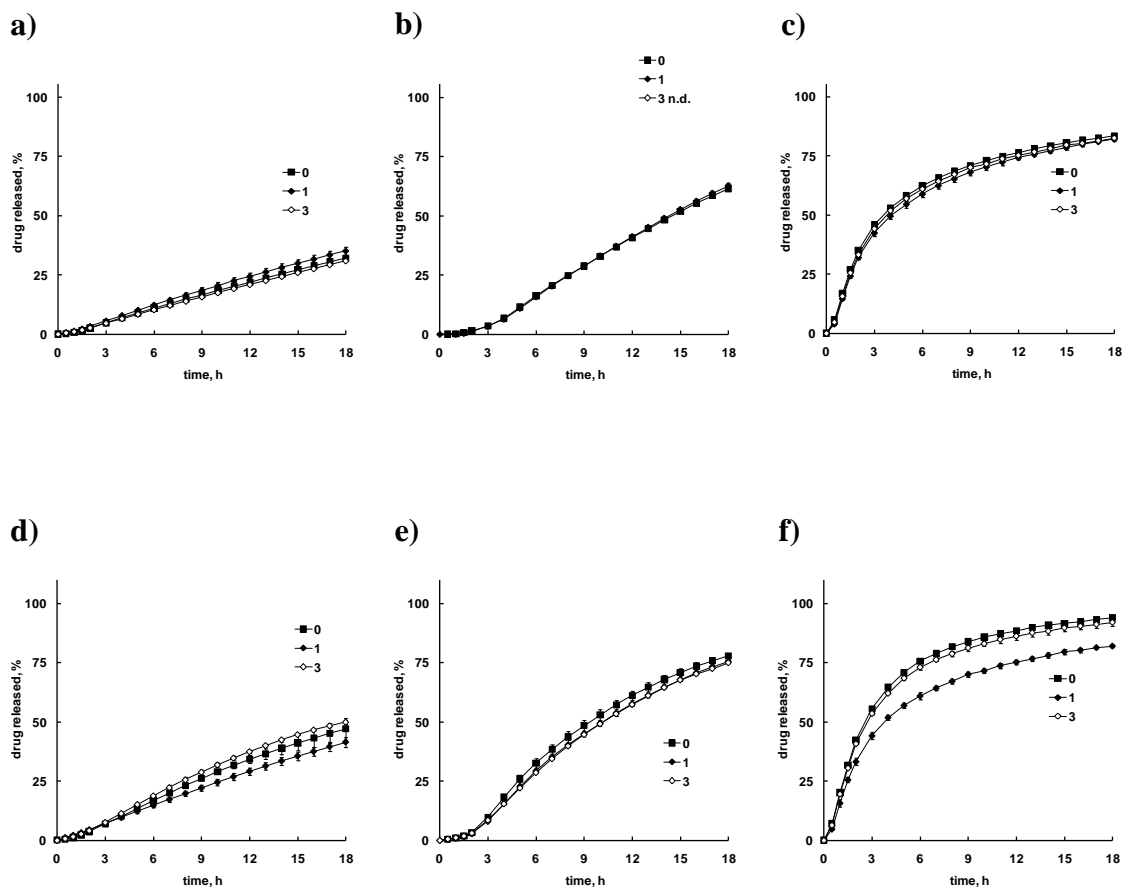
RT/ 60% RH

Figure 72: Effect of storage (RT/60% RH, 1 and 3 months) on drug release from uncured organic ethylcellulose solution-coated pellets. a-c) drug-layered sugar cores and d-f) drug-layered MCC cores. First column: paracetamol (10% coating level), second column: propranolol HCl (15% coating level) and third column: metoprolol tartrate (15% coating level).

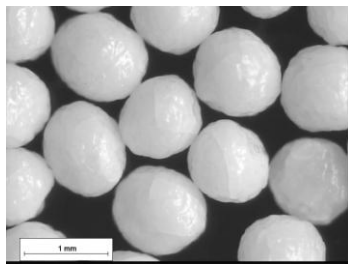


Figure 73: Macroscopic pictures from organic ethylcellulose solution-coated propranolol HCl MCC cores after 3 months storage at 40°C/75% RH.

