NOVEL FORMULATION AND PROCESSING ASPECTS FOR COMPRESSION-COATED TABLETS AND FOR THE COMPRESSION OF POLYMER-COATED MULTIPARTICULATES

Dissertation zur Erlangung des akademischen Grades des
Doktors der Naturwissenschaften (Dr. rer. nat.)

eingereicht im Fachbereich Biologie, Chemie, Pharmazie
der Freien Universität Berlin
vorgelegt von

SORAVOOT RUJIVIPAT
aus Bangkok, Thailand

Juli, 2010

1. Gutachter: Prof. Dr. Roland Bodmeier

2. Gutachter: Prof. Dr. Jürgen Siepmann

Disputation am 5.Juli 2010

To My family, my late father (Pharmacist Wichian Rujivipat),
patients and their family, who suffer from colonic diseases

ACKNOWLEDGEMENTS

First of all, I wish to express my deepest gratitude to my supervisor, Prof. Dr. Roland Bodmeier for his guidance, helpful advices and support throughout my graduate studies. I am very thankful to him for the opportunity to study and do my research in his international group, especial in the research and development work for Pfizer.

I would like to thank Prof. Dr. Jürgen Siepmann for co-evaluating this thesis. Thanks are extended to Prof. Dr. Johannes Peter Surmann, Prof. Dr. Heinz Pertz and Dr. Martin Körber for serving as members of my thesis advisor committee.

I deeply thank to Dr. Neti Woranuch and Dr. Nuwat Visavarungroj for his help, suggestion and recommendation to do PhD. work with Prof. Dr. Roland Bodmeier; the Higher Education Commission of the Royal Thai Government for the scholarship.

I am particularly thankful to Dr. Nantharat Pearnchob, Dr. Mesut Ciper, Dr. Martin Körber, Dr. Andrei Dashevsky, Dr. Florence Siepmann, Dr. Ildiko Terebesi for the useful discussion; Nutsawadee Apichatwatana, Joana Mota, Zahra Galnbor, Julia Herrman, Mirko Voigt, Katrin Steiner, Hyun-jin Kim, Armin Hosseini for evaluating parts of this thesis; Burkhard Dickenhorst for his help with complex computer problems; Angelika Schwarz and Gabriela Karsubke for their assistance with administrative issues; Andreas Krause, Eva Ewest and Stefan Walter for the prompt and diligent technical support.

In addition, I would like to thank all present workgroup members and alumni I had the pleasure of getting to know for the friendly atmosphere in our workgroup and in particular for the stimulating discussions and the enjoyable atmosphere during lunchtime.

Finally, my deepest gratitude is dedicated to my family for their love and ongoing support.

TABLE OF CONTENTS

CHAPTERS **PAGE**

1. INTRODUCTION

1.1. Tableting of coated multiparticulates

Oral controlled release dosage forms comprising multiparticulates provide various advantages over single unit dosage forms: risk reduction of local irritation; less variable bioavailability; decrease of inter and intra-individual variation in bioavailability and various drug release profiles can be obtained by simple mixing pellets with different release characteristics. The preparation of multiparticulates in easy administrative form (single dosage form) can be manufactured by filling multiparticulates into hard gelatin capsules or compression them into tablets. The latter offers some advantages such as protection of tampering, reduction of difficulty in esophageal transport and less production cost. Preferably, tablets containing beads should disintegrate rapidly into individual beads and drug release should not be affected by the compression (Bodmeier, 1997). Tableting of reservoir type multiparticulates is more challenging than tableting of matrix type multiparticulates in term of film damage during compression. Parameters affecting the tableting of reservoir type pellets: polymer coating, pellet cores, tableting excipients and tableting process parameters (tableting machine speeds and pellets loading) are needed to be considered.

Polymer coating

The polymer coating is the most important parameter among key parameters for tableting of coated pellets. Polymers used in the film coating can be divided as cellulosic polymers, acrylic polymers and polyvinyl acetate. The film coating should be highly elastic and flexible enough to adapt to the deformation of pellets without rupturing (Chang and Rudnic, 1991). Polymeric coating should contain sufficient mechanical stability and remain intact during compression in order to control drug release. Lehmann et al. (1994) have revealed that at least 75% of elongation at break was required for compression of coated pellets without or with small damage of release controlling film. Solvent based coatings have been found to be more flexible and have a higher degree of mechanical stability than aqueous-based ones, and therefore less affected by compaction (Bodmeier and Paeratakul, 1994a). Ethyl cellulose films cast from the plasticized pseudolatexes, Aquacoat®, and Surelease® were very brittle and weak with low values of puncture strength and elongation (< 5%). The possible explanation could be incomplete fusion of latex spheres; molecular weight change due to the pseudolatex manufacture; stabilizer; stabilizer and plasticizer used in the formulation (Chang and

Rudnic, 1991). Comparing to ethyl cellulose films, the films prepared from acrylic and polymers and polyvinyl acetate are more flexible and therefore more suitable for the coating of pellets to be compressed into tablets. The flexible films reported to withstand the compression of pellets are Eudragit® NE 30D, Eudragit® RS 30D, Eudragit® RL 30D, Eudragit® FS 30D, (Wagner et al., 2000a and b) and Kollicoat® SR30D. Bodmeier and Paeratakul (1994) found that films of Eudragit® NE30D dispersion were very flexible with the elongation value in excess of 365%. With plasticized Eudragit® RS and RL30D, which are dispersions based on the cationic polymer, flexible films were obtained with elongation values in excess of 125%. Plasticized Kollicoat® SR30D became flexible with elongation values > 137% and coated pellets could be compressed into tablets with negligible damage (Dashevsky et al., 2004 and 2005; Sawicki and Łunio, 2005; Wei et al., 2009). The new enteric coating Eudragit® FS 30D was introduced as flexile film former and suitable for the tableting of coated beads. Coated pellets of this polymer coating (with 10% TEC plasticization) were compressible (Wagner et al., 2000a; Fürst, 2009).

Tableting of multiparticulates coated with brittle films (ethylcellulose and enteric films) would result in the damage of coating. The blends of flexible and brittle polymer for pellet tableting were investigated. The damage of enteric film (Eudragit® L 30D) during compression could be avoided with increasing film flexibility by blending the enteric polymer with flexible Eudragit® NE 30D (Lecomte et al. 2005). The coating thickness can play a role in protecting the film integrity during compression. Thicker coatings would increase in the mechanical strength of film to withstand the damage during the compression better than a thinner coating (Beckert et al., 1996).

The approach of multiple layered coating with different enteric coating on lansoprazole pellets was claimed to improve flexibility against tableting of pellets, stability of drug and taste of pellets (Shimizu et al., 2003). Since triethyl citrate had an unpleasant bitter taste and showed incompatibility with lansoprazole, PEG 6000 was applied in inner and outer of enteric coating.

Pellet core

Pellet cores also affect the compaction behavior of coated pellets. The core should contain some degree of elasticity, which can accommodate changes in shape

during compression. The desirable mechanical properties of the core should be strong, not brittle and have a low elastic resilience (Aulton et al., 1994).

Soft pellet cores have been used to prepare reservoir type pellets (Beckert et al., 1996). These soft pellets were prepared by a powder layering method using sucrose crystal as seed, adherent powder (a mixture of Lactose D80, Aerosil and Kollidon 25 as adherent) and binder dispersion (Eudragit® NE30D, sucrose and water). Adherent powder was poured into the coating pan during the spraying of the binder dispersion on sucrose crystal. The deformation of single pellets with and without maximum crushing strength has been presented from hard pellets (prepared by extrusion-spheronization) and soft pellets, respectively.

The incorporation of a soft waxy material: glyceryl behenate (Iloañusi and Schwartz, 1998); glyceryl monostearate (Pinto et al., 1997; Lundqvist et al., 1998); polyethylene glycol 6000 (Nicklasson and Alderborn, 1999a); paraffinic wax (Vergote et al., 2002), into pellet forming matrix in order to modify the compactability and to protect reservoir pellets has been studied. The improvement on deformation behavior is attribute to increasing pellet slide past each other; reduction in pellet thickness and porosity; facilitation of pellet deformation at low pressures.

Extrusion-spheronization pellets (40-80% ibuprofen, blends of Eudragit® RS PO/RL PO, Avicel® PH 101 and PVP K30 as binder) have been prepared (Abbaspour et al., 2007). The cured pellets containing 40% or 60% drug and more Eudragit® RS PO in the polymer blend underwent plastic deformation without fracture under mechanical tests. The change of Eudragit pellets from glassy to rubbery state upon curing was responsible for the observed plastic behaviour of the cured pellets. These results revealed that thermal treatment of Eudragit based pellets could be advantageous in the production of plastic pellets that are intended to be coated and compressed into tablets.

Pellet porosity can play a role on the compaction pattern and thereby affects the polymer coat integrity during compression. The pellet porosity was found to control the degree of deformation that the pellets underwent during compression (Johansson et al., 1995). The degree of deformation caused by a reposition of primary particles within the pellet, seemed to be controlled by the total air volume surrounding the primary particles in the pellets. Increasing pellet porosity increased the degree of deformation of the pellets during compression and the tensile strength of the tablets

because of the formation of stronger intergranular bonds. This was confirmed through a study of drying rate effect on porosity and compaction behaviour of microcrystalline cellulose pellets (Berggren and Alderborn, 2001). An increased drying rate gave more porous pellets, due to decreased pellet densification during the drying process which were more deformable and which formed tablets of a higher tensile strength. However, the incorporation of dicalcium phosphate dihydrate resulted microcrystalline cellulose pellets less compressible during compaction and the pore structure of the tablets more closed (Nicklasson et al., 1999b). This suggested that the primary particles are harder, it will be more difficult for them to flow within the pellet and the pellets will thus be more rigid and less prone to deform and densify during compression.

The similar finding of the pellet porosity on the degree of deformation was found (Tunón et al., 2003). The compaction behavior of EC reservoir pellets; extrusion-spheronisation pellets (containing microcrystalline cellulose and salicylic acid) and coated with EC, of three different porosities was investigated. Insignificant effect of the coating on the compression behaviour of the pellets was shown. Compacted pellets of high porosity were highly densified and deformed, while drug release was unaffected. In contrast, drug release of compacted pellets of low porosity was markedly increased while there was only slight densification and deformation.

Tableting excipients

The ideal tableting excipients used for compression of coated pellets should prevent the direct contact of pellets and act as cushioning agent during tablets compression. The excipients should result in robust tablets at low compression force, rapidly disintegrating and no influence on drug release (Bodmeier, 1997).

To obtain desired tablets: acceptable content uniformity of pellets, without the direct contact of pellets and absence of coating rupture, pellet to excipient proportion and compression are needed to be considered. Theoretically, 29% of excipient is needed to fill the void space between closely packed pellets in tablet formulation (Beckert et al., 1998). Soft tableting materials: carrageenan (Picker, 2004); chitosan and alginates (Schmid and Picker-Freyer, 2009) were used as soft excipients to avoid the damage of coat during compression. Deformable of kappa carrageenan was presented by deformation with minimal fragmentation of drug matrix pellets of this material (Ghanam et al., 2010).

The attempts to overcome the segregation of pellets and excipients have been performed by (1) tableting of pellets with comparable size of granulated excipients or cushioning pellets or (2) adhesion (spraying or granulation) of cushioning agent on pellets to be compressed.

Tunón et al. (2003) showed that ethylcellulose coated pellets could withstand the compression with an incorporation of microcrystalline cellulose pellets with different physical properties. The reservoir pellets were shown to undergo extensive deformation and densification during compaction and more preserved with small size and high porosity microcrystalline cellulose pellets.

Hot tableting of coated pellets could be applied when low melting point materials are incorporated as cushioning excipient. The successful tableting of ethylcellulose coated pellets into tablets were performed using PEG 3000 granules as cushioning excipient and processed at 56 °C with 1 kN (Sawicki and Magalski, 2009). EC coated pellets were compressed and embedded within molten PEG. Additional layer coating of cushioning agents on pellets was applied to avoid segregation and to protect coated pellets during tableting.

Ethylcellulose coated pellets with sufficient coating (about 8% weight gain) were less damaged during compaction by blending with soft pellets (30% glyceryl mono-stearate, 20% microcrystalline cellulose and 50% barium sulphate) and disintegrant pellets (Lundqvist et al.,1998). The soft pellets added restricted the drug pellets from deforming and to hold the tablet together by deformation during the compaction. Similar result, compression of coated pellets into tablets with incorporation of wax beads (paraffinic wax) as cushioning materials was investigated by Vergote et al. (2002).

The adhesion of cushioning agent on coated pellets to be compressed has been applied studied. Altaf et al. (1999) used polyethylene oxide as the cushioning agent by spray coating on ethylcellulose coated pellets and microcrystalline cellulose was coated on the top. The compacted PEO layered beads with 5% sodium starch glycolate (Explotab®) disintegrated into individual beads and provided sustained release up to 8 h. However, it was postulated that the PEO was hydrated and formed a gel that acts as a sealant for the cracks formed in the ruptured polymer coating. The overcoating of HPMC as a protective layer to minimize coating film damage during compression was studied (Chambin et al., 2005), but this layer affected drug release behavior also. The fast applying compressible excipient onto coated pellets by centrifugal granulation method

was introduced by Pan et al. (2010). In this granulation process, binder solution was sprayed in parallel with powder excipients. However, the influence of some cushioning agent (sodium alginate) on the drug release retard was observed.

Tableting process parameters

The proper adjustment for tablet shape, having the smallest surface area/volume ratio, would result in better pellet protection during compression was found by Wagner et al. (2000b). The influence of tableting machine speeds on the film coating integrity is one parameter needed to be considered. Increasing the machine speeds led to increasing the bisacodyl release from Eudragit® FS30D after 2 h in pH 1, indicating an increase of coating damage Wagner et al. (2000a).

The loading of coated pellets in compressed tablets is needed to be concerned for good drug uniformity and preventing segregation of coated pellets. Beckert et al. (1998) found that mixtures with 30% w/w pellets showed good uniformity with granulated excipients. With 50-70% w/w pellets in a tablet, good content uniformity was found. This can be explained by the formation of a percolating cluster of the pellets, which prevented segregation. A threshold of at least 50% w/w, corresponding to 30 % vol./vol. pellet content has to be reached. The maximum achievable pellet content is reached by a rhombic lattice and is 71% v/v. However, damages of pellets and coatings during tableting increase upon increasing the pellet content of the mixture (Aulton et al., 1994). With higher coated pellets loading, non-segregating mixtures of coated pellets and filler-binders are necessary to obtain tablets of uniform weight and drug content. Granules or pure microcrystalline cellulose, having a large surface area and a fibrous surface texture built a close percolating infinite cluster stabilizing the pellets at their location in the mixture (Wagner et al., 1999).

1.2. Plasticization of polymer coating

Plasticizer is a necessary component for pharmaceutical formulation especially for coating and hot melt extrusion. The addition of plasticizer in the formulation can provide advantages and disadvantages especially for film coating. The main advantage of using plasticizers is to increase film toughness or resiliency by

increasing flexibility, decreasing tensile strength and increasing elongation. However, plasticizers also have the disadvantage of increasing film permeability, depending on the type of plasticizer. For instance, hydrophilic plasticizers are low barriers to moisture and tend to have a more pronounced effect on increasing water vapor permeability compared to oxygen permeability. This would result to the lost of controlled release of polymeric coating. Recently, plasticizing effects from some pharmaceutical ingredients (drug, surfactant, preservative, moisture) or environmental condition have been published. To avoid the toxicity of plasticizers, these ingredients and environmental treatment might be used for plasticization. Plasticizers in the formulation have been found to conduct a plasticization and antiplasticization.

Plasticization and Antiplasticization

Plasticizers can increase the polymer flexibility or plasticity, and occasionally they are used only to facilitate the polymer processing. Ideal plasticizers are miscible and compatible in all proportions with plastic components, and they may be added to polymers in solution (dispersion technique) or after solvents have been removed (absorption technique) (Santosa and Pauda, 1999). Some theories have been proposed to explain the mechanisms of plasticization action (Kern Sears and Darby, 1982; Di Gioia and Guilbert, 1999; Marcilla and Beltrán, 2004).

The lubrication theory postulates that plasticizers act as internal lubricants by reducing frictional forces by interspersing themselves between polymer chains.

The gel theory postulates that the rigidity of polymer comes from three-dimensional structures through the center of force (e.g., hydrogen bonds and Van der Waals or ionic forces), and plasticizers take effect by breaking polymer-polymer interactions and masking these center of force.

The free volume theory states plasticization as a study of ways to increase free volume and is useful in explaining the lowering of the T_g by a plasticizer. The free volume or free space of a crystal, glass or liquid may be defined as the difference between the volume observed at absolute zero temperature and the volume measured for the real crystal, glass or liquid at a given temperature. This may be expressed by the equation:

$$V_f = V_t - V^0$$

Where V_f is the free volume, V_t is the specific volume (cc/g) at temperature *t*, and $V°$ is the specific volume at some reference point. Unfortunately, it is difficult to determine the volume at 0° K and not all substances behave as we might predict as they approach absolute zero. The free volume concept therefore remains somewhat vague and confusingly defined in the literature because of these difficulties with the lower reference point.

In an ideal crystal at absolute zero we can imagine all atoms or molecules perfectly compact in a completed lattice. In a real crystal they are not this compact, supposedly as a result of nonharmonic vibrations and because of imperfections in the lattice structure, commonly called holes. In a liquid, the number or volume of these holes has increased greatly. The free volume is divided into two parts: (1) a continuous part that results from oscillations and that persists and increases slightly as the temperature is raised and (2) a discontinuous part called holes, which increases greatly with temperature.

In specific volume of material and temperature relationship, the glassy matter becomes rubbery or fluid (obviously increasing specific volume). When the temperature is above Tg, the molecules have enough energy to move, bend or rotate. The Brownian motion of molecules or segments of molecules produces a greater amount of free volume (the torsional or hole free volume).

Free volume comes from three principal sources: (1) the motion of chain ends, (2) the motion of side chains and (3) the motion of the main chain. These motions, and therefore the free volume of a resin system may be increased by:

1. Increasing the number of end groups. (lower the molecular weight).
2. Increasing the number or length of (proper) side chains. (internal plasticization)
3. Increasing the chance for main chain movement by inclusion of segments of low steric hindrance and low intermolecular attraction (low polarity and H bonding). (internal plasticization)
4. Inclusion of a compatible compound of lower molecular weight that acts as though it does all of 1 through 3 above. (external plasticization)
5. Raising the temperature.

The anti-plasticization in polymer-plasticizer (small amount) system has been observed; starch-glycerol (Lourdin et al., 1997) and chitosan-5% propylene glycol (Suyatma et al., 2005). They may be almost totally immobilized by attachment to the resin *(bound plasticizer)* by various forces including hydrogen bonding, resulting in a "cross-link" effect. This can decrease the free volume and molecular mobility of the polymer chain leading to restrict the freedom of small portions of the polymer molecule, side chains and segments, which is necessary for the absorption of mechanical energy. Therefore, it results in a more rigid resin (increasing the crystallinity) with higher tensile strength and modulus than the base polymer itself but with poorer impact resistance and less elongation.

For hydro-plasticization, water could provide a plasticizing effect or may form stable bridges through hydrogen bond resulting in an antiplasticization. The antiplasticization of water has been found in starches (little crystallinity in dry state) with the introduction of 4-5% water which could initiate the appearance of crystallinity. This could be explained by the hydration of amylose leading to increasing the major intermolecular forces from H-bond between hydroxyl groups of different anhydro-glucose units and those between these unit and water (Zografi and Kontny, 1986).

Kern Sears and Darby (1982) have illustrated the explanation diagram of plasticization and antiplasticization with plasticizer (Fig. 1) using the arrangement of polymer according to the fringed micellae theory. The large polymer molecules can arrange themselves, line up together and compactly form crystallites, which confer rigidity to the polymer. The amorphous area (short chains, abnormal branching, impurities or irregularities of the polymer chain) has associated more free volume, since conformational changes are permitted and so tend to be more flexible. Plasticizer molecules situate themselves around the polymer chains, preferentially in the amorphous areas. The introduction of plasticizer molecules into the polymer involves the addition of more free volume resulting in more flexibility and ease of movement to macromolecules. When a small quantity of plasticizer is added, many polymers tend to increase the number and size of their crystallites. This results in a more rigid resin with higher tensile strength and modulus as antiplasticization. Increasing amount of plasticizer added to the polymer, the crystallinity may increase, but the amorphous areas are swollen, resulting in a softer material. The polymer becomes more flexible. When even more plasticizer is added the crystallites could be dissolved and a gel is obtained.

Pharmaceutically acceptable plastcizers used (traditional plasticizers)

Plasticizers are generally non-volatile, high boiling, non-separating substances. Plasticizers used in a polymeric system should be miscible with the polymer and exhibit little tendency for migration, exudation, evaporation, or volatilization. Many compounds can be used to plasticize polymers. Phthalate esters such as diethyl phthalate, sebacate esters such as dibutyl sebacate, and citrate esters such as triethyl citrate and tributyl citrate are commonly used as plasticizers. Various glycol derivatives including propylene glycol and polyethylene glycol have also been used to plasticize polymeric films (Felton, 2007).

Plasticizers can be divided into water-soluble and -insoluble plasticizers. Water-soluble plasticizers are dissolved, while insoluble plasticizers have to be emulsified in the aqueous phase of the polymer dispersions. The effectiveness of plasticization is resulted from the partition of plasticizer from the solvent phase into the polymer phase and subsequently diffuses throughout the polymer to disrupt the intermolecular interactions. The rate and extent of this partitioning for an aqueous dispersion have been found to be dependent on the solubility of the plasticizer in water and its affinity for the polymer phase. The partitioning of water-soluble plasticizers in an aqueous dispersion occurs rapidly, whereas significantly longer equilibration times are required for water-insoluble plasticizing agents (Bodmeier and Paeratakul, 1994b). The amount of lipophilic plasticizer taken up by the polymer phase in aqueous dispersion as a function of contact time was elucidated by Siepmann et al.(1998).