Organic ethylcellulose solution-coated pellets were stable under storage at all conditions (Figure 71 and 72). Only metoprolol migration was observed upon storage at 40°C/75% RH, similar to aqueous coatings (Figure 71). On the other hand, coatings did not rupture under humid conditions. However, below the coating, propranolol HCl layer was ruptured (Figure 73) in case of coated MCC cores. Organic coatings are mechanically stronger than aqueous coatings and thus could withstand volume changes in the core. In addition, organic coated pellets absorbed less moisture than aqueous coatings (e.g. organic coated propranolol HCl had 3% moisture uptake in contrast to 5% from the corresponding Aquacoat ECD-coated cores, after 1 month storage at 40°C/75% RH), resulting in less core swelling.

Table 7: Effect of storage conditions (40°C/ 75% RH, RT/60%RH and 40°C for 1 month) on f_2 similarity factor from uncured coated pellets

coatings	similarity factor, f_2																	
	40°C/75% RH				RT/60% RH				40°C									
	paracetamol	propranolol HCl	metoprolol tartrate	MCC sugar	paracetamol	propranolol HCl	metoprolol tartrate	MCC sugar	paracetamol	propranolol HCl	metoprolol tartrate	MCC sugar						
Kollicoat SR 30D	56	86	66	49	51	42	83	82	73	49	58	57	94	67	95	42	52	51
Eudragit NE 30D	19	35	45	36	38	22	53	40	83	63	37	35	62	35	62	43	27	24
Eudragit NM 30D	63	n.d.	33	n.d.	41	n.d.	38	n.d.	28	n.d.	35	n.d.	37	n.d.	29	n.d.	33	n.d.
Organic ethylcellulose	100	76	86	63	70	63	95	78	97	68	89	80	n.d.	68	84	73	79	70

n.d. not determined

Table 8: Effect of storage conditions (40°C/ 75% RH, RT/60%RH and 40°C for 1 month) on f_2 similarity factor from cured coated pellets

coatings	similarity factor, f_2																	
	40°C/75% RH				RT/60% RH				40°C									
	paracetamol	propranolol HCl	metoprolol tartrate	MCC	paracetamol	propranolol HCl	metoprolol tartrate	MCC	paracetamol	propranolol HCl	metoprolol tartrate	MCC						
Kollicoat SR 30D	83	81	57	51	40	65	89	73	66	55	87	77	94	91	68	80	79	78
Eudragit NE 30D	54	n.d.	47	n.d.	47	n.d.	99	79	38	n.d.	62	70	56	60	41	n.d.	41	70
Eudragit NM 30D	76	n.d.	62	n.d.	44	n.d.	74	n.d.	84	n.d.	73	n.d.	67	n.d.	70	n.d.	70	n.d.
Surelease	81	18	55	4	46	47	64	8	47	1	50	38	65	94	59	80	93	87
Aquacoat ECD	43	60	60	2	62	49	59	36	60	2	95	85	57	56	47	99	76	77

n.d. not determined

In conclusion, upon storage, drug release profiles could be changed due to: 1) further gradual polymer particles coalescence (continuous film formation process), resulting in denser film structures and reduced permeability for water and drug, consequently drug release decreased upon storage. Further gradual coalescence or continuous film formation resulted from uncured samples. Comparing f_2 similarity values (Table 7 and 8), pellets coated with aqueous dispersion of low MFT require curing prior to storage (any condition). The curing step strongly improved drug release profiles upon storage of Eudragit NE 30 D- and Eudragit NM 30 D-coated pellets. Kollicoat SR 30 D-coated pellets had minor improvement by the curing step. The other reason for continuous film formation was insufficient curing conditions. The curing conditions (thermal, thermal/humidity and time) should be optimized for each formulation; 2) drug dissolution and migration through the coating. Upon exposure to high temperature/humidity, hygroscopic drugs can absorb high quantities of water, dissolve and migrate through the coatings. Sugar cores enhanced metoprolol tartrate dissolution and migration, due to a decrease in critical relative humidity (of sucrose and/or drug) for deliquescence to take place. As a result a burst release was observed; 3) migration of film components (e.g. emulsifier) as in case of Eudragit NE 30 D coatings. Upon storage at 40°C/75% RH, nonoxynol 100 migrated through the coating, acting as a pore former and increasing drug release. Interestingly, surfactant's migration and consequently increase in drug release was just observed in case of coated paracetamol sugar and MCC cores. As a result, the type of drug had an influence on surfactant migration. Besides drug, core type strongly modified the rate and extent of surfactant's migration; 4) coating ruptures due to volume changes in the core. Upon storage at elevated humidity and moisture uptake, core swelled leading to ruptures in Eudragit NE 30 D, Surelease and Aquacoat ECD coatings. These ruptures were more pronounced in case of brittle Surelease and Aquacoat ECD, than Eudragit NE 30 D coatings (due to its higher flexibility). In addition, drug layer mechanical stability also had a significant influence in inducing or shielding the coating from rupture. Metoprolol tartrate layer could withstand core swelling, reducing the internal stress in the coatings and avoiding rupture of the coating. In an opposite way, very brittle propranolol HCl layer ruptured and subsequently coating ruptured. MCC and sugar core swelling was essentially different and much less pronounced with coated sugar cores, higher f_2 values for Surelease and Aquacoat ECD-coated sugar cores upon storage with elevated humidity (Table 8). Kollicoat SR 30 D- and organic ethylcellulose-coated pellets could resist to

core swelling. Kollicoat SR 30 D coatings are flexible and probably deformed along with the core. On the contrary, organic ethylcellulose coatings are brittle but mechanically strong and could withstand the change in volume.

4. Summary

Matrix Coated Systems

The major aim of this work was to identify the major parameters affecting drug release from matrix cast films and matrix coated pellets. Geometry of the device, drug type, drug loading, additive, polymer type, core type and size, as well as osmolality of the medium were investigated.

Drug release from matrix cast films was slower than from coated pellets due to smaller surface area to volume ratio, longer diffusion pathway (higher thickness) and also film structure in which denser films are obtained by casting and more porous films result from spraying method. The differences in drug release rate were smaller for ibuprofen (solid solution), where geometry of the device was the main contribution. In case of a solid dispersion (diclofenac Na and metoprolol tartrate), besides geometry, the higher porosity of coated pellets contributed to a faster release rate.

The influence of drug type on release from both matrix cast films and matrix coated pellets was opposite to aqueous drug solubility. Drug release order was: diclofenac Na > ibuprofen > metoprolol tartrate. Diclofenac Na was in the form of big crystals at matrix surface resulting in very fast release, while ibuprofen was dissolved and drug diffusion through the polymer controlled the release rate. Metoprolol tartrate, very soluble drug, was homogeneously entrapped in the matrix and thus release rate was very slow.

Increasing drug loading of a solid solution increased release rate in a monotonic trend. With a solid dispersion, increasing drug loading had no effect on release rate up to a critical drug loading. Below the critical drug loading (percolation threshold), drug was entrapped in clusters in the matrix without pore connection, while above that, connection of pores caused an increase in drug diffusion.

Adding HPC and PVP as pore formers increased the matrix's surface area exposed to the medium (matrix disintegration) and complete ibuprofen release was reached. In case of metoprolol tartrate, HPC, PVP and mannitol increased just the initial phase of drug release but complete release was not achieved. This might be explained by the unconnected pores and drug clusters entrapped in the matrix. Opposite to ibuprofen and metoprolol tartrate, diclofenac Na crystals were better distributed and more entrapped when PEG was included in the matrix, leading to the reduction of diclofenac Na release.