Non-traditional plasticizers used in pharmaceutical technology

Drug

The plasticizing effects of active pharmaceutical ingredients (APIs) on polymers have been presented. Influence of drugs (acetaminophen, naproxen, propranolol hydrochloride, salicylamide, carbamazepine, griseofulvin) on the glass transition temperature of poly(vinylpyrrolidone) was investigated using thermodynamic and spectroscopic determinations (Nair et al., 2001). The presence of hydrogen bonding between these drugs with PVP (through carbonyl group) was the explanation for the plasticizing effect (Sekizaki et al., 1995; Bogdanova et al., 2005). Zhu et al. (2002)

studied the plasticization influence of chlorpheniramine maleate (CPM) on Eudragit® RS PO from hot-melt extruded matrix tablet and from compressed granules prepared by thermal processing, comparing to triethyl citrate (TEC). Wu and McGinity (1999) investigated the influence of ibuprofen and CPM on the thermal and mechanical properties of polymeric films prepared from aqueous dispersions of Eudragit® RS 30D. Both drugs were found to decrease the tensile strength of the polymeric films and the Young's modulus of the coated pellets. Drug release decreased with increasing drug level in the polymeric film coating, indicating an increasing degree of coalescence between the latex particles, which is observed with increasing levels of usually used plasticizers). Scanning electron microscopy pictures of pellets coated with ibuprofen-containing Eudragit® RS 30D dispersions confirmed this hypothesis (Wu and McGinity, 2001). An increase in the drug content of film coatings resulted in smoother film surfaces. Fourier Transform Infrared Spectroscopy (FTIR) revealed that ibuprofen interacted with the acrylic copolymer via hydrogen bonding. In addition, Kangarlou et al. (2008) showed the higher plasticizing effect of cholecalciferol and α-tocopherol in ethylcellulose casted films compared to DBS with a concentration range of 40-50% (w/w) based on ethylcellulose.

Preservative

The plasticizing effect of methyl-paraben on the thermal and mechanical properties of Eudragit® RS 30D films and hot melt extrudates was found by Wu and McGinity (1999 and 2003). Increasing of methylparaben in the film resulted in a decrease in tensile strength of the film. This could be demonstrated by decreasing of glass transition temperature in the presence of ibuprofen and methylparaben in the film.

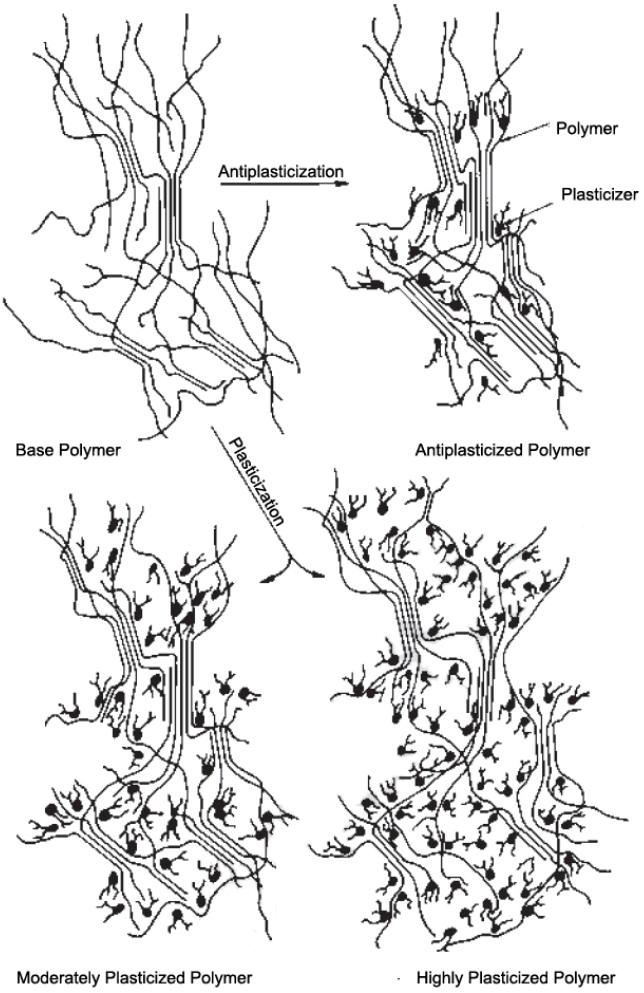


Fig. 1 The concept of plasticization of a resin, explaining plasticization and anti-plasticization (Kern Sears and Darby, 1982)

Surfactant

The plasticizing effect from the use of surfactants to prepare solid dispersions of poorly soluble APIs is other instances of non-traditional plasticizer. Ghebremeskel (2007) has incorporated some surfactants (Tween-80, docusate sodium, Myrj-52, Pluronic-F68 and SLS) into the physical blends of the poorly soluble API and hydrophilic polymers such as PVP-K30, Plasdone-S630, HPMC-E5, HPMCAS, and Eudragit® L100 (mass ratio 1:1). The thermal analysis of the API–polymer–surfactant blends suggested that the surfactants caused solvation/plasticization, manifesting in reduction of (1) the melting (T_m) of API (2) T_g of the polymers and (3) the combined T_g of the solid dispersion formed from quench cooling. Furthermore, extruded matrices containing different API–polymer (PVP-K30, Plasdone-S630, and HPMC-E5) mixtures

prepared with or without surfactants were produced by feeding the powder blend through a hot-melt extruder. The results from differential scanning calorimetry, X-ray diffraction, raman spectroscopy and polarized microscopy illustrated that the glass transition temperature of the carrier polymers decreased as direct result of the surfactants in the extrudate. The decrease of glass transition temperature leads to a increase in the chain mobility of polymers and a decrease in the melt viscosity for hot melt extrusion process.

Process condition

Abbaspour et al. (2007) have employed thermal treating to prepare plastic pellets based on Eudragit® RS PO and RL PO aimed for tableting. The mechanical test of matrix pellets containing ibuprofen, Eudragit® RS PO/RL PO, 3% w/w PVP K30 and 10% Avicel PH101 showed the brittle behavior. Cured pellets at 60 °C/ 24 h exhibited a plastic deformation without any fracture under mechanical tests. The transition of pellet deformation behavior from brittle to plastic upon curing was attributed to changing of Eudragit structure from glassy to rubbery state which was supported by DSC results.

Pearnchob and Bodmeier (2003a) have reported that even with a high concentration of plasticizer used in dry coating of micronized Eudragit® RS on pellets, a thermal treatment was necessary to achieve complete film formation and extended drug release. In addition, moisture could be applied as auxiliary plasticizer. The chemical and mechanical properties of cellulose acetate phthalate (CAP) free films plasticized with diethyl phthalate or triethyl citrate were compared following heat-only (50 °C for 24 h) and heat-humidity curing (50 °C/75% RH for 24 h) conditions (Liu and Williams III, 2002). The superior mechanical properties of heat-humidity curing films were attributed to (1) the plasticizing effect of moisture in creation the driving force for film coalescence when exposed to heat and (2) the suppression of plasticizer evaporation, resulting in higher plasticizer levels remaining in the films, as compared to the heat-only curing condition. As many previous reports about the application of thermal treatment used in curing coated films, moisture treatment would be also used as plasticizer in coated film.

Water

The potent plasticizing effect of water for amorphous and partially amorphous solids has been revealed, regarding to glass transition temperature of water about 135 K or -138^{o}C (Sugisaki et al, 1968). Most amorphous solids spontaneously

absorb moisture from the environment especially for hydrophilic polymers. The behaviors of absorbed water in a polymer have been studied using calorimetric and spectroscopic techniques and classified into three species.

(1) *non-freezable bound water*; this specie is defined as the water closely associated with the polymer matrix and does not cause to observable phase transitions by calorimetric analysis. This water is not crystallized even when the swollen sample is cooled down to -100°C

(2) *freezable bound water*; this water is the fraction less closely associated to the matrix and exhibit a melting/crystallization, showing considerable super cooling and remarkably smaller enthalpy than that of bulk water. This water is crystallized at a temperature lower than 0°C.

(3) *freezable free (bulk) water*; this specie shows the melting/ crystallization temperature and the relative enthalpy is not significantly different from that of normal (bulk) water.

The non-freezable bound water is responsible for the plasticizing effect on the polymer. Water molecules, interacting with the polar chain groups, disrupt polymer chain-chain hydrogen bond, resulting in bond rotation and chain mobility could be attributed to the free volume theory. The interactions with the polar chain groups, which contribute to the changes of water thermodynamic characteristics, could contribute to the lubrication effect. These mechanisms are postulated for the plasticizing effect of water in poly (vinyl alcohol) (Hodge et al., 1996). Moreover, the hydration of poly (methacrylic acid) and the resulting interference of water with the intra- and inter-chain hydrogen bonding caused by carboxyl group (Tajiri et al., 2009).

Hancock and Zografi (1994) revealed the lowering of glass transition temperature of amorphous pharmaceutical solid by increasing water content. Sebhatu et al. (1997) have found that compression of amorphous lactose powder was facilitated by increased moisture content. Steendam et al.(2000) showed the plasticizing effect of moisture on the compression characteristics of amylodextrin powders and the porosity of

tablets. Bravo-Osuna et al. (2007) have reported the plasticizing effect of absorbed water on compressibility of methyl methacrylate-starch copolymers.

Amighi and Moes (1996) found that the curing rate of Eudragit® RS 30D coated pellets increased as the storage humidity was increased. In high relative humidity environment, the water within film functions as a plasticizer that increases the polymer chain mobility in polymer inter-diffusion leading to the enhancement of the coalescence process. Chen et al. (2005) revealed the moisture in ambient environment significantly influenced the glass transition temperature and microstructures of the glycerol-plasticized soy protein sheets, leading to the changes of the mechanical and thermal properties.

Bodmeier and Paeratakul (1994a) explored that films based on enteric acrylic latex, Eudragit® L30D-55[poly(methacrylic acid-ethyacrylate) with a ratio of 1:1], were brittle and Eudragit® L30D-coated pellets were ruptured after pellets compression. Dry Eudragit® L30D-55 was weak and brittle (elongation less than 1%), however, the wet films became flexible and have enough elasticity to deform on coated pellets during compression without rupture (elongation more than 365%).

Garcia et al. (2004) revealed the effects of moisture content on adjusting stiffness of a useful plastic material for dog chew preparation. Meat and bone meal were extrusion-processed along with sodium caseinate. The glass transition temperature and elastic modulus decreased with the plasticization of water. A particular desired stiffness can be maintained by applying an edible moisture barrier to the surface of the material.

Kojima and Nakagami (2002) studied the use of water as the plasticizer in development of controlled release matrix pellets from micronized ethylcellulose and hydroxypropylmethylcellulose acetate succinate (HPMCAS-HF). The annealing temperature needed for control-released matrix forming was reduced with water.

Tableting of coated multiparticulates into tablets can be achieved, mainly by increasing the film flexibility. Some pharmaceutical excipients (drug, surfactant or preservative) or environment condition (thermal and/or moisture) could be employed as non traditional plasticizer to decrease glass transition temperature of polymeric films, resulting in improving of film flexibility. Water having low glass transition temperature and small molecule can be applied as a potent plasticizer for tableting of coated pellets, therefore was investigated in this study.

1.3. Compression coated tablets as drug delivery system

Pharmaceutical coatings are an essential tool to achieve the desired formulation of pharmaceutical dosage forms. Coatings are applied to achieve superior aesthetic property of a dosage form (e.g. color, texture, mouth feel and taste masking), physical and chemical protection for the drugs in cores, and modified drug release characteristics. Coating techniques mostly used in pharmaceutical industry are aqueous or organic coating, which present some disadvantages: time consuming, stability for heat labile and hydrolysis of degradable drug and polluted environment problem. Thereby, non-solvent coating is introduced as alternative coating technique to overcome these disadvantages. Non-solvent coatings have been categorized as press coating, hot melt coating, supercritical fluid spray coating, electrostatic coating, dry powder coating and photocurable coating (Bose and Bogner, 2007). Among these techniques, compression coating is the absolute dry coating without solvent and heat use. Aditionally, compression coating has no limitation for the cores and hence overcomes the adhesion problem found in spraying methods. Tablets with cylinder or special shapes can be press-coated.

Application of compression coating technique in pharmaceutical formulation

Compression coating, or press-coating, has been introduced during the period 1950-1960 (Windheuser and Cooper, 1956) to formulate incompatible drugs. This coating became interesting in the last two decades owning to the advantages over liquid coating, since the process does not need the use of solvents, requires a relatively short manufacturing process and allows greater weight gain to the core tablet. Nowadays, pharmaceutical aspects of compression-coated tablets in dosage form development are: (1) to protect hygroscopic, light-sensitive, oxygen labile or acid-labile drugs; (2) to separate incompatible drugs from each other and achieve sustained release; (3) to modify drug release pattern (delayed, pulsatile and programmable release for different drugs in one tablet). However, some drawbacks of compression-coating technique are: (1) the requirement of reliable and reproducible central positioning of the core tablet within compression-coated tablet, the need of a multiple-step process or a special tableting machine. Recently, the common manufacturing problems for compression-coated tablets, such as central positioning of the core in the compression-coated tablets and absence of

core in coat, have been overcome by applying a novel one-step dry coated tablet (OSDRC) method invented by Ozeki et al.(2003a).

The OSDRC system has been introduced to improve tableting of low compressible material (such as acetaminophen) as the core, with no diluents by using high tabletability excipient as the coat (Ozeki et al.,2003b). The radial tensile strength of OSDRC tablets was the same or superior to that of physical mixture tablets. However, the advantage of OSDRC compared to physical mixture in term of drug loading has not been mentioned. A novel sugar coating method by compression using OSDRC system for moisture protection has been introduced by Ando et al. (2007a).

The application of compression-coating technique to protect acid labile biomaterials; probiotic (Chan and Zhang, 2005) and Nattokinase (Law and Zhang, 2007) has been studied. Successful gastric protection and colonic delivery of probiotic has been achieved in carboxymethyl high amylose starch compression-coated tablets (Calinescu and Mateescu, 2008).

A fix dose combination drug comprising telmisartan (angiotensin II receptor antagonist), ramipril (angiotensin converting enzyme) and optionally, a diuretic such as hydrochlorothiazide, was innovated in form of an immediate release multilayer tablet (Kohlrausch, 2005). The tablet combined the features of pharmacological efficacy, adequate drug stability (due to the incompatibility between telmisartan and ramipril) and a robust manufacturing method was successfully prepared using compression coating technique.

The uses of compression coating technique in controlled release drug delivery systems have been recently published. pH independent matrix tablets containing a weakly basic drug with controlled microenvironmental pH was studied by Siepe et al.(2006). The release of soluble pH modifiers out of tablet cores was retarded by compression coating technique, when compared to normal matrix tablet. In this case, compression-coated tablets, which contained a core of succinic acid as a pH modifier reservoir and a coat of dipyridamole, HPMC K100 and succinic acid, could successfully increase the release of the weakly basic drug in higher pH medium by reducing the microenvironment pH in the matrix coat.

Nowadays, the use of compression-coated tablets in colon drug delivery systems (Colonic DDS) by applying time, pH, and microbial control has been investigated.

Classification of compression-coated tablets based on core surface coating

The application of compressed polymeric coat on tablets for modified or controlled drug delivery systems have been developed and investigated to improve the performance of drugs, to increase the pharmacological effect and reduce side effects. Based on the simplest matrix device where the drug is homogenously dispersed in the polymer network. If surface of cores is partially coated with different properties of polymer, a variety of modified or controlled release can be obtained (Conte and Maggi, 2000; Abdul and Poddar, 2004; Efentakis and Politis, 2006a-b). The preparation development based on this concept can improve or adjust the drug release in a desired manner.

Multilayer compressed tablets consisting of a drug layer and one or more barriers (compression coats) applied by tableting, have been studied (Conte and Maggi, 1996; Chidambaram et al., 1998; Streubel et al., 2000). These barriers can provide a delayed or modified drug release by limiting or reducing the available surface for drug release and controlling the medium penetration rate. The core in impermeable cup systems (Efentakis et al., 2006) has been used for delayed drug release. Drug releases after the erosion of top surface, while impermeable cup prevents the release from the lateral side.

A compression-coated tablet is a system in which the all surface of an inner core is completely surrounded by coat. These coats prevent drug release from the core until the polymeric coat is entirely eroded, dissolved or removed (breaking down). Different drug release fashion could be obtained depending on coating layer and core composition.

Controlled release systems from compression-coated tablets

Compression-coated tablet consists of a core (fast disintegration or modified release) which is coated by compression with a solid barrier. The barrier could contain polymeric material, diluent (as a release modifier) and drug (for extended release). Compression-coated tablets could be modulated to provide different release patterns depending on the drug distribution and plus with different type of controlling polymer used in core and coat. Based on this concept, the possibly obtainable modified drug

releases are extended release and delayed release (time, pH and microbially control) for specific region of gastrointestinal tract.

Multiphasic release

Multiphasic release is a delivery system designed for many diseases which have marked diurnal rhythms, while constant drug release does not meet the optimum therapeutic efficiency. In such diseases, drug concentrations are needed to vary during the day. Drug levels need to be highest when symptoms are most severe. In the system, drug is presented in coat and core as a non uniform drug distribution matrix which results in biphasic drug release. For instance, Adalat® CC is a compression-coated matrix tablet that provides zero-order sustained release, followed by a delayed burst release.

Sirkiä et al. (1994) have prepared salbutamol sulphate compression-coated tablet which provided extended drug release pattern in early period and increasing drug release rate after 4-6 h. By varying the amount of salbutamol sulphate and HPMC used in the coat, drug release rate could be programmed.

With the combination of therapeutic drugs in one tablet, a variety of drug release: sequential release of different drugs or multi-phasic release of drugs is achievable. Sucralfate (a protective agent for the treatment of gastro-duodenal ulcer) was compressed as the immediate release shell on sodium diclofenac-HPMC extended release tablets, which could overcome the problem of peptic ulceration associated with NSAIDs therapy (Maggi et al., 1993). Compression-coated tablets of antihistamine and decongestant, cetrizidine dihydrochloride and pseudoephedrine HCl, were prepared by Waterman and Fergione (2003). Cetirizine dihydrochloride was compress-coated as immediate release layer on pseudoephedrine HCl osmotic controlled release tablets. The release of pseudoephedrine hydrochloride from osmotic controlled release tablet cores was not influenced by the compression coating.

Compression-coated tablets containing methylphenidate HCl (water soluble drug) have been prepared with a formulation comprising a soluble drug and a waxy material (carnauba wax) as a core. Different controlled release coats comprising of HPMC and carnauba wax have been used to adjust the release of drug. Zero, first and second order release profiles could be obtained with the variation of drug distribution in core and coating (Vilkov, 2004). A quick/slow biphasic release of ibuprofen from compression-coated tablets was prepared (Lopes et al., 2007). The fast release layer of

ibuprofen was compressed with microcrystalline cellulose and sodium croscarmellose on an ibuprofen extended release core. A good *in vitro/in vivo* correlation was obtained from HPMCs compression-coated tablets which contained one part of pseudoephedrine HCl in the cores and the other part of drug in the coats (Halsas et al., 2001).

The TIMERx Burst CR from Penwest Pharmaceuticals Co. was formulated as an immediate release of decongestant and plus with 24 h extended release. Drug for the immediate release was incorporated in the coating and the remaining drug was formulated in the matrix to achieve a 24-hour release profile. The matrix consisted of two polysaccharides, xanthan and locust bean gum. Interactions between these components, they form a tight gel in an aqueous environment with a slowly-eroding core.

Compression-coated tablets with multiple layers for desirable therapeutic use can be prepared. Multiple layer compression-coated tablets containing immediate release (outer coat), extended release (middle coat) and immediate release (core), have been patented by Impax Pharmaceuticals Inc. (Ting and Hsiao, 2002). Different drug release patterns can be obtained with adjusting drug loading and polymer type in each layer.

Delayed release

Delayed release, defined with lag phase and followed with release phase, is obtained when all surface of core is compression-coated. Pulsatile release defined by fast drug release after a certain lag time could be categorized within this group as well. Lag time for drug release could be controlled by the application of different polymeric coats which were differentiated with triggering factors to control drug release as mainly mentioned in colonic drug delivery system.

Time controlled release

A delayed release tablet consists of a drug core which is compression-coated with different polymeric (pH independent) barriers. This delayed drug release is programmed for the treatment of disease that depends on circadian rhythms. The lag time of drug release is controlled by the compression coating, which prevents drug release from the core until the polymer coat is completely eroded, swollen or ruptured. Drug release pattern depends on the compression-coat properties. The press-coating could be performed with water soluble polymers (hydroxypropylcellulose, hydroxylpropyl-

methylcellulose, pectin, polyethylene oxide), water insoluble polymer (ethylcellulose) and wax (Behenic acid).

Lodotra®, a delayed-release of glucocorticoid for rheumatoid disease, is prepared using compression coating technnique (Geoclock® from Skyepharma) (Schaeffler, 2008). The compression-coat comprising 30-50% of glycerol behenate, 40-60% of insoluble filler (eg. dibasic calcium phosphate) and 7-10% of polyvinyl-pyrrolidone (binder) was compression-coated on a fast disintegrating tablet.

Verapamil HCl tablets with floating-pulsatile release properties were prepared by compression coating of the drug core in an hydroxylpropylmethylcellulose compression-coat (Zou et al., 2008). The buoyant layer, consisted of hydroxylpropyl-methylcellulose K4M, Carbopol® 934P and sodium bicarbonate to prolong the retention of the tablet in the stomach, was additionally compressed on the hydroxylpropyl-methylcellulose press-coated tablet.