Varying the type of the polymer had a higher impact on metoprolol tartrate than ibuprofen release. Metoprolol tartrate release was much faster from Eudragit RS than from ethylcellulose matrix films and this was attributed to the higher polymer permeability of Eudragit RS. Moreover, amorphous metoprolol tartrate could be formed in Eudragit RS matrix, being a reason for the extremely fast drug release. In case of ibuprofen, drug release was as follows: Eudragit RL > ethylcellulose > Eudragit RS. The drug release order was in agreement drug partition into the polymer, thus suggesting that release order was related with permeability of the matrix.

Increased metoprolol tartrate release from coated pellets was observed when the core size was decreased, due to an increase in surface area to volume ratio. In addition, drug release from coated MCC cores was faster than sugar cores. The slower metoprolol tartrate release from coated sugar cores might be due to drug diffusion hindered by sucrose or drug release firstly taking place towards the dissolved core. Increasing medium osmolality resulted in decreased drug release. This is in agreement with diffusion controlled systems, in which increasing the osmolality of the medium, decreases water penetration rate and consequently drug release decreases.

Reservoir Coated Systems

The major aims of this work included: (i) the preparation of different types of aqueous polymeric dispersions as well as organic ethylcellulose solution coated sugar and MCC cores; (ii) characterization of drug release profiles; (iii) identification and quantification of curing effect on drug release; (iv) investigation of the influence of storage conditions on drug release from coated pellets.

Drug release from Kollicoat SR 30 D-, Eudragit NE 30 D-, Eudragit NM 30 D-, Surelease-, Aquacoat ECD- and organic ethylcellulose-coated pellets was investigated. Drug release was strongly affected by the type of drug and core used. In case of an uncharged and sparingly soluble drug (paracetamol), drug release from coated sugar and MCC cores was similar since drug diffusion through the coating was the main mechanism controlling drug release. Propranolol HCl (charged and freely soluble drug) release from coated sugar and MCC cores differed in lag time and release rate. The differences in lag time were attributed to different mechanical behavior of the coatings when facing different types of stress (osmotic or swelling). The drug release rate was generally faster from coated MCC cores than sugar cores, attributable to the swelling of MCC cores that compensated the loss of osmotic pressure of coated sugar cores. Metoprolol tartrate (charged and very soluble drug) release from coated sugar and MCC cores was identical. Drug release was mainly controlled by drug solubility with minor contribution from the core.

Coated pellets were cured at 40°C, 60°C and 60°C/75% RH for 24h and the curing effect on drug release was studied. The extent of thermal curing effect on drug release from coated pellets was evaluated and ranked in the following order: Aquacoat ECD >> Eudragit NE 30 D ~ Eudragit NM 30 D > Surelease > Kollicoat SR 30 D > organic ethylcellulose. Drug release from Kollicoat SR 30 D- and organic ethylcellulose-coated pellets was almost unaffected by thermal and thermal/humidity curing. It was concluded that film formation was complete during coating process. Drug release from Eudragit NE 30 D- and Eudragit NM 30 D-coated pellets was strongly affected by increasing temperature of curing and similarly decreased by thermal and thermal/humidity curing. This was attributed to an increase in polymer particle coalescence with increasing curing temperature, with no additional contribution of humidity in film formation. On the other hand, drug release from cellulosic aqueous coated pellets (Surelease and

Aquacoat ECD) was more decreased by thermal/humidity than thermal curing. Increasing temperature increased the mobility of the macromolecules, facilitating the fusion of bordering particles. An increase in relative humidity increased the water content in the systems and water is mandatory for the capillary forces driving the polymer particles together and water acts as plasticizer for ethylcellulose, leading to a denser film. Consequently, the permeability of coatings for water and drug decreased. Dissolution and migration of hygroscopic metoprolol tartrate through the coatings occurred upon thermal/humidity curing, resulting in a burst release. The burst release was more evident with coated sugar cores than MCC cores.

Upon storage at 40°C/75% RH, RT/60% RH and 40°C for 1 and 3 months, drug release profiles could be changed due to: 1) further gradual coalescence of polymer particles (incomplete film formation) due to insufficient curing (time and/or temperature) and absence of a curing step in case of low MFT Eudragit NE 30 D and Eudragit NM 30 D aqueous dispersions. This resulted in decreased drug release profiles; 2) drug migration through the coating, resulting in a burst release upon storage at 40°C/75% RH. The burst was more pronounced for coated sugar cores than coated MCC cores due to higher moisture uptake from metoprolol tartrate in the presence of sugar cores. The critical relative humidity for deliquescence to occur of sugar and/or metoprolol tartrate decreased, resulting in dissolution and migration of both components; 3) migration of film components within the coating (e.g. surfactant), acting as pore formers resulting in increased drug release from Eudragit NE 30 D-coated pellets; 4) ruptures in the coating under storage with humid conditions, due to moisture uptake and swelling of the core, resulting in increased drug release profiles from Eudragit NE 30 D-, Surelease- and Aquacoat ECD-coated pellets. Core swelling induced a very high internal stress in the film coating, causing ruptures. In addition, the mechanical stability of the drug layer had a significant influence in inducing or shielding the coating from rupture. For example, at RT/60% RH, metoprolol tartrate layer, due to higher flexibility could withstand core swelling and reduced the internal stress in the coatings, avoiding rupture of the coating. In an opposite way, very brittle propranolol HCl layer ruptured and simultaneously the coating ruptured. Kollicoat SR 30 D and ethylcellulose coatings could resist to volumetric changes of the core. This was due to high flexibility of Kollicoat SR 30 D coatings and high mechanical stability of organic ethylcellulose coatings.

This work shows the importance of some key factors to consider when designing coated multiparticulates (matrix and reservoir) and provides deeper information about the appropriate storage conditions to guarantee an optimized finished product.

5. Zusammenfassung

Matrix-überzogene Systeme

Das Hauptziel dieser Arbeit war es, die wichtigsten Parameter für die Wirkstofffreisetzung aus gegossenen Matrixfilmen und mit Matrix-überzogenen Pellets zu bestimmen. Die Geometrie des Produktes, die Art des Wirkstoffes, die Wirkstoffbeladung, Zusätze, die Art des Polymers, die Art des Kernes und dessen Größe, sowie die Osmolalität des Mediums wurden untersucht.

Die Wirkstofffreisetzung aus den gegossenen Matrixfilmen war langsamer als die aus den überzogenen Pellets aufgrund des kleineren Verhältnisses von Oberflächengröße zu Volumen, des längeren Diffusionsweges (größere Schichtdicke) und auch aufgrund der Filmstruktur. Durch das Ausgießen wird ein dichter Film erhalten als mit der Sprühmethode. Die Unterschiede der Wirkstofffreisetzung waren für Ibuprofen kleiner (feste Lösung), die Geometrie des Produktes leistete hier den hauptsächlichsten Beitrag. Im Falle einer festen Lösung (Diclofenac-Na und Metoprololtartrat) trägt neben der Geometrie die höhere Porosität der überzogenen Pellets zur höheren Freisetzung bei.

Der Einfluss der Wirkstoffart auf die Freisetzung aus gegossenen Matrixfilmen und mit Matrix-überzogenen Pellets war umgekehrt zur Wasserlöslichkeit der Wirkstoffe. Die Reihenfolge der Wirkstofffreisetzung war: Diclofenac-Na > Ibuprofen > Metoprololtartrat. Diclofenac befand sich in Form von großen Kristallen auf der Matrixoberfläche; dies resultierte in einer sehr schnellen Freisetzung, während Ibuprofen gelöst vorlag und die Wirkstoffdiffusion durch das Polymer die Wirkstofffreisetzung kontrollierte. Metoprololtartrat, ein leicht löslicher Wirkstoff, war homogen in die Matrix eingelagert und somit war die Wirkstofffreisetzung sehr langsam.