In addition, thermosensitive polymers have been studied for the use in time controlled release. Eeckman et al. (2002 and 2003) have employed poly (N-isopropyl acrylamide); a thermoresponsive polymer, as compression coating material for time controlled release by using salts or surfactants in the coat as controlling agents. Type and amount of salts and surfactants can control the lag time of drug release by changing the solubility of this polymer. The influence of both could be explained by lowering the critical point solution temperature (LCST) or inverse phase transition temperature of the polymer. As the temperature increases beyond the LCST, polymer become insoluble and phase separation occurs. Below this temperature, the polymer is soluble in aqueous media and the polymer chains are extended and surrounded by water.

pH controlled release

A delayed release system using enteric polymers as a coating can provide site-specific drug delivery especially for colon. This system has attracted a great interest for the local treatment of a variety of bowel diseases and for improving systemic absorption of therapeutic agents susceptible to enzyme digestion in the upper gastrointestinal (GI) tract, while time controlled release can not achieve owing to large variations in gastric emptying time.

Fukui et al. (2001a) have prepared the compression-coated tablets of diltiazem hydrochloride intended for the colon targeting. HPMCAS (AQOAT©AS-LF), 80% w/w of coat, and calcium stearate/magnesium stearate (1:1), 20% w/w of coat, were applied as the coat in their study. Compression-coated tablets for colonic drug delivery which suppress drug release in pH 1.2 for 12 h and have a lag time of 3±1 h in pH 6.8, could be achieved. In addition, Nattokinase (a fibrinolytic enzyme which can prevent the coagulation of blood and dissolve existing thombus) was unstable below pH 5.0 and susceptible to hydrolysis. Nattokinase could be successfully protected from gastric juice and released in the lower GI tract by compression coating with Eudragit® L100-55 and hydroxypropylcellulose (as release modifier) (Law and Zhang, 2007). Besides, time controlled release compression-coated tablets could also be modified to pH/ time controlled release by additional enteric coating on compression-coated tablet (Fukui et al., 2000b).

Microbial controlled release

A delayed release system may be aimed for colon drug targeting. This system is based on the degradation of the polymeric compression-coat by specific enzymes produced by entero-bacteria in the colon. Microbially degradable polysaccharides containing glycosidic bonds such as alginates, amylase, arabinogalactan, arabinoxylan, cellulose, chitosan, chondroitin sulfate, dextran, galactomannan (guar gum, locust bean gum), inulin, karaya gum, laminarin, pectins, starch, tragacanth gum, xanthan gum and xylan, could be employed as a coat. The investigated polysaccharides used for colonic-specific drug delivery which could also be used in compression-coated tablets included high methoxy pectin (Ashford et al., 1993), pectin plus HPMC (Ugurlu et al., 2007) and guar gum (Krishnaiah et al., 2002). Site specific DDS for colon would be expected, however drug release take considerable time to degrade and there are potential issues with the impact of diet and disease on the GI–tract microbial population (Basit, 2005).

Combinations of these systems are employed in compression coating for colonic DDS. Time and pH controlled system from Eudragit® S 100 spray coating on HPMC E15 compression-coated tablets (Gohel et al., 2008). Combination of time (pH)

and bacterially controlled systems by using of spray-dried chitosan acetate and ethyl cellulose was investigated by Nunthanid et al. (2009a).

Factors affecting on the drug release

Tablet cores

Drug solubility

Lin et al. (2002) have investigated the effect of drug solubility: diclofenac sodium, theophylline anhydrous and salbutamol sulfate in cores containing sodium starch glycolate (50% of drug) as disintegrant and ethylcellulose (fined powder) was used as the compression-coat. Higher solubility drug containing cores in compression-coated tablets provided shorter lag time than lower solubility drug containing cores. Rapidly and completely release of diclofenac sodium and salbutamol sulfate was presented, while theophylline anhydrous exhibited fast release and curved down after 60%. The partial transformation of theophylline anhydrous to theophylline hydrate was their explanation for the retardation release behavior.

Tablet core formulation

Conte et al. (1993) showed that drug release from compression-coated tablet containing a fast release core was faster than extended release core containing coated tablet when the same coating composition was used. Lin et al. (2002) have revealed that the release behavior and the lag time were dependent on the type of excipient used in the core. Lag times for diclofenac sodium release from ethylcellulose compression-coated tablets which comprised cores containing spray-dried lactose, HPMC 2910 (Metolose 60 SH50), sodium starch glycolate and microcrystalline cellulose as diluent were 8.5 h, 12.4, 14.6 and 15.8 h, respectively. The lag time of compression-coated tablet containing only drug was 16.8 h. The higher solubility of spray-dried lactose and HPMC facilitated the dissolution in the core to make a faster disintegration time and a shorter lag time.

The effect of core erosion ratio of acetaminophen compression-coated tablets on the bioavailability in dogs has been investigated by Sawada et al. (2003). The compression-coated tablets containing the same coat but different cores showed identical in vitro release profile but they were different in the bioavailability. The in vivo results

(the area under the curve of acetaminophen plasma concentration–time) revealed that compression-coated tablets having larger core erosion could provide the higher drug absorption from the GI tract.

González-Rodríguez et al. (2003) found faster release of sodium diclofenac from core containing PEG 4000, compared to lactose which had 50% Eudragit® RSPO and 50% sodium chloride as compression-coat. This was probably due to solid dispersion formation of PEG 4000 and sodium diclofenac during core preparation. Improvement in wettability and solubility of drug was obtained.

Nuntanid et al. (2009b) revealed the influence of different composition of cores on drug release from spray-dried chitosan acetate/ HPMC compression-coated tablets. Soluble diluent and appropriate amount of super disintegrant in core tablets enhanced drug release while osmotic agent slightly retarded drug release.

Felodipine (poorly soluble drug; 0.5 μg/ml) was formulated as a pulsatile release in HPMC-PVP compression-coated tablets (Karavas et al., 2006). Increasing felodipine solubility by a drug/ PVP (10:90 w/w) solid dispersion was the response for pulse release after certain lag time.

Compression coating

Polymer type

The pharmaceutical polymers used (single or combination) in compression coating are cellulose derivatives (e.g. hydroxypropylmethylcellulose acetate succinate, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose and hydroxyethyl-cellulose), polysaccharides (e.g. guar gum, sodium alginate and pectin), water soluble polymer (polyethylene oxide) and wax (behenic acid) and methacrylate copolymers (Table 1). The coats containing these polymers could be divided into groups such as water insoluble (ethylcellulose), erodible (low molecular weight hydroxypropylmethyl-cellulose, hydroxypropylcellulose, polyethylene oxide), gellable or swellable (high molecular weight hydroxypropylmethylcellulose), pH dependent soluble (hydroxypropyl-methylcellulose acetate succinate, methacylic acid copolymer), waxy and bacterial digestible. The properties of these polymers control drug release in different manners as previously mentioned.

Conte et al. (1993) showed that the release behavior from compression-coated tablets was controlled and modulated by type and molecular weight of the polymer

used as shell. Drug release starts when the shell is completely eroded swollen or dissolved. A purely erodible coating is supposed to prevent drug release from the core until it is removed from by dissolution medium. The release behavior of the cores from compression-coated tablets containing erodible shell would not be modified by the erodible coating. Instead, drug release from compression-coated tablets which have a gellable coat would be delayed and altered the release performance. Smaller molecular weight of gellable coat (hydroxypropylmethylcellulose 2208) would provide a faster release rate after lag time than higher molecular weight (Qi et al., 2003).

Eeckman et al.(2002) have used thermoresponsive polymers for time controlled release of compression-coated tablets at a constant temperature using salts as a controlling agent. Poly (N-isopropyl acrylamide) was used as compression-coat. The delayed release of drug was controlled by the type and the amount of salt incorporated in the core. This was attributed to the effect of lowering the LCST (lower critical point solution temperature) or inverse phase transition temperature of the polymer by the added salt. As the temperature increased beyond the LCST, polymer became insoluble and phase separation occurred. Below this temperature, the polymer was soluble in aqueous media and the polymer chains were extended and surrounded by water.

Particle size of polymer used

Lin et al. (2001b) revealed that compression-coated tablets prepared with smaller particles sizes of ethylcellulose provided longer lag time. The smaller particle size of ethyl cellulose used in coat provided less porosity and higher tortuous path for medium infiltration, then the longer lag time of drug release was obtained. Lag time of compression-coated tablets containing ethylcellulose mixtures (granules and fine powder, 1:1) as coat was only slightly different from tablets containing fine powder as coat (Lin et al., 2004b) because fine ethylcellulose powder was filled the inter- and intraparticulate gaps of coarse ethylcellulose powder. The influence of particle size of coating material in form of granules was more pronounced than in form of powder (Guo and Shi, 2009). Compression-coated tablets from granulated coat provided faster drug release and shorter lag time compared to tablets from fine powder coat. Different lag time and drug release mechanism of ethyl-cellulose compression-coated tablets were illustrated by incorporation of different excipients into the upper coat of compression-coated tablets with the same lower coat, ethylcellulose coarse powder (Fig. 2).

Table 1 Polymers used as a coat of press-coated tablets

Polymer	**Drug**	**Controlled release type**	**Reference**
Hydroxypropylmethylcellulose (HPMC E3, E5, E50 and HPMC K100, K4M, K15M and K100M)	diltiazem HCl, sodium diclofenac	Time and/ or extended controlled release (drug presented in core and coat)	Conte et al., 1993; Sirkia et al.,1994 ; Wu et al., 2007
Hydroxypropylcellulose (HPC-SL, HPC-L, HPC-M and HPC-H)	diltiazem HCl	Time controlled release	Fukui et al., 2000a, c
Hydroxyethylcellulose	diltiazem HCl	Time controlled release	Matsuo et al., 1996
Hydroxypropylmethylcellulose (HPMC K4M) Opadry© enteric	Tinidazole	Time controlled release (colonic DDS)	Qi et al., 2003
Hydroxypropylmethylcellulose (HPMC K100M) Pectin (Pectinex 3XL and Ultra SP-L)	5-aminosalicylic acid	Delayed controlled release (colonic DDS)	Turkoglu and Ugurlu, 2002
Pectin (high degree of methoxylation >70%)	sodium fluorescein	Time controlled release (colonic DDS)	Ashford et al., 1993
Alginate-Chitosan complex (spray-dried)	acetaminophen	Time controlled (colonic DDS)	Takeuchi et al., 2000
Eudragit® L100-55	Nattokinase	pH controlled (colonic DDS)	Law and Zhang, 2007
Hydroxypropylmethylcellulose acetate succinate (AQOAT© AS-LF)	diltiazem HCl	pH controlled (colonic DDS)	Fukui et al., 2001a, b
Polyethylene oxide (PEO, mw.7 million)	Nifedipine	Time controlled release	Sawada et al., 2004
Ethyl cellulose, micronized (EC10cp)	sodium diclofenac	Pulsatile release release	Lin et al., 2001, 2002, 2004
Behenic acid	pentoxifylline, indomethacin	Time controlled release	Otsuka and Matsuda, 1995; Peerapattana et al., 2004
Eudragit ®RS	sodium diclofenac	Time controlled (colonic DDS)	González-Rodríguez et al., 2003
Guar gum	5-fluorouracil, metronidazole	Time controlled (colonic DDS)	Krishnaiah et al., 2002
Xanthan gum, guar gum and maize starch	5-fluorouracil	Time and microbially controlled	Sinha et al., 2004
Cross-linked amylose	acetaminophen	Extended release	Moussa and Cartilier, 1997
Carboxymethyl high amylose starch	Probiotic	pH controlled (colonic DDS)	Calinescu and Mateescu, 2008

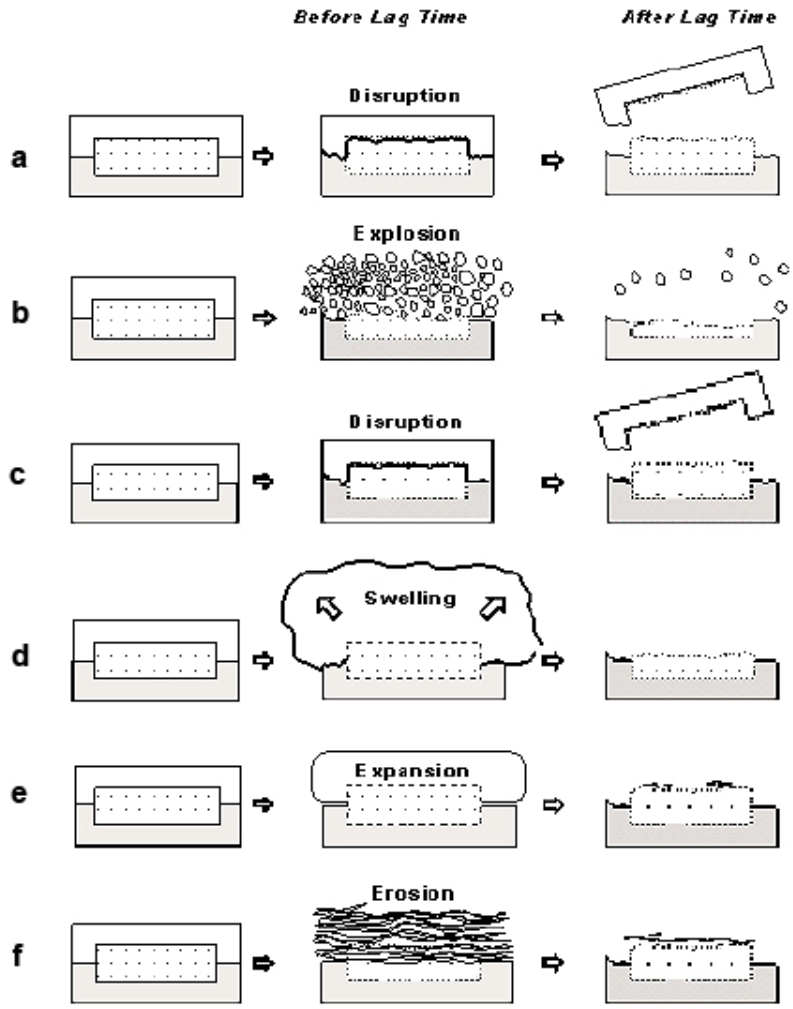


Fig. 2 Schematic dissolution process for drug release from compression-coated tablets containing the same lower compression-coat (ethylcellulose coarse powder) and different upper compression-coats: (a) EC coarse powder and EC fine powder = 6:1; (b) ethylcellulose coarse powder and Explotab = 6:1; (c) EC coarse powder and Avicel = 6:1; (d) ethylcellulose coarse powder and hydroxylpropylmethyl-cellulose = 6:1; (e) ethylcellulose coarse powder and spray dried lactose = 6:1; (f) ethylcellulose coarse powder and dibasic calcium phosphate = 6:1 (Lin et al., 2004b)

Porosity or release modifier incorporated in coat

When hydrophilic excipients are incorporated into an insoluble coating, they possibly act as a pore-forming agent for water penetration and the higher content of water soluble excipient in the coating results in shorter lag time. Different release behaviors from compression-coated tablets containing different hydrophilic excipients were resulted from different physiochemical properties. Lin et al. (2004a) have shown that the lag time from press-coated tablets containing an ethylcellulose/hydroxypropyl-methylcellulose E4M shell was longer when compared with ethylcellulose/spray dried lactose shell due to higher water solubility of the latter. The viscous hydroxypropyl-methylcellulose gel deposited within and on the surface of compression-coated tablet prolonged the lag time. The delay release after the lag time was found for compression-coated tablet containing a high content of HPMC in the compression coat.

For compression-coated tablets comprising cores in impermeable cup devices with modified surface matrix layer, the lag time for drug release was controlled by varying the ratio of water soluble diluent (lactose) and behenic acid in surface layer. A higher ratio of lactose to behenic acid resulted in shorter lag time of drug release obtained. This could be attributed to the more porous after lactose leakage or less tortuous surface layer (Peerapattana et al., 2004).

The influence of pore size created by excipients (sodium chloride, calcium tartrate, mannitol, sucrose and directly compressible dextrose, in compression coat has been investigated and described by the influence on the lag time and drug release from compression-coated tablets (Shivanand and Sprockel, 1998; González-Rodríguez et al., 2001). At the certain amount of pore former used, the larger particle size of pore former used, the larger pore size formed in the compression coat. This was explained by the formation of conducting channels, which cause faster drug release.

Poor wettability additives (magnesium stearate and calcium stearate) were added in HPMCAS coat to prevent the penetration of gastric medium through the pores in the coat before tablets arrived in the proximal colon (Fukui et al., 2001a).

Core-coat ratio

For the time controlled release system from compression-coated tablets, the amount of the outer shell is a key factor for controlling the lag time. Higher amount

of the outer coating added would prolong the lag time of drug release. For insoluble polymer coat like ethyl cellulose, the influence of polymer amount or thickness of coat on the lag time and drug release was investigated (Lin et al., 2001a). Insufficient polymer amount of coat would result in absent of the lag time, since the drug might be released through the incomplete form of ethylcellulose compression-coat.

Compression force

The effect of compression force applied to inner core on drug release from ethylcellulose compression-coated tablet was studied by Lin et al. (2001a). Absence of compression force effect on drug release was found when the compression force for coating was constant. In addition, the influence of compression force applied to the coat on the drug release of ethylcellulose compression-coated tablets was presented. When an insoluble coat is applied on a core with different compression forces, the lag time and drug release rate will be modified. The lag time of drug release increased and the release rate decreased when the compression force applied to the coating increased till a critical point. Their result could be explained by a decrease of coat porosity with higher compression forces leading to slower diffusion or lower permeability of water through the porous polymer matrix as compression coat (Ritschel et al., 1990). Higher compression force applied in compression coating leading to lesser porosity in the coat results in longer lag time. When the applied compression force for the coating was higher than the critical point, absence of the compression parameter was shown due to no further reduction in porosity. The same relationship was found for erodible shells. The lag time and release rate of diltiazem hydrochloride release from HPMCAS-LF compression-coated tablets in pH 6.8 were affected by changing the applied force on the HPMCAS coating (Fukui et al., 2001b).

In case of an swellable shell, applied compression force to the coating showed less effect on drug release from compression-coated tablet compared to insoluble and erodible shell. Turkoglu and Ugurlu (2002) presented no effect of compression force applied to the pectin-hydroxypropylmethylcellulose K100M coat on the erosion rate of coat resulting in no difference in drug release of 5-amino salicylic acid core. Pectin and HPMC are hydrophilic materials, therefore an outer coat from a mixture of these polymers would swell and form a hydrogel layer when they are placed in an aqueous

medium. Different results of compression forces applied on gellable coating were shown by Qi et al. (2003). Different lag times from different hardness of compression-coated tablet could be attributed to the influence of excipients incorporated in the coat (HPMC, lactose and microcrystalline cellulose).

Formulation consideration of compression-coating technique

Compression-coating amount

Coating amount is the most important parameter to achieve a coating uniform for compression-coated tablets. A compression-coated tablet requires a coating which is about twice the weight of the core or, more general, the volume must be greater than that of the core itself. If the cores are comprised mainly of low density materials, such as fats and waxes, the amount or weight of coating must be even greater to assure a uniform volume of coating material for covering the core and adhesion of core and coating. Recently, increasing the drug loading by decreasing the compression coat could be performed with a novel compression tool (one-step dry coated tablet manufacturing method; OSDRC-system) (Ozeki et al., 2004). In addition, the compression coating of low amount of drug as immediate release layer on the osmotic controlled release tablet using Eudragit® RLPO as adhesives was performed by Waterman and Fergione, 2003.

Position of core in coated layer

The main drawback of this system is the centralization of core in the compression-coated tablets. The reproducibility of drug release from compression-coated tablet is questionable, since the faults of press-coating can happen. Examples of press-coating fault are unequal coating, cocking and off-center. However, this drawback has been recently overcome by the novel compression tools (OSDRC-system) which placed a core in a certain position. Tokudome et al. (2009) have introduced X-ray computed tomography as non-invasive and rapid characterization method in online processing control for press-coated tablets. This technique provided cross-sectional images, which can be accumulated and built up three-dimensional images. This is based on the difference in X-ray transmittance, depended on the density of the tablet reflecting geometrical structure of compressed tablets.

Compression force and Compressibility of materials

The compressibility of coated tablets is mainly depended on the coating material. Thus, cohesiveness and plasticity of the powder coat are needed to obtain satisfactory mechanical strength of the coating. The cohesiveness indicates the continuity of the coating around the edge of the core, which depends on its strength and the plasticity responses for the expansion of the core after the final tablets are released from the die. The final compression force applied to prepare compression-coated tablets need to be higher than the compression force which was applied to the core, to ensure the adhesion between core and coat. Tablets with adhesive coating can be applied as core to ensure adhesion of compression coat and core (Waterman and Fergione, 2003).

Susceptibility of enzyme or biomaterial to compression has been reported. The loss of activity of wheat germ lipase caused by tablet compression has been found by Zarrintan et al. (1990). Inactivation of α-amylases enzyme was prevented by using k-carrageenan as excipient for tableting (Picker, 2002). The enzyme protection of k-carrageenan was attributed to its properties like required little compaction pressure to form a tablet and are the ability to release the mechanical stress in the form of expansion. In contrast, some enzyme exhibited less tableting influence on stability. Nattokinase was successfully stabilized and showed no significant loss of enzyme activity during tableting (Law and Zhang, 2007). In addition, the compression pressure may cause polymorphic transformation of some drugs leading to an alteration of the dissolution rate, stability and the bioavailability of the drug formulation. Some drugs have been reported to show compression-induced conversion of unstable to stable crystal forms: caffeine, maprotiline hydrochloride, sulfabenzamide (Chan and Doelker, 1985) and famotidine (Cheng et al., 2008). Multiple compressions in a tableting machine caused inter-conversion of the polymorphic forms of chlorpropamide (Otsuka et al., 1989).

Interaction between drug and compression coat

The interaction of drug and coating is needed to be considered when gellable compression coats are used for drug release control. Drug in compression-coated tablets diffuses through the swollen coat. This process might enhance some possible interaction between drug and coat. The difference in drug release of the enantiomers of verapamil hydrochloride from compression-coated tablets containing chiral polymers (pectin, galactomannan and scleroglucan) as the coat has been found by Maggi et al.

(1996). The slightly higher dissolution rate of the R-enantiomer of verapamil, compared to S- enantiomer, through the swollen coat of tablets has been explained by the stereoselective dissolution properties.

1.2.6. Recent technologies used in compression coating method

Compression coating technique has been described as compressing a coat around a core using specially designed processes. The process involves preliminary compression of the core, which is then transferred to a large die already containing some (a half) coating material. After centralizing the core, further coating material is added and the whole compressed to form the compression-coated tablets. The machines available for the preparation of press-coated tablets fall into two basic types: core previously prepared on other machines; compression of core and coat in one continuous circle (Windheuser and Cooper, 1956).

A novel one-step dry coated tablet manufacturing method (OSDRC-system) was introduced by Ozeki et al. (2003a-b). The OSDRC-system was capable of producing compression-coated tablets in one process without previous core tablet preparation.

The core and coat were prepared in the schematic sequence of the OSDRC process (Fig. 3). First, the lower-outer layer was formed by pre-compression from the upper-center punch. Then, the lower-center punch was slid down and the upper-center punch was moved up. The powder for the core was filled and pre-compressed by the upper-center punch. Finally, the lower-outer punch was slid downward and the powder for the 2^{nd} outer layer was filled and compressed by the upper and lower punches in which the center punches are unified with the outer punches. This system can be assembled onto the turn table of a rotary tableting machine and can make a dry-coated tablet in a single turn. By using the OSDRC-system, compression-coated tablets with a side outer coat thickness of 1 or 0.5 mm can prepared (Ozeki et al., 2004).

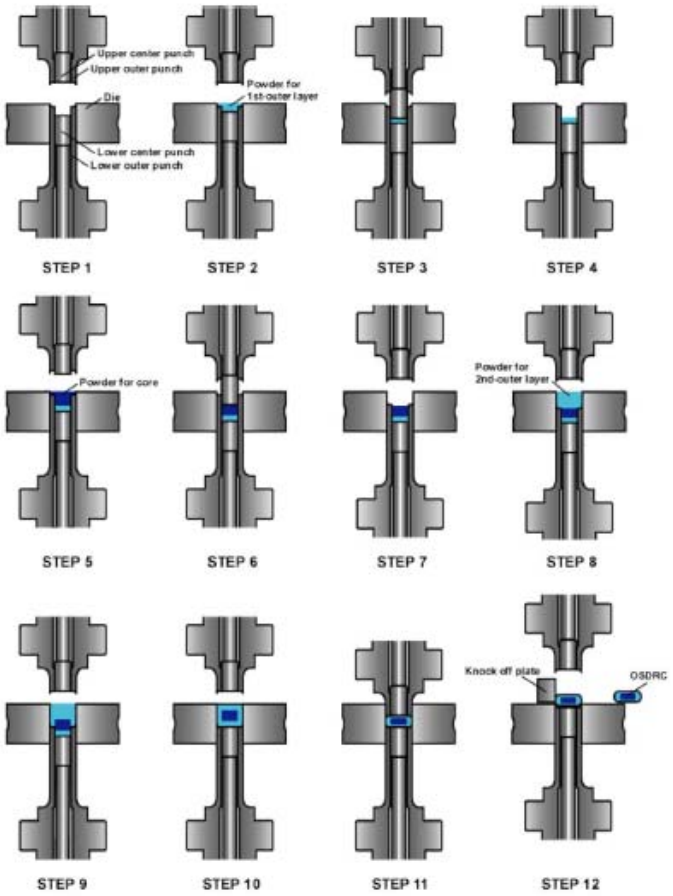


Fig. 3 Process of OSDRC manufacturing method as described by Ozeki et al. (2003)

Ando et al. (2007b) have introduced the use of OSDRC technology for a novel encapsulation of pellets as a substitute for conventional pellet filling in hard gelatin capsules. This technology was used to prepare capsule-like tablets containing 50% w/w of pellets or more. The size difference of the center and outer punch was crucial, which depended on the amount of encapsulated pellets. These encapsulated pellets spread in a cone shape within the compressed tablets, therefore a certain amount of space and density of diluents were required to avoid protruding of the pellets from the compression-coated tablet. However, the problem about pellets damage during compression should be further investigated.

Dividable compression-coated tablets containing two cores in the controlled-release coat (HPMC 2910, 6cP or Eudragit® L100-55) were prepared by Ozeki et al.2004 (Fig. 4). The aim of dividable compressioon-coated tablets development was to match the drug kinetics to individual patients (dose adjustment). The feasibility of this dividable control-released compression-coated tablet has been illustrated with comparable drug release from dividable and non-dividable compression-coated tablets.

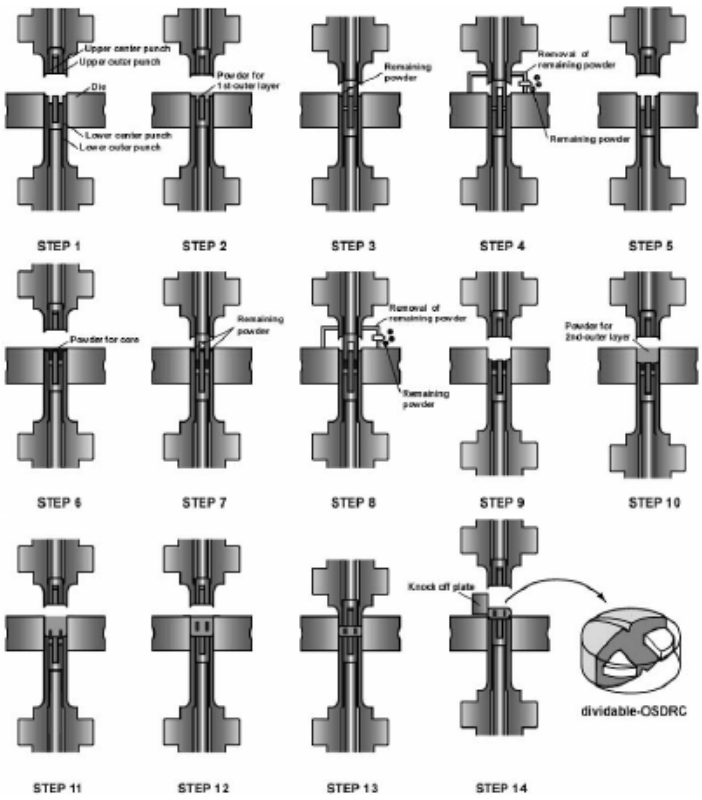


Fig. 4 Manufacturing process of dividable OSDRC (Ozeki et al., 2004)

Compression-coated tablets in form of layer tablets (doughnut-shaped) have been prepared by partial compression coating technique using a specially designed punch set (Sunday et al., 2004). The production process of the Manesty F3 for the three-layered tablets is shown as schematic diagram in Fig. 5.

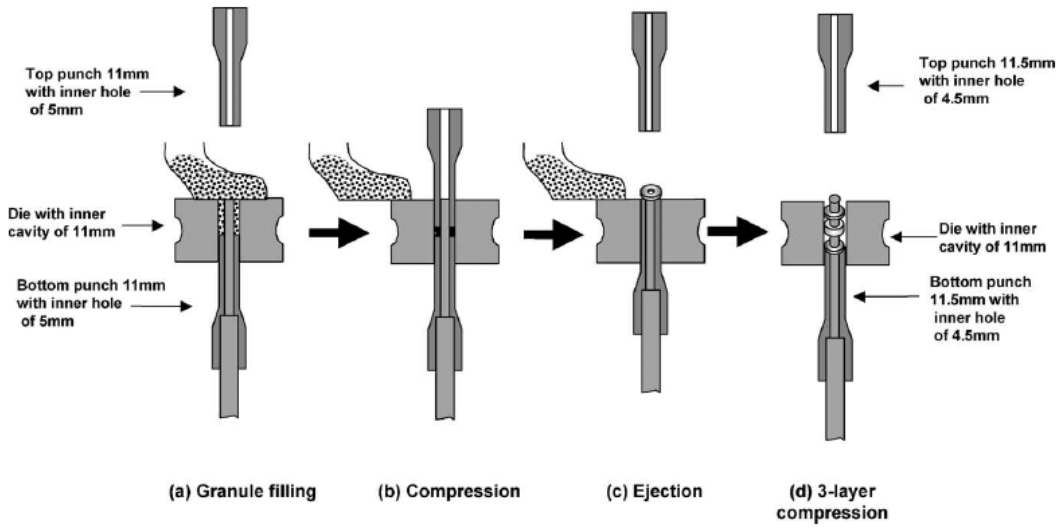


Fig. 5 Schematic diagram of the process of three-layered tablets on the ManestyF3 tableting press (Sunday et al., 2004).

Based on the concept of encapsulation by compression coating as previously described, the controlled release device in form of finish shell or capsules called "Dome Matrix®" is introduced. The Dome Matrix®, an assemblage of hydrophilic matrix presenting its shape of a cup with curved bases (one convex and the other concave), has been developed for time (or site) controlled release (Losi et al., 2006). Versatile drug release systems could be obtained depending on an assemblage of these modules: layered tablets from the *pile configuration* (in the left hand of Fig. 6, the guided insertion of the convex base of a module into the concave base of the adjacent one); delayed release (drug core containing) or gastroretentive system (air entrapment) from the *void configuration* (in the right hand of Fig. 6, the connection of concave base towards concave base). The interlocking between modules has been improved by different design as female and male structure (Casas et al., 2010). The connection gap between these modules would be sealed by the swollen coat.

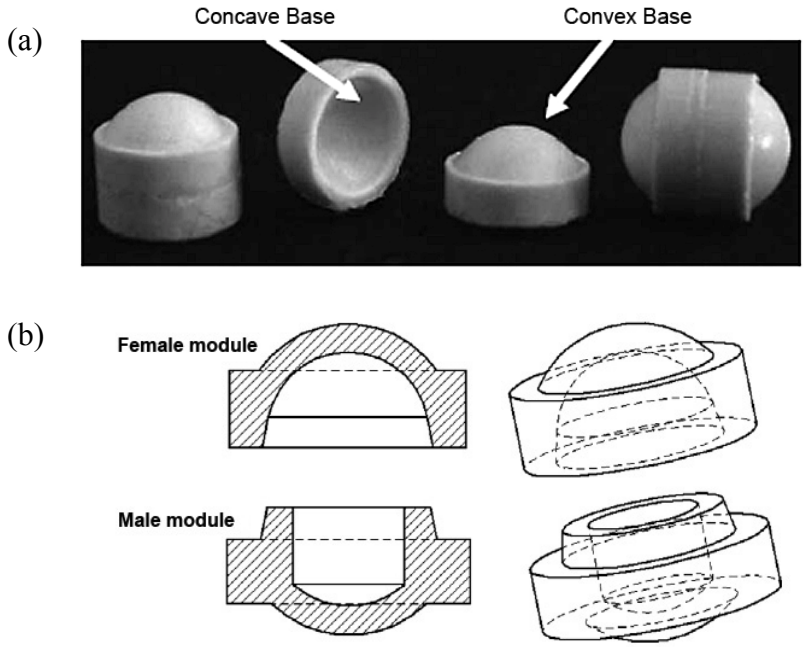
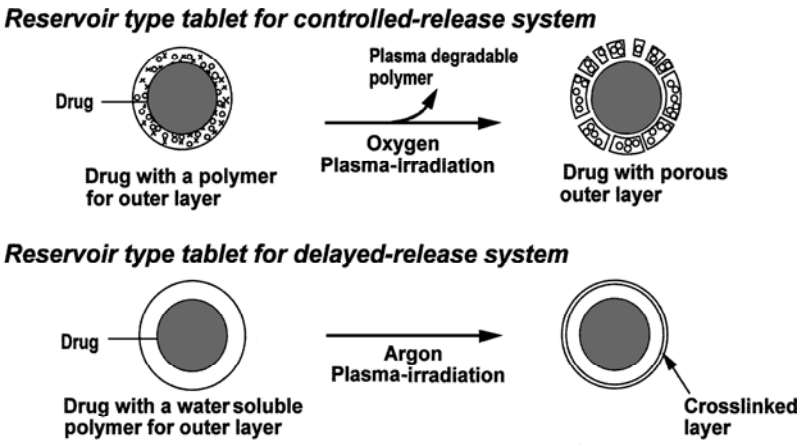


Fig. 6 The Dome Matrix®: (a) individual modules and assembled modules in piled (left) and void (right) configuration (Losi et al., 2006); (b) Female and Male module (Casas et al., 2010)

Additionally as previous mention about the role of compression-coat in the control of drug release from tablets, then the alteration of coat would contribute the influence on the release. The surface modification of compression-coat to control drug release from compression-coated tablets with the application of plasma-irradiation has been studied by Kuzuya's research group. By using low temperature plasma of inert gas, intense UV and/or Vacuum UV rays are generated, which causes an effective energy transfer to solid surface and give rise to a large amount of stable free radicals on the polymer surface. After the plasma-irradiation treatment on compression-coated tablets, a porous or cross-linked layer for drug release control is obtained (Fig. 7a) depending on the nature of the polymer (degradable or cross-linkable polymer), composition of compression-coat, gas (oxygen or argon) and processing condition (Fig. 7b) applied in the irradiation (Kuzuya et al., 2001a). For instance, degradable polymers, which give the end the end-chain alkyl radical, with the plasma irradiation as cellulose derivatives and the cross-linkable polymers providing the mid-chain alkyl radical and polymer with branched structure or aromatic ring like Eudragit® L100-55, Eudragit® L100, Eudragit® S100 have been used (Kuzuya et al., 2001b). The degradation of polymer from argon plasma-

irradiation is generally more prone to undergo surface cross-link reactions than from oxygen plasma-irradiation due to the absence of oxidative decomposition. The degradation rate of polymer has been proportional to the irradiation duration and supplied power. When sodium bicarbonate was incorporated in the compression-coat of tablets, floating drug delivery device could be formed after plasma-irradiation on compression-coated tablets due to the thermal decomposition of sodium bicarbonate to generate carbon dioxide and entrapment of the resultant gases in the bulk phase of compression-coat (Nakagawa et al., 2006).

(a)



(b)

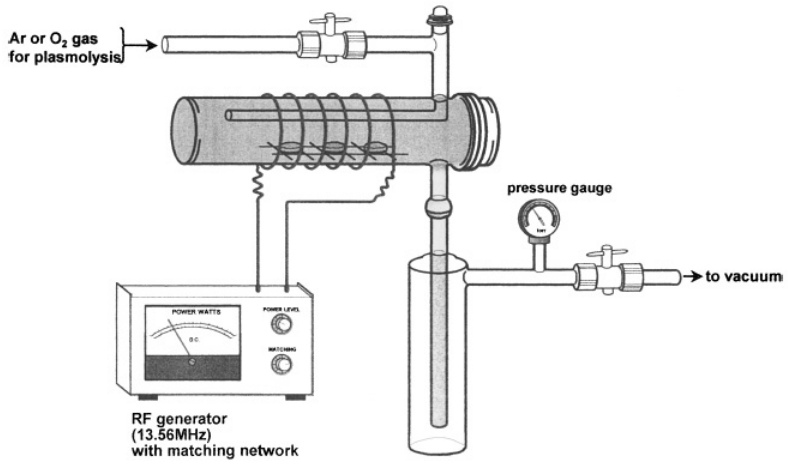


Fig. 7 (a) Conceptional illustration for preparation of drug delivery system by plasma techniques.

(b) Experimental setup for plasma-irradiation on compression-coated tablets (Kuzuya et al., 2001a-b).

In conclusion, the compression coating technique can be applied to obtain flexible drug delivery systems; modified extended release with multiphase pattern and delayed release (based on time controlled, pH controlled and bacterial degradable controlled release). Drug release of compression-coated tablets as extended release can be modified by the adjusting drug-polymer ratio in core and coat. For the delayed release system, lag phase and release phase can be modulated by changing the release controlling parameters (polymer type, particle size of polymer used, pore modifier, compression coating thickness or core and coat ratio, compression force) to achieve programmable drug release for chronotherapy or site specific drug delivery in GI tract. With a novel tableting technology (high precision and accuracy) to position core tablet in the center of the compression-coat, the application of compression-coated tablets as a tool for desirable drug release control is feasible also in industrial scale.

1.3. Objectives

The purposes of this work were:

(1) to investigate the role of humidity treatment prior to compression and thus the role of moisture as potent plasticizer for the successful compression of enterically coated pellets.

(2) to develop pH-erosion controlled compression-coated tablets for potential colonic drug delivery with improved gastric resistance and pulsatile release based on compression-coatings of powder blends of the enteric polymer Eudragit® L 100-55 and the extended release polymer ethylcellulose.

(3) to obtain flexible extended drug release profiles (e.g., sigmoidal, pulsatile, increasing/decreasing release rates with time) with hydroxypropyl methylcellulose.

2. MATERIALS AND METHODS

2.1 MATERIALS

2.1.1. Model drugs

Acetaminophen, acetylsalicylic acid, carbamazepine and propranolol HCl (BASF AG, Ludwigshafen, Germany); chlorpheniramine maleate (STADA GmbH, Bad Vilbel, Germany).

2.1.2. Polymers

Methacrylic acid–ethyl acrylate copolymer (1:1) (Eudragit® L100-55), aqueous dispersion of Eudragit® L100-55 (Eudragit® L30D-55), methacrylic acid-methyl methacrylate copolymer (1:2) (Eudragit® S100) (Evonik Industries AG, Darmstadt, Germany); hydroxypropylmethylcellulose acetate succinate (AQOAT®-AS MF, Harke Services GmbH, Mülheim an der Ruhr, Germany); cellulose acetate phthalate (Eastman® CAP, Eastman Chemical Holding GmbH, Cologne, Germany); ethyl cellulose (EC) (Ethocel® Standard 10 Premium FP, Dow Chemical Company, Midland, MI, USA); hydroxypropylmethylcellulose 2910, 5 cps (Methocel® E5), HPMC 2910, 50 cps (Methocel® E50), HPMC 2208, 4000 cps (Methocel® K4M Premium) (Colorcon Ltd., Orpington, UK); HPMC 2208, 400 cps (HPMC 400) (Metolose® 90SH-400, Shin-Etsu Chemical, Tokyo, Japan).

2.1.3. Plasticizers

Triethyl citrate (TEC, Morflex, Inc., Greensboro, NC, USA); propylene glycol (PG) and polyethylene glycol 4000 (PEG 4000) (BASF AG, Ludwigshafen, Germany).

2.1.4. Other excipients

Microcrystalline cellulose (Avicel®PH200) (FMC BioPolymer, Philadelphia, USA); direct compressible lactose (Ludipress®) (BASF AG, Ludwigshafen, Germany); non-pareils, 710 to 850 µm (Suglets®) (NP Pharm, Bazainville, France); magnesium stearate (Herwe Chemisch-technische Erzeugnisse GmbH, Sinsheim-Dühren, Germany)

2.2. METHODS

2.2.1. Moisture plasticization for enteric Eudragit® L30D-55-coated pellets prior to compression into tablets

2.2.1.1. Preparation of polymer films

Thin films of Eudragit® L100-55, Eudragit® S100, AQOAT®-AS MF, and cellulose acetate phthalate were prepared by a solvent casting technique. Briefly, 45 g of 7.5% w/w enteric polymer solutions in isopropyl alcohol:water (88:12 w/w) containing TEC (20% w/w based on polymer, unless otherwise mentioned) were cast on a Teflon plate (14 x 14 cm2). The films were dried for 48 h at ambient temperature and kept in desiccators until use. The film thickness (approx. 100 µm) was measured with a Minitest 600 (Erichsen GmbH & Co. KG, Hemer, Germany).

Eudragit® L30D-55 films (approx. 250 µm) were prepared with the same procedure. The aqueous polymer dispersion (25 g) was diluted with deionized water to a 15% w/w polymer content and plasticized with TEC or propylene glycol (20% w/w based on the polymer) for 1 h before casting. The films were oven-dried at 60 °C for 48 h, followed by 1 day at ambient conditions.

.

2.2.1.2. Preparation of coated pellets

Drug-loaded pellets (acetaminophen or acetylsalicylic acid, 10% w/w drug loading) were prepared by layering a drug-binder solution (12.2% w/w drug, 1.0% w/w hydroxypropylmethylcellulose, 0.1% w/w PEG 4000, 76.5% w/w ethanol, 10.2% w/w water) on non-pareils in a fluidized bed coater (Aeromatic® Strea1, Muttenz, Switzerland). The layering conditions were: product temperature 36 °C, outlet temperature 26 °C, nozzle diameter 1.2 mm, spray pressure 1.5 bar, spray rate 12.3 g/min, final drying at 40 °C for 15 min.

The drug-layered pellets were coated with Eudragit® L30D-55 (15% w/w solid content), plasticized with 20% w/w TEC based on polymer) in a fluidized bed coater (Uni-Glatt®, Glatt GmbH, Binzen, Germany) to a predetermined weight gain/coating level (cl) (10, 20 and 30% cl based on weight of drug-layered pellets). The coating conditions were: inlet temperature 60 °C, outlet temperature 40-42 °C, nozzle diameter 1.2 mm, spray pressure 1.8 bar, spray rate 4-5 g/min, final drying at 40 °C for 15 min.