Die Erhöhung der Wirkstoffbeladung der festen Lösung führte zu einer erhöhten Wirkstofffreisetzung. Das Erhöhen der Wirkstoffbeladung bei einer festen Dispersion hatte keinerlei Effekt auf die Wirkstofffreisetzung bis zu einem kritischen Wert. Unterhalb der kritischen Wirkstoffbeladung war der Wirkstoff in Clustern in der Matrix eingelagert ohne Porenverbindung; oberhalb dieser Porenverbindungen kam es zu einer Erhöhung der Wirkstoffdiffusion.

Der Zusatz von HPC und PVP als Porenbildner erhöhte die Matrixoberflächengröße, die dem Medium ausgesetzt war (Matrixzerfall) und die Freisetzung von Ibuprofen verlief

vollständig. Im Falle von Metoprololtartrat erhöhten HPC, PVP und Mannitol lediglich die Anfangsphase der Wirkstofffreisetzung, eine vollständige Freisetzung wurde nicht erreicht. Dies könnte damit erklärt werden, dass die unverbundenen Poren und Wirkstoffcluster in der Matrix eingeschlossen waren. Im Gegensatz zu Ibuprofen waren Metoprololtartrat, Diclofenac-Na Kristalle besser verteilt und stärker eingelagert, wenn die Matrix PEG beinhaltete; dies führte zu einer Verringerung der Diclofenac-Na Freisetzung.

Die Änderung des Polymeren hatte einen stärkeren Effekt auf die Metoprololtartrat Freisetzung als auf die von Ibuprofen. Die Metoprololtartrat Freisetzung war viel schneller aus Eudragit RS als aus einem Ethylcellulosematrixfilm. Dies konnte der höheren Polymerpermeabilität von Eudragit RS zugeschrieben werden. Zudem konnte das amorphe Metoprololtartrat innerhalb der Eudragit RS Matrix verformt werden und der Grund für die extrem schnelle Wirkstofffreisetzung sein. Im Falle von Ibuprofen war die Freisetzung wie folgt: Eudragit RL > Ethylcellulose > Eudragit RS. Die Reihenfolge der Wirkstofffreisetzung war in Übereinstimmung mit der Verteilung der Wirkstoffe innerhalb des Polymers. Damit kann angenommen werden, dass die Reihenfolge der Freisetzung im Verhältnis steht zur Wirkstofflöslichkeit und Diffusion in den Polymeren.

Die Erhöhung der Wirkstofffreisetzung aus überzogenen Pellets wurde beobachtet, wenn die Kerngröße verringert wurde, bedingt durch die Vergrößerung der Oberfläche. Außerdem war die Wirkstofffreisetzung von überzogenen MCC-Kernen schneller als von Zuckerkernen. Die langsamere Metoprololtartrat Freisetzung von überzogenen Zuckerkernen mag durch die Hinderung der Wirkstoffdiffusion durch die zuerst stattfindende Freisetzung des Zuckers bedingt sein oder die Wirkstoffdiffusion findet zunächst in Richtung des gelösten Kernes statt. Die Erhöhung der Osmolalität des Mediums führt zu einer Verringerung der Wirkstofffreisetzung. Das stimmt mit diffusionskontrollierten Systemen überein, bei denen eine Erhöhung der Osmolalität des Mediums die Wasserpenetration und demzufolge die Wirkstofffreisetzung verringert.

Reservoir-überzogene Systeme

Die Hauptziele dieser Arbeit war: (i) die Herstellung verschiedener Arten von mit wässrigen Polymerdispersionen sowie mit organischer Ethylcellulose-Lösung überzogenen Zucker- und MCC-Kernen; (ii) die Charakterisierung der Freisetzungprofile (iii) die Identifizierung und Quantifizierung der thermischen Nachbehandlung auf die Wirkstofffreisetzung; (iv) die Untersuchung des Einflusses der Lagerungsbedingungen auf die Wirkstofffreisetzung der überzogenen Pellets.