The coated pellets were equilibrated at room temperature for 1 day and then stored in desiccators at ambient temperature for further studies.

2.2.1.3. Moisture treatment of polymer films and coated pellets

Eudragit® L30D-55 films, acetaminophen-layered pellets and Eudragit® L30D-55 coated acetaminophen pellets were stored at different humidities [0% RH (silica gel); 52% RH (saturated $NaHSO_4$.H2O solution); 75% RH (saturated NaCl); 84% (saturated KCl); 95% RH (Na_2HPO_4.12H2O); 100% RH (demineralized water)] at room temperature for 3-24 h and 1 month for moisture-equilibrated samples. The moisture content of the samples was determined by weighing samples before and after moisture treatment and was calculated as percent based on the initial weight.

2.2.1.4. Compression of coated pellets

200 mg coated acetaminophen pellets were mixed with 200 mg Avicel® PH 200 and 0.5% w/w magnesium stearate in a 2 ml microcentrifuge tube using a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 2 min. The mixture was then compressed into a 10 mm flat-faced tablet with 15 kN compression force with a single punch tablet press (Korsch EKO, Korsch Pressen GmbH, Berlin, Germany).

2.2.1.5. Drug release study

Acetaminophen release from compressed and uncompressed pellets was determined in a paddle apparatus (USP XXIV) (Vankel® VK 700, Vankel Industries, Edison, NJ, USA) (100 rpm, 37°C, 900 ml, 0.1 N HCl, n = 3). Samples were withdrawn at predetermined time points and analyzed using UV-spectrophotometer (UV-2101PC, Shimadzu Scientific Instrument, Columbia, MD, USA) at 243.6 nm.

2.2.1.6. Dynamic vapor sorption (DVS) measurement

The films were initially dried for 6 h at RH <0.1% to establish the dry mass using an automated moisture sorption instrument (DVS-1000; Surface Measurement Systems Ltd, Alperton, UK). The measurements were performed at a constant temperature of 25 °C. Weight changes were determined with a Cahn D200 ultra-microbalance (±0.1 mg mass resolution). The RH was then increased from 0% to 98% (in

10% steps from 0% to 90%, and one 8% step from 90% to 98%, n=1). For all RH steps, the instrument was run in a dm/dt mode (mass variation over time variation) to detect when equilibrium was reached. The equilibrium mass change (mg), minimum and maximum stage times were set to 0.0005 %/ min, 1 and 3 h, respectively. For the determination of the glass transition RH, the RH was linearly increased from 0% to 90% at 25°C with ramping rates of 10 % RH/h.

2.2.1.7. Glass transition temperature (T_g) of films

The Tg of films before and after storage at different humidities was investigated by differential scanning calorimetry (DSC) (Mettler DSC 821e, Mettler Toledo, Giessen, Germany). Samples (7-10 mg) were accurately weighed, sealed in an aluminium pan and then heated at a rate of 20 °C/min from -100 to 200 °C under a nitrogen atmosphere.

2.2.1.8. Mechanical properties of films and coated pellets

Elongation at break and puncture strength of films were measured using the puncture test and a texture analyzer (TAXT Plus, Winopal Forschungsbedarf GmbH, Ahnsbeck, Germany) (n = 6). Film specimens (7 x 9 cm2) were mounted in a film holder. The puncture probe (spherical end, 5 mm diameter) was fixed on the load cell (5 kg) and driven downward with a crosshead speed of 0.1 mm/s to the center of the film holder's opening (diameter, 10 mm). Force and displacement curves were recorded until rupture of the film. Puncture strength and elongation at break were calculated as described previously (Bodmeier and Paeratakul, 1994).

For the testing of the mechanical properties of single coated pellets, the pellets were compressed with a texture analyzer with a cylindrical, flat probe (3 mm diameter, stainless steel) (n = 20). The parameters for mechanical testing of the single pellets were: test mode (compression), pretest speed (10 mm/sec), test speed (0.1 mm/sec), posttest speed (10 mm/sec), target mode (distance, 0.6 mm) and break sensitivity (0.1 N). Force and displacement curves were recorded.

2.2.1.9. Drug stability after moisture storage

Coated acetylsalicylic acid pellets (10 and 30% coating level) were stored at 84% RH and room temperature for 15 h. The pellets were transferred to 0% RH until

constant weight was obtained. The acetylsalicylic acid content of the pellets was analyzed and compared with moisture-untreated pellet with a two wavelengths UV spectroscopic method at 278 and 306 nm. The difference in acetylsalicylic acid content of Eudragit® L30D-55 coated pellets between moisture-treated and control pellets were calculated by one way ANOVA at 95% significant confidential level.

2.2.2. Improved drug delivery to the lower intestinal tract with tablets press-coated with enteric/nonenteric polymer powder blends

2.2.2.1. Preparation of tablet cores

Acetaminophen and carbamazepine biconvex tablet cores (6 mm diameter tablets: 15 mg drug, 85 mg Ludipress®, 0.5 mg magnesium stearate) and chlorpheniramine maleate tablet cores (6 mm diameter tablets: 40 mg drug, 60 mg Ludipress®, 0.5 mg magnesium stearate; 9 mm diameter tablets: 120 mg drug, 180 mg Ludipress®, 1.5 mg magnesium stearate) were prepared by direct compression (compression force, 15 kN; hardness for 6 and 9 mm tablets, 30 and 70 N; Korsch EKO, Korsch AG, Berlin, Germany). The drug content in the cores was different in order to allow UV detection without dilution of the dissolution samples. Prior to compression, drug and Ludipress® were blended in a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min and additionally blended with 0.5% w/w magnesium stearate for 2 min.

2.2.2.2. Preparation of press-coated tablets

6 mm diameter drug cores were compression-coated into 9 mm diameter tablets with Eudragit L or blends of Eudragit L:ethylcellulose (97.5:2.5, 95:5, 90:10, 85:15, 80:20 and 75:25). The compression-coated tablets (core: coat, 1:2) were prepared by first filling one-half (100 mg) of the polymer powder in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining half (100 mg) of the polymer powder on top and then followed by compression at 10, 15, 20 and 25 kN (Korsch EKO, Korsch AG, Berlin, Germany). Compression-coated tablets with different core:coat ratios (3:1, 2:1, 1:1 and 1:2) were prepared by compression-coating chlorpheniramine maleate cores (6 or 9 mm diameter) with different amounts of Eudragit

L:ethylcellulose 75:25 (100, 150, 100 and 200 mg) resulting in compression-coated tablets with dimensions of core/core+coat of 9/10, 9/11, 6/8 and 6/9 mm, respectively.

2.2.2.3. Drug release

Drug release was studied in a paddle apparatus (USP XXIV) (Vankel® VK 7010, Vankel Industries, Edison, NJ, USA) [100 rpm, 37 °C, 900 ml, 0.1 N HCl (pH 1.0), 50 mM acetate buffer (pH 4.5), 50 mM of phosphate buffer (pH 5.5, 6.8 and 7.4), n=3]. With the medium change method, the release was performed in pH 1.0 for 2 h followed by pH 6.8. Drug release was measured by UV spectrophotometer (Varian Cary 500 UV/Visible spectrophotometer, Varian Deutschland GmbH, Darmstadt, Germany) at wavelengths of 243.6, 285 and 261 nm for acetaminophen, carbamazepine and chlorpheniramine maleate, respectively. The lag time was taken as the time of $\leq 10\%$ drug released. The percentage of acid uptake of compression-coated tablets was determined with the wet tablet weight after the release study in 0.1 N HCl based on the initial weight.

2.2.2.4. Swelling and erosion studies of Eudragit L:ethylcellulose matrices

300 mg tablets (10 mm diameter) containing different Eudragit L:ethylcelllulose blends were compressed at 25 kN. Swelling and erosion of Eudragit L:ethylcellulose tablets were performed in pH 1.0 and pH 7.4 buffers at 100 rpm and 37 °C (Vankel® VK 7010, Vankel Industries, Edison, NJ, USA). In addition, the erosion of Eudragit L tablets was performed in different pH media (5.5, 5.8, 6.0, 6.8 and 7.4). The initial tablet weight (w_i), tablet weight in the wet state (w_t) and tablet weight after drying (w_d) (60 °C, 72 h or until constant weight) were measured to determine the percentage of weight increase (reflecting swelling) and oeweight remaining (reflecting erosion) as swelling in 0.1 N HCl and erosion in pH 7.4 as follows::

$$\text{weight increase (\%)} = \frac{w_t - w_i}{w_i} \times 100$$

$$\text{weight remaining (\%)} = \frac{w_d}{w_i} \times 100$$

2.2.2.5. Drug solubility determinations

The solubility of the drugs was determined by adding an excess amount of drug in vials with 5 ml phosphate buffer pH 7.4 and shaking at 37 °C in an incubator (GFL® 3033, GFL Gesellschaft für Labortechnik, Burgwedel, Germany). After 48 h equilibration, the drug suspensions were adjusted to pH 7.4, if necessary, and further shaken. The suspensions were filtered, and the filtrate was diluted and analyzed UV-spectrophotometrically (Shimadzu UV-2101PC, Shimadzu Europa, Duisburg, Germany) at the same wavelengths used for drug release studies.

2.2.2.6. Wettability of Eudragit L:ethylcellulose matrices with release media

The wettability of matrix tablets prepared from different Eudragit L:ethylcellulose ratios (100:0, 95:5, 85:15 and 75:25 w/w) was investigated by placing a drop of media (approx. 50 µl) on the flat surface of the tablets. Pictures of the water droplet as a function of time were taken with a macroscope (INTEQ GmbH, Berlin, Germany).

2.2.2.7. Tapped density

Tapped densities of Eudragit L and ethylcellulose were determined by a tap density volumeter (Erweka® type SYM 202, Erweka® GmbH, Heusenstamm, Germany). The tapped volume of 35 g polymer powder (2,500 tappings, stroke height 15 mm, 300 strokes/min) was measured.

2.2.3. Modified release system from hydroxypropyl methylcellulose compression-coated tablets

2.2.3.1. Drug solubility determinations

The solubility of drugs was determined by adding an excess amount of drug in vials with 5 ml phosphate buffer pH 7.4 and shaking in a 37 °C incubator (GFL® 3033, GFL Gesellschaft für Labortechnik, Burgwedel, Germany). After 48 h incubation, the drug suspensions were adjusted to pH 7.4, if necessary, and further shaken. The suspensions were filtered, and the filtrate was diluted and analyzed UV-spectrophotometrically (Shimadzu UV-2101PC, Shimadzu Europa GmbH, Duisburg,

Germany) at wavelengths of 243.6, 285, 290 and 261 nm for acetaminophen, carbamazepine, propranolol HCl and chlorpheniramine maleate, respectively.

2.2.3.2. Preparation of tablet cores

Acetaminophen and carbamazepine biconvex tablet cores (6 mm diameter, 15 mg drug, 85 mg Ludipress®, 0.5 mg magnesium stearate), propranolol HCl and chlorpheniramine maleate tablet cores (6 mm diameter, 40 mg drug, 60 mg Ludipress®, 0.5 mg magnesium stearate) were prepared by direct compression (compression force: 15 kN, hardness: 30 N; Korsch EKO, Korsch AG, Berlin, Germany). The drug content in the cores was different in order to allow UV detection without dilution of the dissolution samples. Prior to compression, drug and Ludipress® were blended in a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min and additionally blended with 0.5% magnesium stearate for 2 min.

Eudragit L-subcoated cores were prepared by spray-coating a solution of Eudragit L (7.5% w/w solid content in ethyl alcohol:water, 95:5 v/v) and 10% w/w TEC (based on polymer) on the acetaminophen cores in a fluidized bed coater (Uni-Glatt®, Glatt GmbH, Binzen, Germany) to obtain coating levels of 4.7, 9.5, 14.3 mg/cm^2. The coating conditions were: inlet temperature 26-28 °C, outlet temperature 24-26 °C, nozzle diameter 1.2 mm, spray pressure 1.6 bar, spray rate 1.5 g/min and final drying at 40 °C for 15 min. The coated tablets were equilibrated at ambient temperature for 1 day and stored in desiccators for further studies.

2.2.3.3 Compression-coating of tablet cores

6 mm diameter tablet cores (acetaminophen, carbamazepine, propranolol HCl, chlorpheniramine maleate, Eudragit L-subcoated acetaminophen cores) were compression-coated into 9 mm diameter tablets using various HPMC compression-coating formulations (200 mg; 50-200 mg of HPMC E50, HPMC 400 and HPMC K4M and 0-150 mg of Ludipress® for 25-100% HPMC compression-coating). The compression-coated tablets (core: coat, 1:2) were prepared by first filling one-half (100 mg) of compression-coated powders in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining half (100 mg) of the polymer powder on top and then by compression at 25 kN (Korsch EKO, Korsch AG, Berlin, Germany), unless other compression forces were mentioned. For the compression-coating

amount (thickness) study, 100, 200 and 400 mg of HPMC 400 and HPMC K4M were compression-coated on 6 mm acetaminophen tablet cores to obtain 8, 9 and 11 mm compression-coated tablets, respectively.

300 mg compression-coated tablets comprising HPMC 400 compression-coatings and different amount of drugs in the core and compression-coating (15:100, 15:50, 15:15, 15:7.5, 15:0 and 15:0 for acetaminophen; 40:0, 40:40 and 0:40 for chlorpheniramine maleate) were prepared to study the influence of drug distribution between core and coat.

2.2.3.4 Drug release study

Drug release was studied in a paddle apparatus (USP XXIV) (Vankel® VK 700, Vankel Industries, Edison, NJ, USA) [100 rpm, 37 °C, 900 ml, 50 mM of phosphate buffer pH 7.4, n=3]. Drug release was measured by UV spectrophotometer (Shimadzu UV-2101PC, Shimadzu Europa GmbH, Duisburg, Germany) at the same wavelengths used for drug solubility determination. The lag time (t_{10}) and release time (t_{80-10}) were defined as the times in h of 10% and 80-10% drug released, respectively.

3. RESULTS AND DISCUSSION

3.1. Moisture plasticization for enteric Eudragit® L30D-55-coated pellets prior to compression into tablets

3.1.1. Introduction

Oral modified release pellet-based drug delivery systems are either filled into capsules or compressed into tablets. To achieve compression of polymer-coated pellets into tablets, good flexibility of the polymeric coating is crucial in order not to rupture and to loose the modified release properties (Bodmeier, 1997). Coated pellets with brittle films showed rupturing and increases in drug release during tableting (Miller et al., 1999; Dashevsky et al., 2004); elongation values of film coatings greater than 75% are generally required (Lehmann et al., 1994). The improvement of the film flexibility by increasing the plasticizer amount in coating has limitation due to plasticizer-polymer compatibility, plasticizer evaporation, aging, increased sticking of the pellets during processing and storage and loss of controlled release due to a leaching of hydrophilic plasticizer (Bando and McGinity, 2006a).

Enteric polymers are usually quite brittle and not suitable to be used in compressed pellet systems (Bodmeier and Paeratakul, 1994; Obara and McGinity, 1995; Ahrabi et al., 1999: Liu and Williams III, 2002; Bando and McGinity, 2006b). The use of polymeric blends of the enteric film-former, Eudragit® L30D-55 with the flexible, neutral extended release polymer, Eudragit® NE 30D to increase the film flexibility has been studied (Lecomte et al., 2005). However, the necessary high proportion of flexible polymers altered the drug release profiles (Beckert et al., 1996; El-Malah and Nazzal, 2008).

Absorbed water from the atmosphere can act as a plasticizer in various polymeric film and pharmaceutical solid systems as shown exemplary by the following references. The mechanical properties of dry and wet polymer films obtained from aqueous dispersions of acrylic and cellulosic polymers were compared by Bodmeier and Paeratakul (1994a). Lowering of the glass transition temperature (T_g) of amorphous pharmaceutical solid by increasing water content has been described by Hancock and Zografi (1994). The compression of amorphous lactose powder was facilitated by increased moisture content (Sebhatu et al., 1997). Steendam et al. (2000) showed the plasticizing effect of moisture on compression characteristics of amylodextrin powders.

Bravo-Osuna et al. (2007) reported the plasticizing effect of absorbed water on the compressibility of methyl methacrylate-starch copolymers. The quality of film coalescence from aqueous dispersion coating was improved after heat humidity curing compared to dry-heat curing (Liu and Williams III, 2002; Pearnchob and Bodmeier, 2003a and b). Chen et al. (2005) have revealed that moisture in ambient environment significantly influenced the T_g and microstructures of the glycerol-plasticized soy protein sheets, leading to changes of the mechanical and thermal properties.

The purpose of this study was to investigate a role of moisture as a potent plasticizer for the successful compression of Eudragit® L30D-55 coated pellets. Eudragit® L30D-55 was chosen because its film is brittle in the dry state and thus not compressible, but it is flexible in the wet state (Bodmeier and Paeratakul, 1994). Eudragit® L30D-55 coated pellets were thus stored at elevated humidity prior to compression into tablets with the goal to maintain the enteric release profile.

3.1.2. Results and discussion

Polymer coatings on pellets to be compressed into tablets need to be flexible enough to withstand rupturing during compression. Enteric polymers such as cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate (AQOAT® AS-MF), methacrylic acid–ethyl acrylate copolymer (Eudragit® L100-55) and methacrylic acid-methyl methacrylate copolymer (Eudragit® S100) are quite brittle in the dry state, as shown by low elongation values, even when plasticized with TEC (Table 2). This makes them poor polymer candidates for compressed coated pellets because of the risk of coating rupture and loss of enteric properties. Based on previous studies on the mechanical properties of wet polymeric films and the plasticization effect of water (Bodmeier and Paeratakul, 1994), the polymer films were stored at elevated humidity (84%RH) in order to investigate possible plasticization effects of adsorbed moisture and to obtain an increase in flexibility of the polymer films sufficient for compression. The mechanical properties of Eudragit® L100-55 changed dramatically, while the properties of the other enteric polymers showed only minor changes during storage at higher humidity (Table 2). The significant increase in flexibility of the hydrated Eudragit® L100-55 film could be explained with the hydration/plasticization of the polymer probably caused by interactions of water with the carboxyl groups of the polymer (Tajiri et al.,

2009). The elongation value of Eudragit® L100-55 changed from approx. 3% in the dry state to approx. 140% at the higher storage humidity. The absence of moisture plasticization on Eudragit® S100-55 was probably due to its lower amount of free carboxyl groups (acid:ester group, 1:2 compared to Eudragit® L100-55 1:1). The minor moisture plasticizing effect on cellulose acetate phthalate and hydroxypropyl-methylcellulose acetate succinate could possibly be explained with the interchain hydrogen bonding and the bulkiness of the substitute groups (phthaloyl and succinyl). Therefore, Eudragit® L100-55 was further evaluated as a potential moisture-plasticized enteric polymer candidate for the compression of coated pellets. To avoid organic solvents during coating, the aqueous dispersion Eudragit® L30D-55 was used in the following studies.

Table 2 Mechanical properties of enteric polymeric films stored at 0% and 84% RH for 1 month.

enteric polymer	puncture strength, MPa (mean ± SD)		elongation, % (mean ± SD)	
	0% RH	84% RH	0% RH	84% RH
Eudragit® L100-55	8.1±1.8	13.3±2.4	3.3±1.2	142.5±31.5
Eudragit® S100	9.9±2.8	8.6±2.2	4.1±2.2	4.6±1.7
AQOAT® AS-MF	12.6±2.7	11.6±1.8	11.0±3.9	21.4±3.9
cellulose acetate phthalate	28.4±6.1	12.5±1.6	12.8±4.3	13.7±3.6

Eudragit® L30D-55 coated pellets were stored at different humidities for different time periods and then compressed and evaluated for changes in release (Fig. 8). The release of compressed but nonhumidity-treated pellets (labeled 0 h in the figure legend) increased dramatically when compared to the uncompressed pellets, indicating film rupture and loss of enteric properties. This was consistent with the poor elongation values of dry Eudragit® L films (Table 2). As control, the high humidity treatment did not change the drug release from uncompressed Eudragit® L coated pellets (Fig. 9).

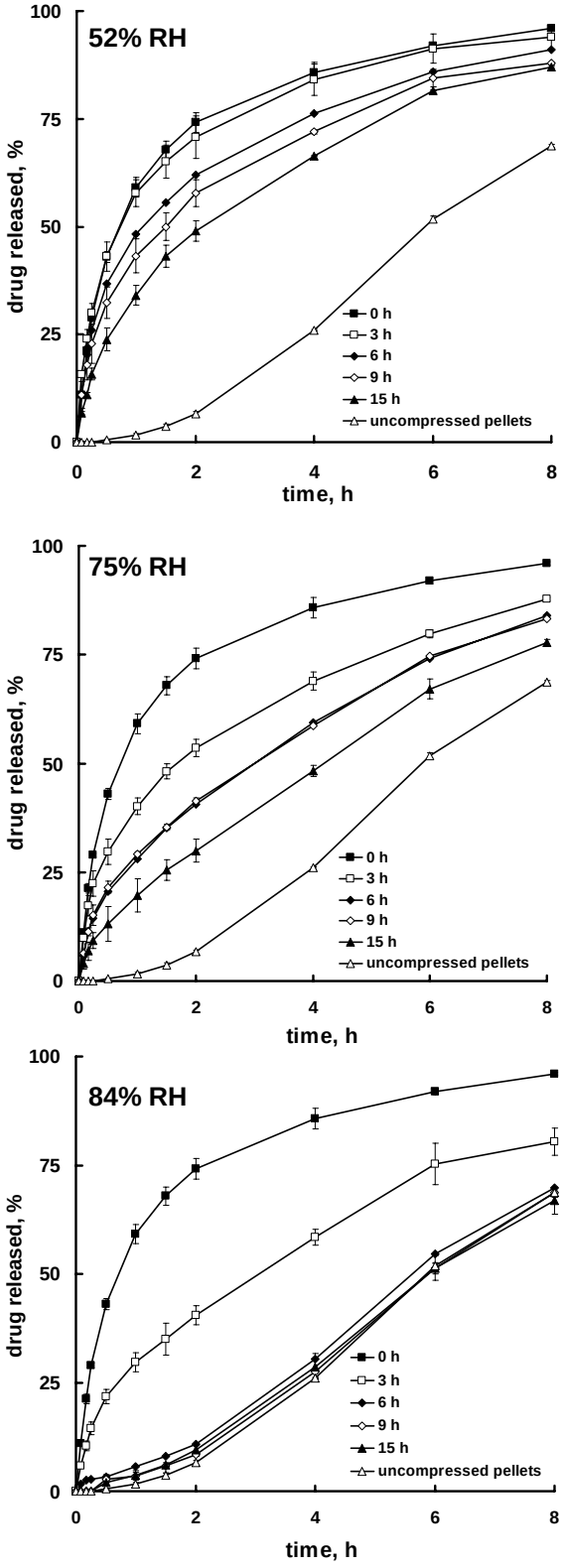


Fig. 8 Effect of storage time (0-15 h) and relative humidity (RH) on acetaminophen release from compressed and uncompressed pellets

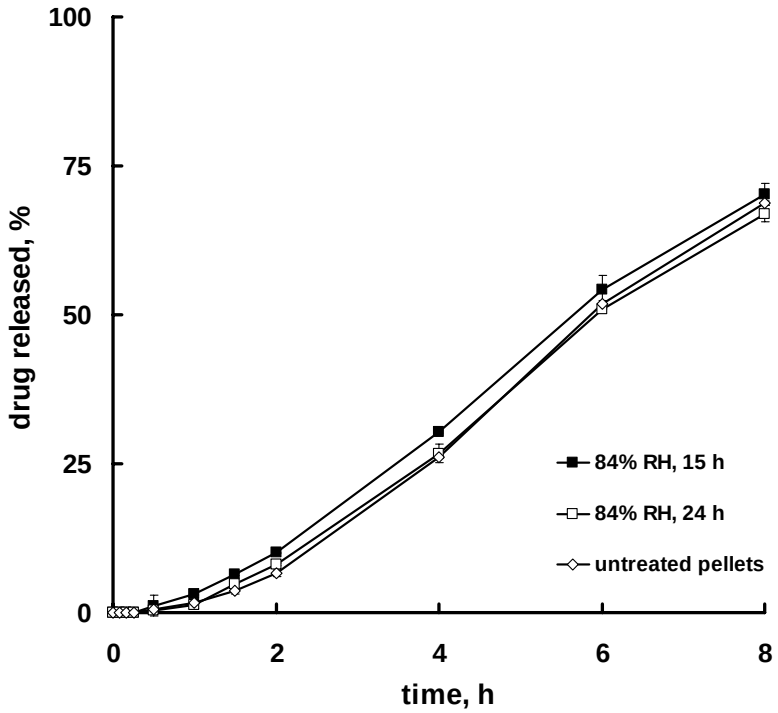


Fig. 9 Effect of moisture storage condition (84% RH) on the acetaminophen release from uncompressed Eudragit ® L30D-55 coated pellets

The damage to the Eudragit® L-coated pellets decreased with increasing storage humidity and storage time, as indicated by a lower increase in release upon compression (Fig. 8). The release profile of the uncompressed pellets was matched with pellets stored at the highest storage humidity (84% RH) for a time period between 3 to 6 h prior to compression. Storage at the lower humidities of 52 and 75% was not sufficient; the drug release increased upon compression. As expected, the moisture uptake of Eudragit® L films and Eudragit® L-coated pellets (containing 0.2 and 0.6% moisture initially) also explained the release data by showing an increased moisture uptake with increasing storage moisture and time (Fig. 10). The moisture uptake ran into a plateau after approx. 24 h. The moisture uptake of the coated pellets (Fig. 10c) resulted from both moisture uptake of the enteric coating (represented by the polymer film data, Fig. 10a) and the drug cores (Fig. 10b). The experimentally determined curve for the coated pellets was similar to the curve predicted from the sum of film and uncoated pellet data.

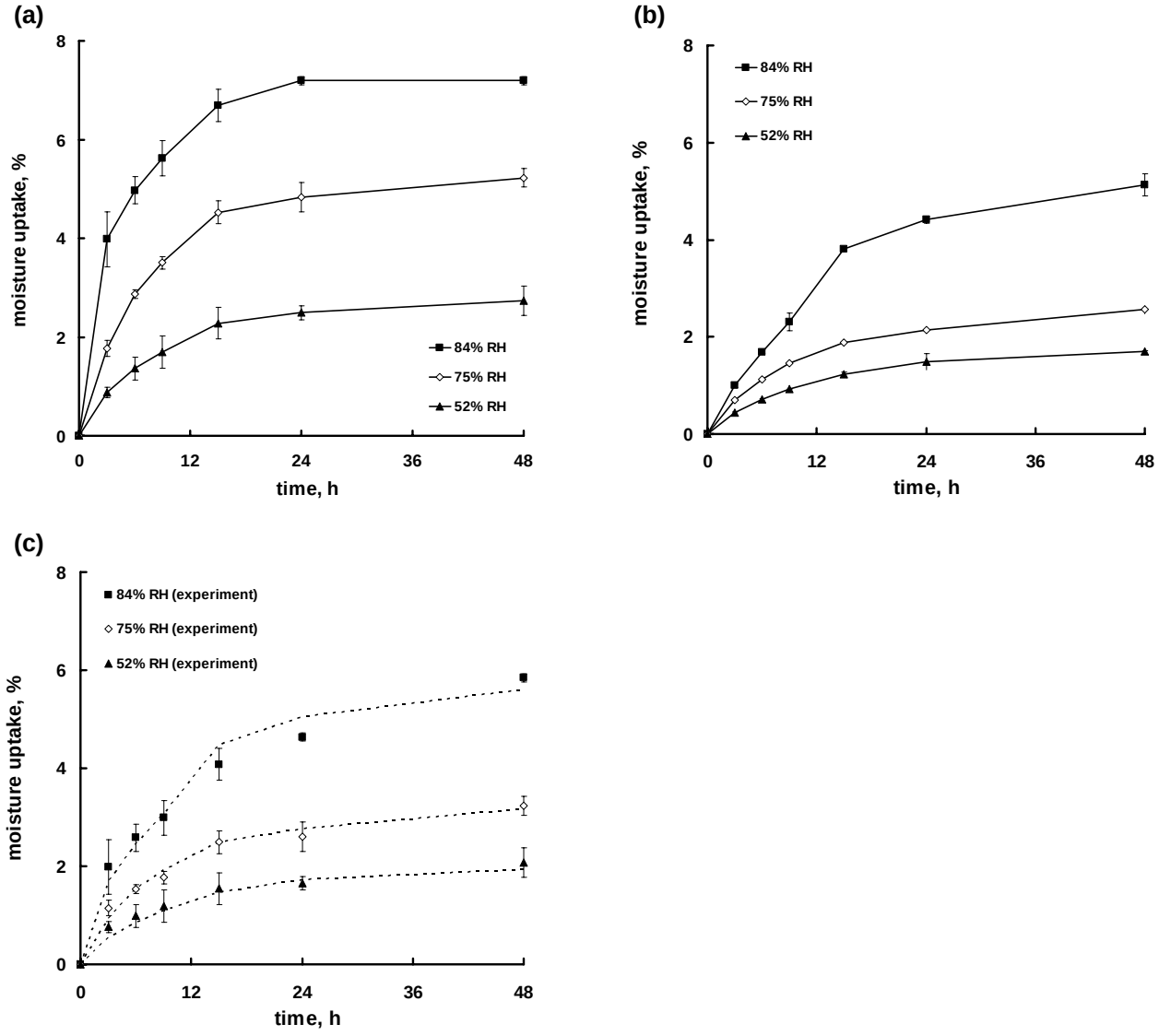


Fig. 10 Moisture uptake as a function of storage time and relative humidity (RH): (a) Eudragit® L30D-55 films; (b) uncoated acetaminophen-layered pellets; (c) Eudragit® L30D-55 coated pellets (dashed line, prediction of moisture absorption of coated pellets (from films and uncoated pellets)

The moisture uptake of the Eudragit® L films increased with increasing storage humidity (Fig. 11). The uptake was higher with plasticized films, whereby the more hygroscopic propylene glycol resulted in a higher uptake than the less soluble triethyl citrate (TEC). A higher storage humidity resulted in an increased water content and plasticization effect of the films as indicated by a decrease in the glass transition temperature (T_g) of films (Table 3). The glass transition temperature decreased below the compression temperature (room temperature) at storage humidities between 75% and 84%.

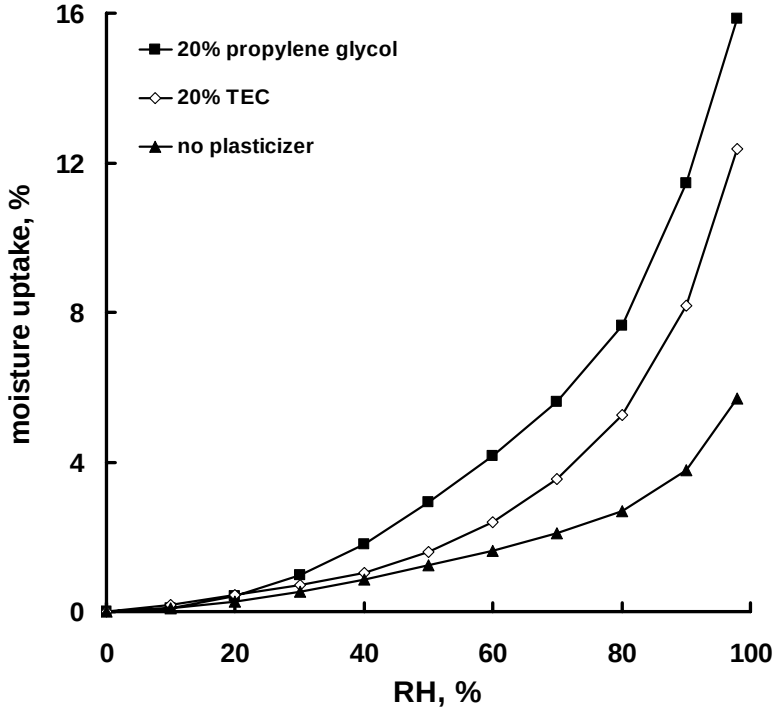


Fig. 11 Effect of plasticizers on moisture sorption of Eudragit® L30D-55 films at 25 °C (DVS; 10% RH steps from 0-90% RH and 8% from 90-98% RH, stage time 1-3 h)

Table 3 Influence of different storage humidities at room temperature on water uptake and glass transition temperature (T_g) of Eudragit® L30D-55 films stored for 1 month.

RH, %	water uptake, %	T_g, °C
0	0.0	61.1
52	3.4	41.9
75	5.9	27.1
84	7.0	2.5
95	10.8	-50.4
100	13.6	-62.5

A DVS study in the ramping mode, whereby the RH was linearly increased from 0% to 98% RH at room temperature (25°C) at different ramping rates (%RH/h), was conducted to identify the glass transition relative humidity (Bley et al., 2009). The ramping rate study with 20% TEC-containing Eudragit® L30D-55 films was conducted at 4%, 6% and 10% RH/h (Fig. 12). The ramping rate influenced the glass transition RH leading to a change from the glassy to the rubbery state. Increasing in the RH ramping rate led to an increase in the glass transition RH. This could be attributed to the shortened storage time at a certain RH to fully equilibrate. The y-axis intercept of the extrapolated line was 76.8% RH, which represented the RH representing the glassy-rubbery state transition; it fell in the range of 75% to 85% RH already described above. This result was also in good agreement with the drug release after compression of humidity-stored pellet (Fig. 8), which revealed a similar drug release from 84% RH compressed-pellets and uncompressed pellets.

Moisture was a much more effective plasticizer for Eudragit® L than the conventionally used plasticizer triethyl citrate (TEC) (Fig. 13). The mechanical behavior of moisture-equilibrated films changed from brittle to flexible with increasing moisture content (Fig. 13a), while the TEC plasticized films remained fairly brittle (Fig. 13b). The decreasing puncture strength and increasing elongation of films with increasing moisture content (Fig. 13c) could be clearly attributed to water plasticization. In comparison, an increase in TEC concentration did not improve the puncture strength and elongation of films except at the high TEC content of 50% (Fig. 13d).

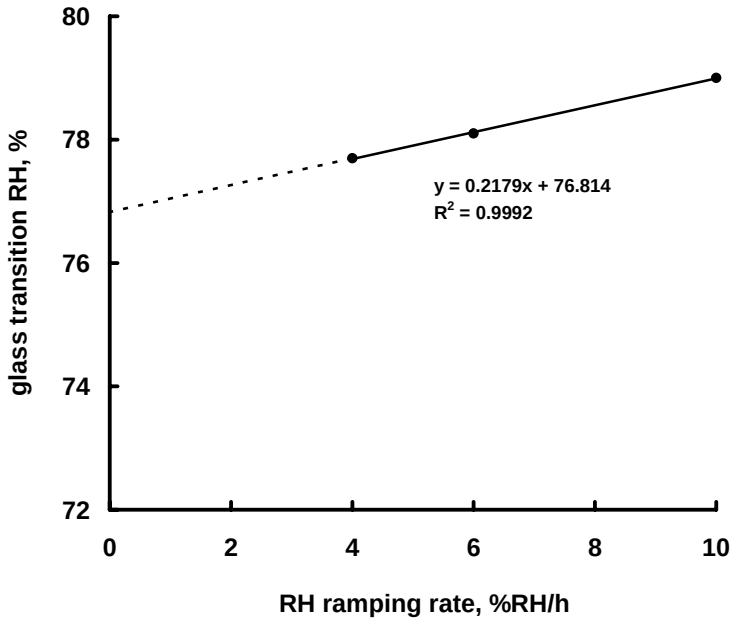


Fig. 12 Effect of RH ramping rate (dynamic vapor sorption measurements) on the glass transition RH of Eudragit® L30D-55 films

Table 4 Acetylsalicylic acid content in coated pellets after storage at 84% RH for 15 h at room temperature

coating level, %	acetylsalicylic acid content , % (mean ± SD)	
	0% RH	84% RH, 15 h
10	12.97 ± 0.1	12.97 ± 0.2
30	10.65 ± 0.1	10.62 ± 0.1

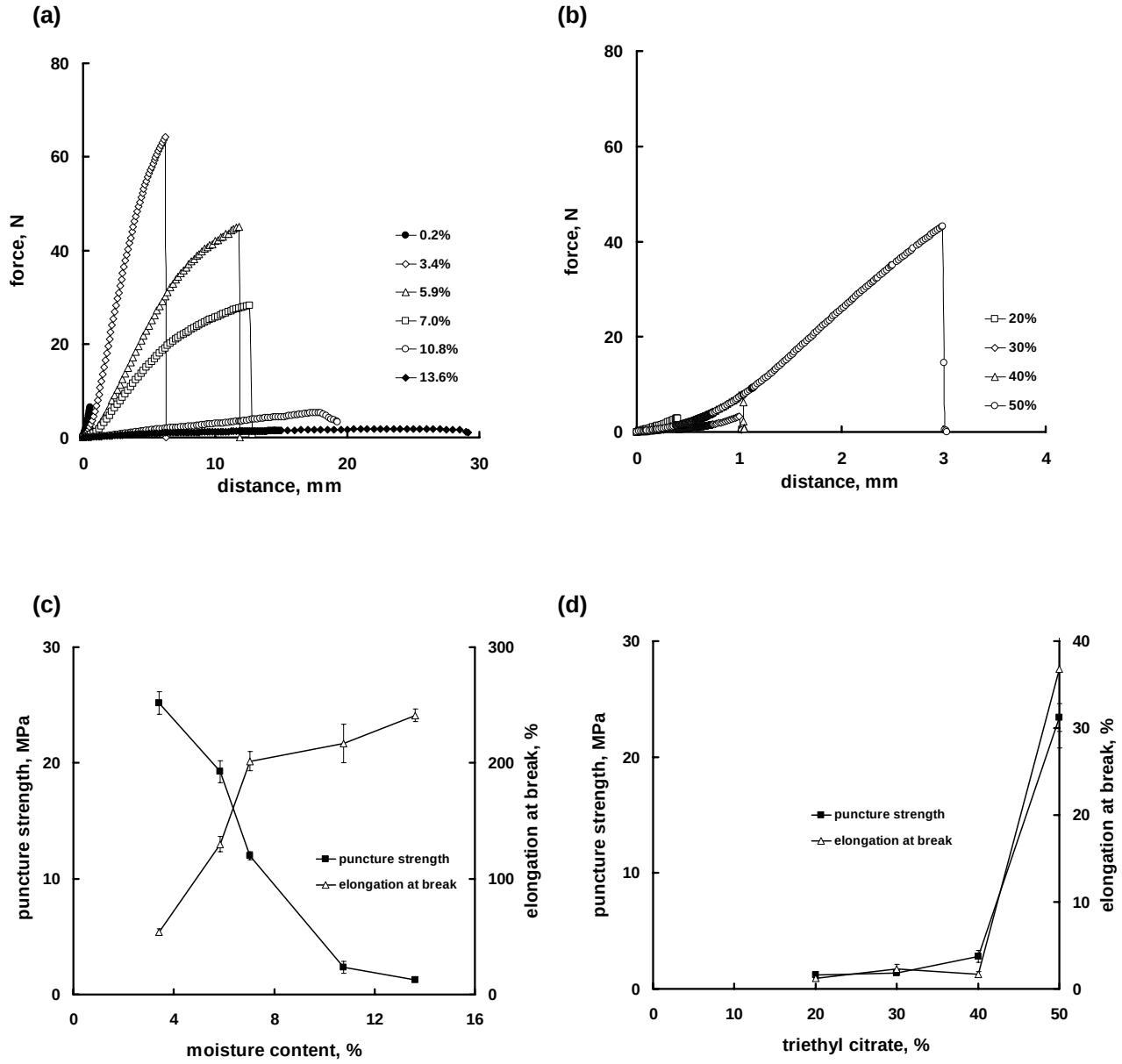


Fig. 13 Effect of (a, c) moisture content and (b, d) triethyl citrate (TEC) content on force-displacement plots (a, b) and mechanical properties (puncture strength, elongation) (c, d) of Eudragit® L30D-55 films:

Next, the influence of moisture level and storage time on the crushing strength-deformation (force-displacement curves) of individual Eudragit® L-coated pellets was investigated (Fig. 14). The crushing force (max. force prior to the rapid decrease in force) and distance to crushing (deformation) increased only marginally after storage at 52 and 75% RH when compared to pellets stored at 84% RH, where the force and deformation prior to crushing increased significantly. This correlated well with the drug release data in Fig. 8.

The moisture plasticization of Eudragit® L-coated pellets results in moisture uptake of not only the coating but also of the other formulation excipients (Fig. 10). This could potentially cause degradation of the drug or other excipients during at least the high moisture storage. The moisture-sensitive model drug acetylsalicylic acid was thus investigated. The acetylsalicylic acid content in the pellets independent of coating level remained constant after treatment at 84% RH for 15 h followed by drying (Table 4). A drying step after compression of the coated pellets could be used if needed with highly moisture-sensitive drugs.

In summary, moisture plasticization in the form of high humidity storage of the coated pellets prior to compression was a highly effective tool to enable the successful compression of pellets coated with the brittle enteric polymer Eudragit® L.