Die Wirkstofffreisetzung der mit Kollicoat SR 30D, Eudragit NE 30D, Eudragit NM 30D, Surelease, Aquacoat ECD und mit organischer Ethylcellulose überzogenen Pellets wurde untersucht. Die Art des benutzten Wirkstoffes sowie des Kerns beeinflusste die Wirkstofffreisetzung stark. Im Falle eines ungeladenen, wenig löslichen Wirkstoffes (Paracetamol) war die Freisetzung vom überzogenen Zucker- und MCC-Kern gleich, weil in beiden Fällen die Diffusion des Wirkstoffes durch den Überzug der hauptsächlich freisetzungskontrollierende Mechanismus war. Die Freisetzung von Propanolol HCl (geladen und löslich) aus überzogenen Zucker- und MCC-Kernen unterschied sich in der Verzögerungszeit (lag time) und Freisetzungsrate. Die Unterschiede bei der lag time rührten von den unterschiedlichen mechanischen Eigenschaften der Überzüge her, sofern sie unterschiedlichen Belastungen ausgesetzt wurden (osmotische oder Schwellung). Die Freisetzungsrate war generell schneller für überzogene MCC-Kerne als für Zuckerkerne, da das Schwellen der MCC-Kerne den Verlust des osmotischen Druckes von überzogenen Zuckerkernen kompensiert. Die Freisetzung von Metoprololtartrat (geladen und leicht löslich) aus überzogenen Zucker- und MCC-Kernen war identisch. Die Wirkstofffreisetzung war hauptsächlich durch die Löslichkeit des Wirkstoffes kontrolliert mit geringem Einfluss des Kerns.

Die überzogenen Pellets wurden thermisch nachbehandelt bei 40°C, 60°C und 60°C/75% RH für 24h und auf die Wirkstofffreisetzung untersucht. Das Ausmaß der thermischen Nachbehandlung auf die Wirkstofffreisetzung aus den überzogenen Pellets wurde bewertet und folgende Reihenfolge aufgestellt: Aquacoat ECD >> Eudragit NE 30D ~ Eudragit NM 30D > Surelease > Kollicoat SR 30D > organische Ethylcellulose. Die Wirkstofffreisetzung aus mit Kollicoat SR 30D und organischer Ethylcellulose überzogenen Pellets wurde kaum durch die thermische und die thermische/Feuchtigkeit Behandlung beeinflusst. Es wurde geschlussfolgert, dass die Filmbildung

während des Überziehungsprozesses komplett verlief. Die Wirkstofffreisetzung aus mit Eudragit NE 30D und Eudragit NM 30D überzogenen Pellets war gleichermaßen durch die thermische sowie thermische/ Feuchtigkeit Behandlung herabgesetzt. Dies kann der verstärkten Koaleszenz der Polymerpartikel mit steigender Temperatur zugeordnet werden ohne zusätzlichen Anteil von Feuchtigkeit bei der Filmbildung. Andererseits wurde die Wirkstofffreisetzung aus mit wässriger Cellulosedispersion überzogenen Pellets (Surelease und Aquacoat ECD) stärker durch die thermische/ Feuchtigkeit Behandlung herabgesetzt als die alleinige thermische Behandlung. Die Temperaturerhöhung erhöht die Beweglichkeit der Makromoleküle, ermöglicht die Vereinigung von randständigen Partikeln. Die Erhöhung der relativen Luftfeuchtigkeit erhöht den Wassergehalt des Systems und Wasser ist ausschlaggebend für die Kapillarkräfte, die die Polymerpartikel zusammenführen. Zudem fungiert das Wasser als Weichmacher für die Ethylcellulose, das zu einem dichteren Film führt. Folglich sinkt die Permeabilität des Überzugs für Wasser und Wirkstoff. Die Auflösung und Migration des hygroskopischen Metoprololtartrats durch den Überzug trat beim thermischen/ Feuchtigkeit Behandeln auf, das zu einem burst führte. Der burst war deutlicher bei überzogenen Zuckerkernen als bei MCC-Kernen.