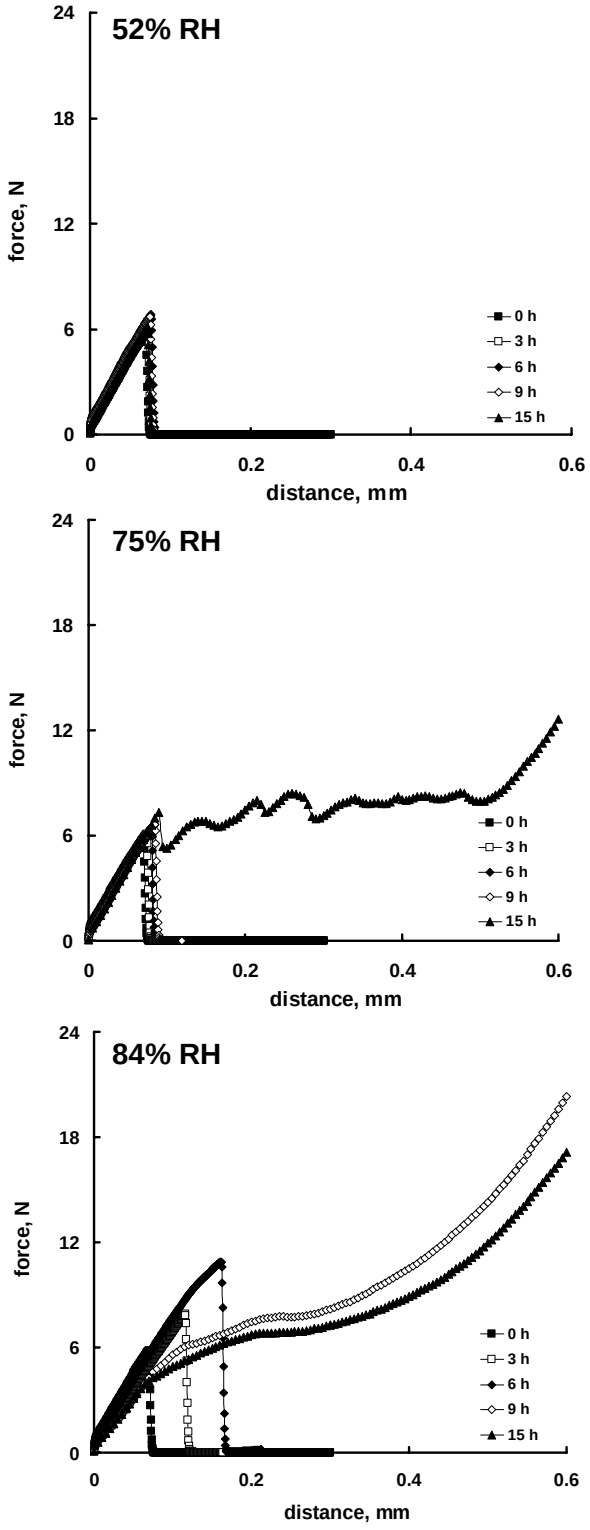


Fig. 14 Effect of storage time and relative humidity (RH) on force-displacement profiles of Eudragit® L30D-55 coated single pellets

3.1.3. Conclusion

Enteric polymers such as cellulose esters (cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate) and methacrylic acid–acrylate copolymers (Eudragit® L100-55 and S100) are quite brittle in the dry state and thus not suitable as pellet coatings for compression into tablets. The objective of this study was to investigate the role of humidity treatment prior to compression and thus the role of moisture as potent plasticizer for the successful compression of enterically coated pellets. The mechanical properties of Eudragit® L100-55 improved dramatically, while the properties of the other enteric polymers showed only minor changes after storage at higher humidity. The significant increase in flexibility of the Eudragit® L film was caused by hydration/plasticization; its elongation value changed from approx. 3% in the dry state to approx. 140% at the higher storage humidity. Storage at 84% relative humidity resulted in comparable release profiles of compressed and uncompressed pellets. The glass transition temperature of Eudragit® L films decreased below the compression temperature (room temperature) at storage humidities between 75% and 84%. The glass transition relative humidity leading to a change from the glassy to the rubbery state was determined by dynamic vapor sorption (DVS) to be 76.8%. Moisture was also a much more effective plasticizer for Eudragit® L than the conventionally used plasticizer triethyl citrate. The improved compressibility of moisture-treated Eudragit® L-coated pellets was also shown with single pellet compression data as indicated by an increased crushing force and deformation. In conclusion, moisture plasticization was a highly effective tool to enable the successful compression of pellets coated with the brittle enteric polymer Eudragit® L.

3.2. Improved drug delivery to the lower intestinal tract with tablets press-coated with enteric/nonenteric polymer powder blends

3.2.1. Introduction

Oral drug delivery to the colon has become attractive during the past two decades for reasons including a reduced dosing frequency, high local drug concentration for the treatment of large bowl diseases, chronotherapeutic drug delivery and the delivery of peptides/protein drugs and drugs unstable in the upper gastrointestinal tracts (Van den Mooter, 2006). Colonic delivery systems include pH-, time-, bacterial- and pressure-responsive systems (Yang et al., 2002; Singh, 2007; Liu et al., 2009). Also combinations of these approaches in the form of a pH-responsive and bacterially-triggered system (Ibekwe et al., 2008) or of a time- and microbial-controlled system (Sinha et al., 2004) have been investigated. Among these approaches, pH- and time-responsive system are relatively simple in structure and to prepare, but their suitability as colonic delivery system has been doubtful because of the variable physiological or pathological conditions along the gastrointestinal (GI) tract (Ashford et al., 1993). Since the small intestinal transit time in humans is approximately 3±1 h (both fasted and fed state) and less variable (Davis et al., 1986; Ibekwe et al., 2008), combinations of pH- and time-controlled systems were successfully developed (Gupta et al., 2001).

Colonic drug delivery systems should overcome problems associated with the variation of gastric emptying time (less than 2 h under fasting and 2-12 h under fed conditions in humans) (Kenyon et al., 1994) and with mechanical destructive forces in the gastrointestinal tract (Egorov et al., 2002). Feasible pH- and time-controlled systems include enteric coatings (with high pH-threshold and/or thicker film coating), enteric coatings on HPC compression-coated tablets or matrix tablet (Fukui et al., 2000a and 2000b; Alvarez-Fuentes et al., 2004) or coating blends of extended release and enteric polymer (Lecomte et al., 2003; Akhgari et al., 2006). Besides gastric protection, the enteric coating has to be robust to ensure upper GI-tract passage of the delivery system.

Besides dry powder-coating techniques (Pearnchob and Bodmeier, 2003a and 2003b), compression-coating of tablets is attractive for thicker coatings since traditional liquid coating processes are time-consuming and often not solvent-free. Compression-coating provides thick coatings within short processing time. For example,

hydroxypropylmethylcellulose acetate succinate (HPMCAS) compression-coated tablets have been investigated for colonic DDS (Fukui et al., 2001).

The purpose of this study was to develop compression-coated tablets suitable for colonic drug delivery. Eudragit® L100-55, a methacylic acid-ethylacrylate copolymer, was chosen as enteric polymer for compression-coating because of its good flow properties (spray-dried powder), good compressibility and acid resistance. In particular, the addition of the water-insoluble polymer ethylcellulose was investigated to overcome problems of only enteric coated colonic delivery systems, such as a too short gastric resistance and premature release.

3.2.2. Results and discussion

Colonic drug delivery systems should not release the drug in the stomach/upper intestine but in the lower intestinal tract after about 3-4 h intestinal passage. An erosion-controlled enterically compression-coated tablet was investigated in this study as a potential delivery system to the large intestine. Eudragit L (soluble at pH > 5.5) and blends of Eudragit L with the nonenteric, water-insoluble polymer ethylcellulose were evaluated as pH-controlled erodible coatings resulting ideally in drug release only after erosion of the coating. Drugs of varying solubility (solubilities of carbamazepine, acetaminophen and chlorpheniramine maleate are 0.2, 20 and 562 mg/ml, respectively) were incorporated into the core in order to evaluate the flexibility/limitations of the compression-coated system with regard to different drug candidates.

All drug cores (without compression-coating) resulted in complete release within 15 min (data not shown). Thus, in the ideal case, a rapid drug release after erosion of the coat in intestinal fluids was guaranteed. Eudragit L compression-coated tablets released less than 10% chlorpheniramine maleate in 4 h and less than 10% acetaminophen in 12 h in 0.1 N HCl (Fig. 15a). The water-insoluble carbamazepine was not released at all. The Eudragit L coating is insoluble in gastric juice, however it swells (Fig 15c). Drugs could thus only be released in 0.1 N HCl by diffusion through the swollen coating; this occurred to a higher extent with the more water-soluble chlorpheniramine maleate (approx. 75% released in 12 h) than with the other two drugs. Interestingly, chlorpheniramine maleate tablets swelled more than the other two less water-soluble drugs, probably because of the higher osmotic activity of the chlorpheniramine maleate

(Fig 15c). Although Eudragit L is brittle and not flexible in the dry state, it is very flexible upon contact with dissolution media because of the plasticization effect of water (Bodmeier and Paeratakul, 1994), thus explaining the expansion of the chlorpheniramine maleate tablet.

As desired, the release was independent of drug type in pH 7.4 (Fig. 15b). All three drugs were released rapidly and similar after a lag time of about 2.5 h. The release profile was pulsatile; no drug was released until almost complete dissolution/erosion of the Eudragit L compression-coat. The individual release profiles (n=3) were very close in most cases and showed the good reproducibility of the compression-coating process. This initial study proofed the potential of erosion-controlled Eudragit L compression-coated tablets for delivery of drugs of varying solubility to the lower intestine. Chlorphenireamine maleate, the drug with the highest water solubility and thus the most challenging one to retard, was selected for further studies.

Ethylcellulose, a water-insoluble and directly compressible fine polymer powder, was added to the enteric Eudragit L to decrease the release of chlorpheniramine maleate at low pH. Surprisingly, the addition of only 2.5% ethylcellulose prolonged the gastric resistance beyond 18 h (Fig. 16a). 5-25% ethylcellulose resulted in no release in 0.1 N HCl. This was attributed to the decrease in acid uptake with increasing ethylcellulose content (Fig. 16b). Tablets containing 10% ethylcellulose had only 8.5% weight increase (acid uptake) in 0.1 N HCl after 18 h, when compared to more than 80% uptake with pure Eudragit L compression-coated tablets. Ethylcellulose FP grade is a micronized powder (6.1 μm mean diameter) (Akhgari et al., 2006) and thus was very effective in inhibiting rapid penetration of the dissolution medium when compared to the larger sized Eudragit L powder (≥95% smaller than 250 μm) (Evonik Industries AG). In addition, a comparison of the tapped densities of Eudragit L and ethylcellulose (0.56 and 0.32 g/ml, respectively) also explained a higher volume- than mass-fraction of ethylcellulose in the Eudragit L:ethylcellulose compression-coat (80:20 w/w vs. a volume ratio of 70:30 v/v).

The incorporation of ethylcellulose prolonged the lag time in pH 7.4 from 2.5 h to approx. 5 h for 0–10% ethylcellulose followed by a big jump in lag time for ethylcellulose concentrations in excess of 15% (lag time > 15 h) to no release within 18 h for > 20% ethylcellulose (Figs. 16c-d). Ethylcellulose thus significantly retarded the erosion of the Eudragit L coating (Lecomte et al., 2003), especially in thick compression-

coatings. The release profiles remained steep, indicating rapid, pulsatile release after the lag time.

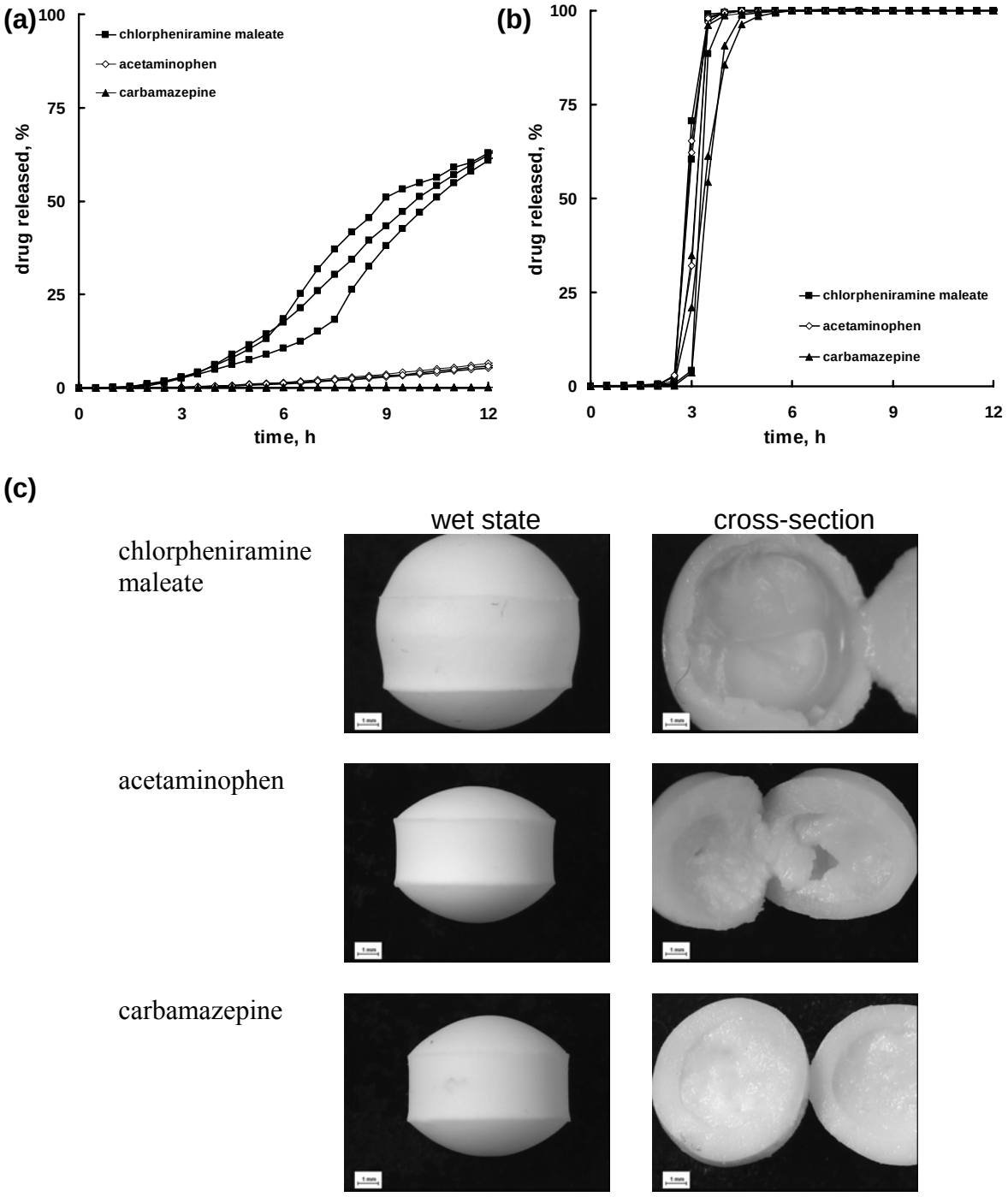


Fig. 15 Drug release of Eudragit L compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) pH 1.0; (b) pH 7.4 (n=3, individual release profiles shown); (c) wet state and cross section of compression-coated tablets in pH 1.0

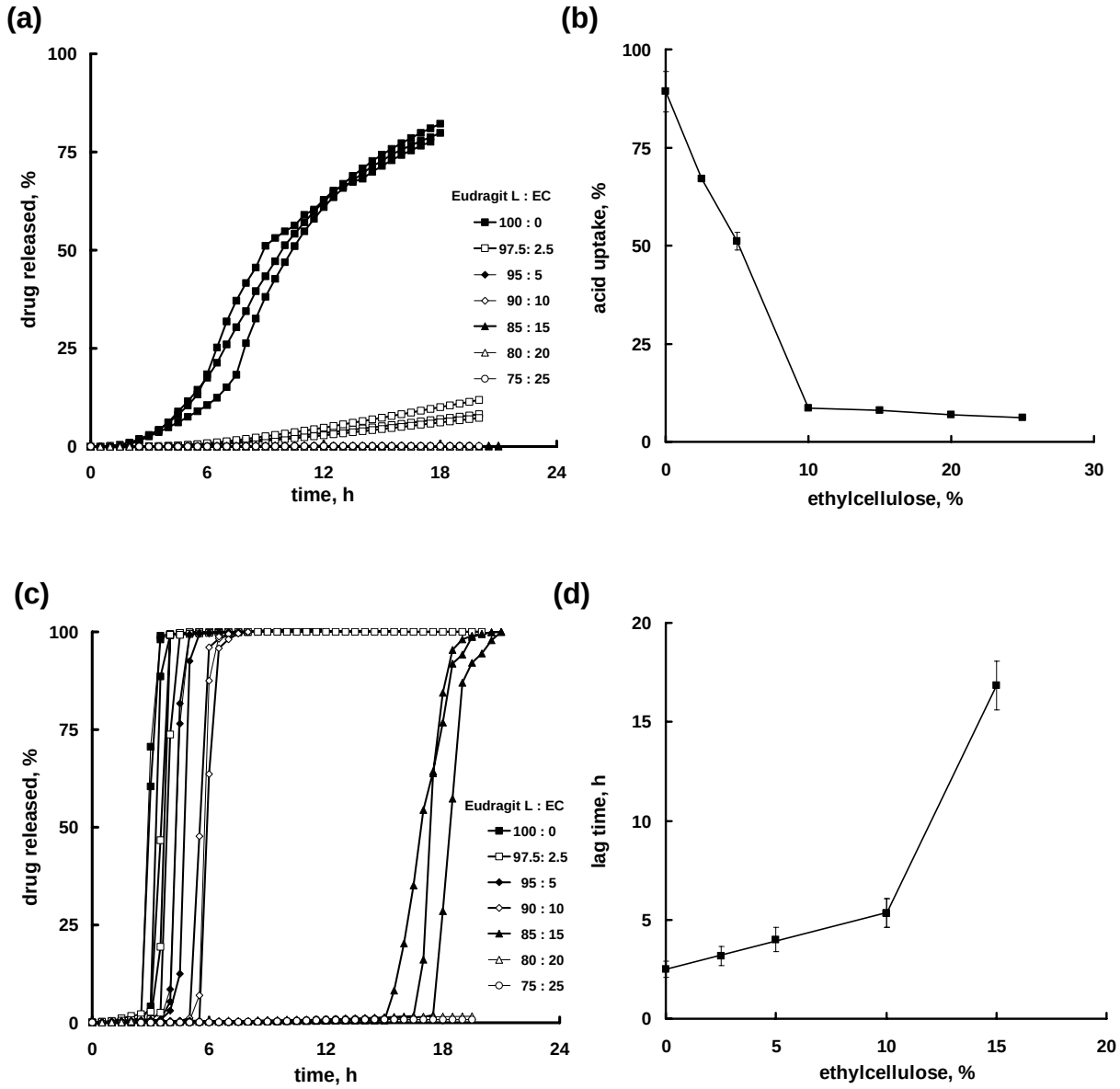


Fig. 16 Influence of Eudragit L:ethylcellulose (EC) in the compression-coating on chlorpheniramine maleate release from compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) drug release in pH 1.0; (b) acid uptake in pH 1.0; (c) drug release in pH 7.4 (n=3, individual release profiles shown); (d) lag time in pH 7.4

The swelling and erosion behavior of the Eudragit L:ethylcellulose matrix tablets were investigated in pH 1.0 and pH 7.4 in order to further clarify the influence of Eudragit L:ethylcellulose ratio on the drug release. Increasing the ethylcellulose amount decreased the weight increase (swelling) in 0.1 N HCl and decreased the weight loss and erosion (increased weight remaining) in pH 7.4 (Figs. 17a-b), thus paralleling the findings of drug release. Eudragit L matrix tablet containing 5% ethylcellulose had a 50% weight increase in 0.1 N HCl; this coating provided already full gastric protection (> 18 h) (Fig. 16a). Eudragit L tablets with > 10% ethylcellulose significantly decreased the weight increase to < 10%. The weight loss studies in pH 7.4 confirmed the decrease in erosion with increasing ethylcellulose coating. In addition, the wettability of Eudragit L:ethylcellulose matrix tablets (0-25% ethylcellulose) with release medium decreased with increasing amount of ethylcellulose (Fig. 18). The 0.1 N HCl drop penetrated quickly into Eudragit L-only tablets and was not visible after 6 min, while the 0.1 N HCl drop penetrated much slower into ethylcellulose-containing tablets. The visible drop of pH 7.4 buffer on Eudragit L-only tablets after 360 min was explained with the gradual dissolution of Eudragit L without swelling in this medium.

These results strongly support the excellent suitability of ethylcellulose as erosion-controlling (retarding) excipient in Eudragit L compression-coatings for colonic delivery.

Next, the effect of the pH of the dissolution medium on the drug release for Eudragit L:ethylcellulose (95:5 and 90:10) compression-coated tablets was investigated (Figs. 19a -b). The drug was not released below pH 6. The threshold pH for dissolution of Eudragit L is above pH 5.5. A large decrease in lag time was seen from pH 6 to pH 6.8 or 7.4, which could be explained with the faster erosion of Eudragit L in higher pH media (Fig. 20). Importantly, the addition of ethylcellulose reduced the pH-dependency of the erosion process between pH 5.5 and 7.4 as indicated by a flatter curve (Fig. 20). Increasing the amount of ethylcellulose lead to an increase in lag time (Fig. 19b), as already seen before. The observed gastric resistance of the compression-coated tablets in the pH range of 1.0-5.5 could reduce inter- and intra-subject variability in vivo and ensure the release of drug in the lower intestinal tract.