Anhand der Lagerung bei 40°C/75% RH, RT/60% RH und 40°C für 1 und 3 Monate konnte das Freisetzungsprofil der Wirkstoffe verändert werden durch: 1) weitere sukzessive Koaleszenz der Polymerpartikel (unvollständige Filmbildung) durch unzureichende Nachbehandlung (Zeit und/oder Temperatur) und das Fehlen eines Nachbehandlungs-Schrittes im Falle von wässrigen Dispersionen mit niedriger MFT Eudragit NE 30D und Eudragit NM 30D. Dies führt zu einem herabgesetzten Freisetzungsprofil des Wirkstoffes; 2) die Wirkstoffmigration durch den Überzug, resultierend in einem burst, bei der Lagerung bei 40°C/75% RH. Der burst war stärker ausgeprägt bei den überzogenen Zuckerkernen als bei den überzogenen MCC-Kernen aufgrund einer höheren Wasseraufnahme der überzogenen Zuckerkerne in Anwesenheit von Metoprololtartrat. Die kritische relative Luftfeuchtigkeit für das Zerfließen, das bei Zucker und/oder Metoprololtartrat auftritt, wurde herabgesetzt, resultierend in der Auflösung und Migration beider Komponenten; 3) die Migration der Filmkomponenten innerhalb des Überzugs (z.B. des Tensids), die als Porenformer agiere, führte zu einer erhöhten Freisetzung aus Eudragit NE 30D überzogenen Pellets.; 4) Risse im Überzug aufgrund der Lagerung unter feuchten Bedingungen, entstanden durch

Feuchtigkeitsaufnahme und das Schwellen des Kernes, führten zu einem erhöhten Freisetzungsprofil des Wirkstoffes aus mit Eudragit NE 30D, Surelease und mit Aquacoat ECD überzogenen Pellets. Außerdem hatte die mechanische Stabilität der Wirkstoffschicht einen signifikanten Einfluss beim Induzieren oder Abschirmen des Überzugs vor Rissen. Metoprololtartrat-Schichten, zum Beispiel, konnten aufgrund ihrer hohen Feuchtigkeitsaufnahme dem Schwellen des Kernes standhalten und die Belastung innerhalb des Überzugs reduzieren, und so Risse im Überzug verhindern. Dem gegenüber riss die sehr brüchige Propanolol HCl-Schicht und gleichzeitig riss der Überzug.

Diese Arbeit zeigt die Wichtigkeit einiger Schlüsselfaktoren, die bei der Entwicklung von überzogenen Pellets (Matrix und Reservoir) beachtet werden müssen und bietet tiefere Informationen über geeignete Lagerungsbedingungen, um ein optimiertes, fertiges Produkt zu garantieren.

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7. Publications and Presentations

Research Articles

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Mota, J., Dashevsky, A., Kolter, K., Bodmeier, R., Aqueous polymeric film coatings (flexible and brittle): from curing to storage stability (in preparation).

Oral Presentations

Mota, J., Hoffart, V., Maincent, P., Bodmeier, R., Coated matrix multiparticulates drug delivery systems. 5th Galenos Thematic Workshop: “*GALENOS – TOWARDS A EUROPEAN PhD IN ADVANCED DRUG DELIVERY*” Dublin, Ireland, 2007.

Mota, J., Hoffart, V., Maincent, P., Bodmeier, R., Key parameters affecting metoprolol tartrate release from matrix cast films and coated pellets. *European Intensive Program - Galenos Course 2007*, Lyon, France, 2007.

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Mota, J., Körber, M., Hoffart, V., Bodmeier, R. Drug-containing polymer films used for the prediction of drug release from coated matrix pellets. 2006 *AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists*, San Antonio, Texas, USA, # 12173, 2006.

8. Curriculum Vitae

For reasons of data protection,
the curriculum vitae is not included in the online version