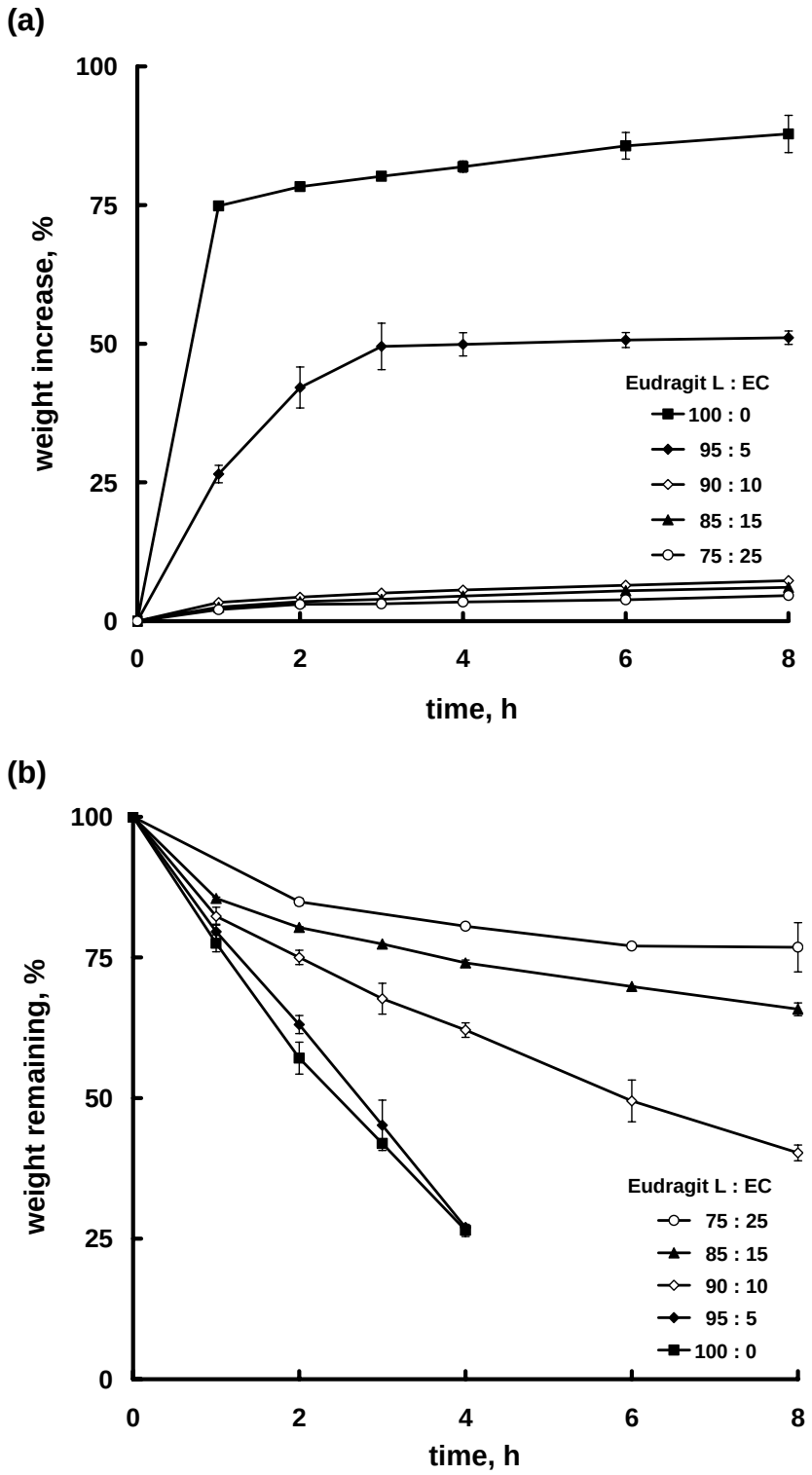


Fig. 17 Weight increase (reflecting swelling) and weight remaining (reflecting erosion) of drug-free Eudragit L:ethylcellulose (EC) matrix tablets (9 mm diameter, 25 kN compression force): (a) pH 1.0; (b) pH 7.4 (n=3)

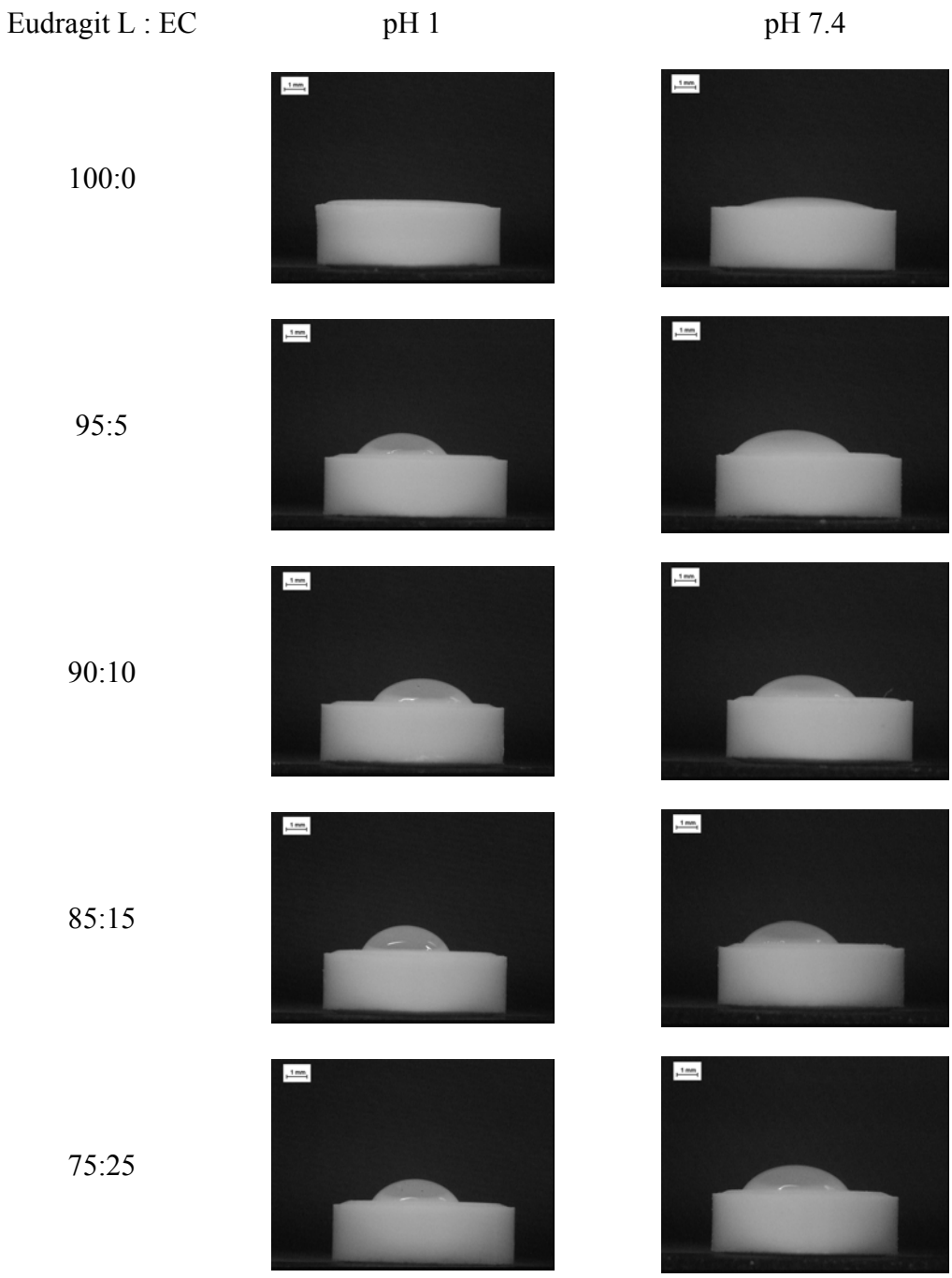


Fig. 18 Influence of ethylcellulose on the wettability of drug-free Eudragit L: ethyl-cellulose (EC) matrix tablets (300 mg, 9 mm diameter, 25 kN compression force) with pH 1.0 and pH 7.4 after 6 min

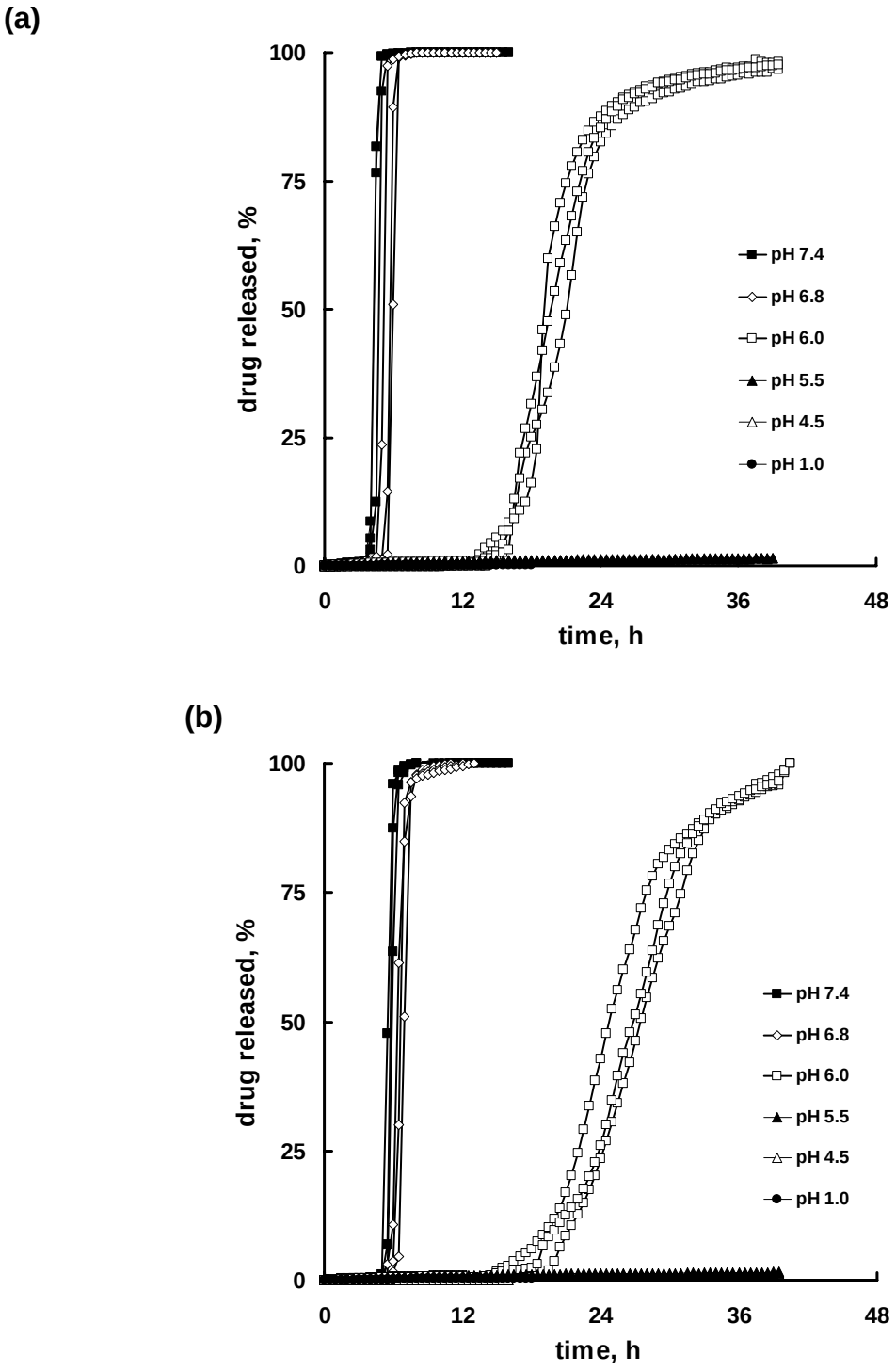


Fig. 19 Effect of pH of the release medium on the chlorpheniramine maleate release from compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) Eudragit L:ethyl cellulose, 95:5; (b) Eudragit L: ethylcellulose, 90:10 (n=3, individual release profiles shown)

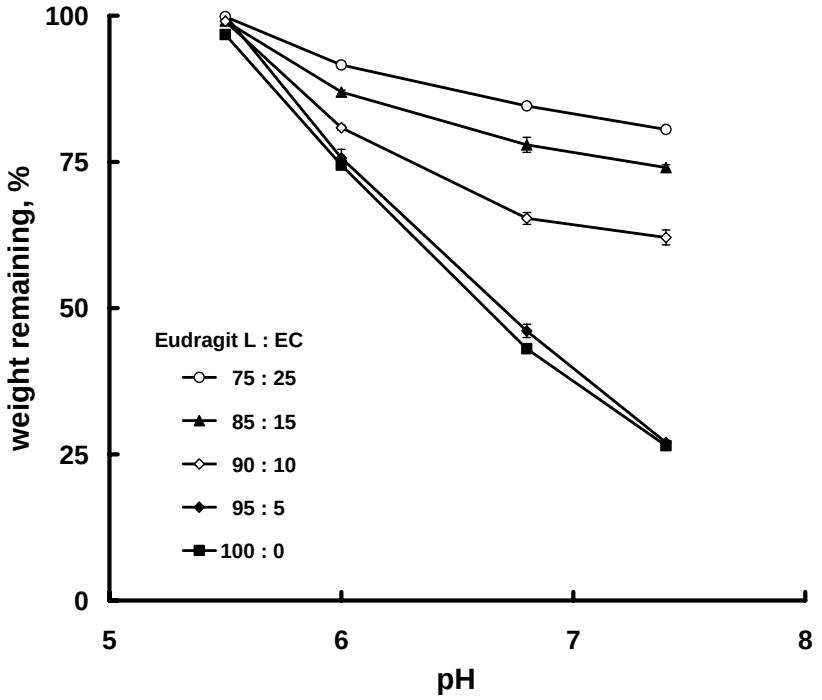


Fig. 20 Effect of pH of release medium on the weight remaining (reflecting erosion) of drug-free Eudragit L:ethyl cellulose (EC) tablets (300 mg, 9 mm diameter, 25 kN compression force) after 4 h (n=3)

The influence of pH-change of the dissolution medium on the drug release was investigated. Previously, a longer lag time after acid treatment of HPMCAS compression-coated tablets has been reported. This was explained by a decrease of the microenvironmental pH due to the acid uptake of the swollen HPMCAS coat (Fukui et al., 2001). The swelling of HPMCAS matrix tablets in pH 1.0 after 2 h was high (80%) (Streubel et al., 2000). In our study, the pH-change had no influence on the drug release (Fig. 21) because of the low swelling or acid uptake of Eudragit L:ethylcellulose blends after 2 h in pH 1.0. This was due to the presence of ethylcellulose; the acid uptakes were 42% and 3% for Eudragit L:ethylcellulose blends of 95:5 and 90:10, respectively (Fig. 17a). This shows again the value of adding small amounts of ethylcellulose to the enteric polymer in order to get a more robust release.

As expected, the lag time increased with increasing compression force (10 kN to 25 kN) (Fig. 22a-b) because of a decreased porosity/higher density of the polymer compression-coating. The release phase after the lag time was still rapid and not affected by the compression force. Compression force is thus also a parameter to control the lag time.

One potential disadvantage of compression-coated tablets is the limitation in maximum drug dose because of the relatively large amount of compression-coating. In order to maximize the potential drug loading, different tablet core:compression-coat ratios of 3:1 (9 mm core in 10 mm compression-coated tablet), of 2:1 (9 mm core in 11 mm compression-coated tablet), of 1:1 (6 mm core in 8 mm compression-coated tablet) and of 1:2 (6 mm core in 9 mm compression-coated tablet) were investigated. All formulations had no release in pH 1.0 for 20 h (data not shown) and a pulsatile release in pH 7.4 after a distinct lag time, which decreased with increasing core:coat ratio (Fig. 23a) because of the thinner compression-coating (Fig. 23b) and thus faster erosion.

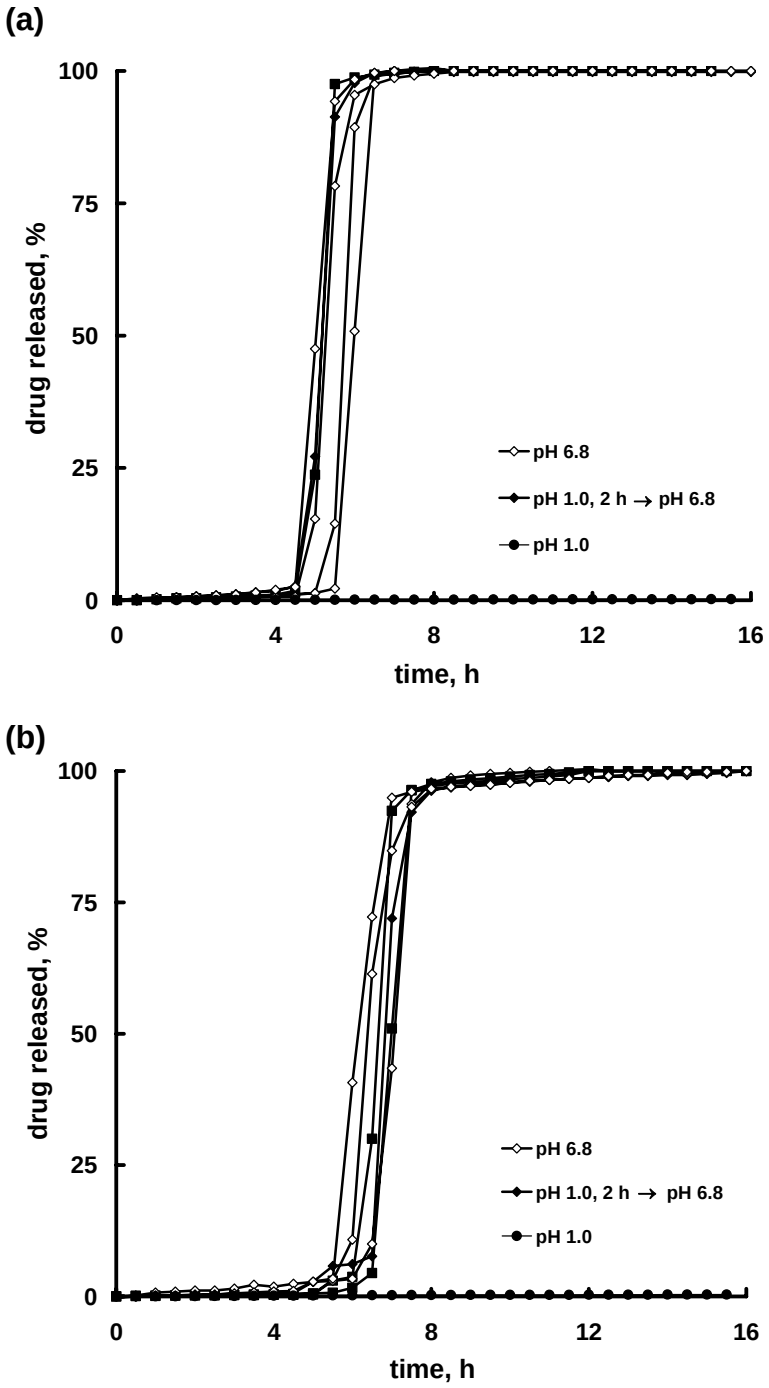


Fig. 21 Effect of pH-change of the dissolution medium on the chlorpheniramine maleate release from compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) Eudragit L:ethyl cellulose, 95:5; (b) Eudragit L:ethylcellulose, 90:10 (n=3, individual release profiles shown)

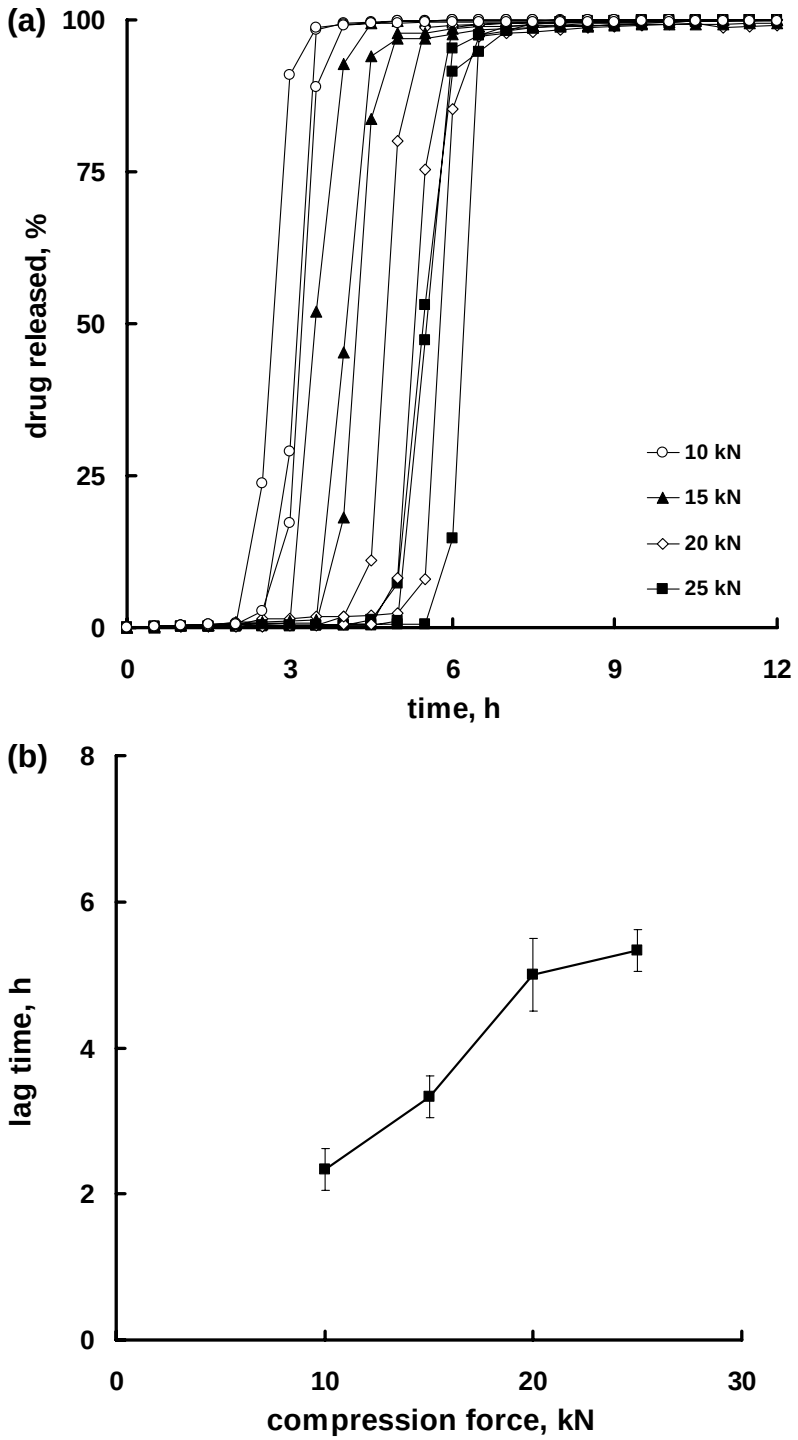


Fig. 22 Effect of compression force on chlorpheniramine maleate release from Eudragit L:ethylcellulose (90:10) compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) drug release (n=3, individual release profiles shown); (b) lag time

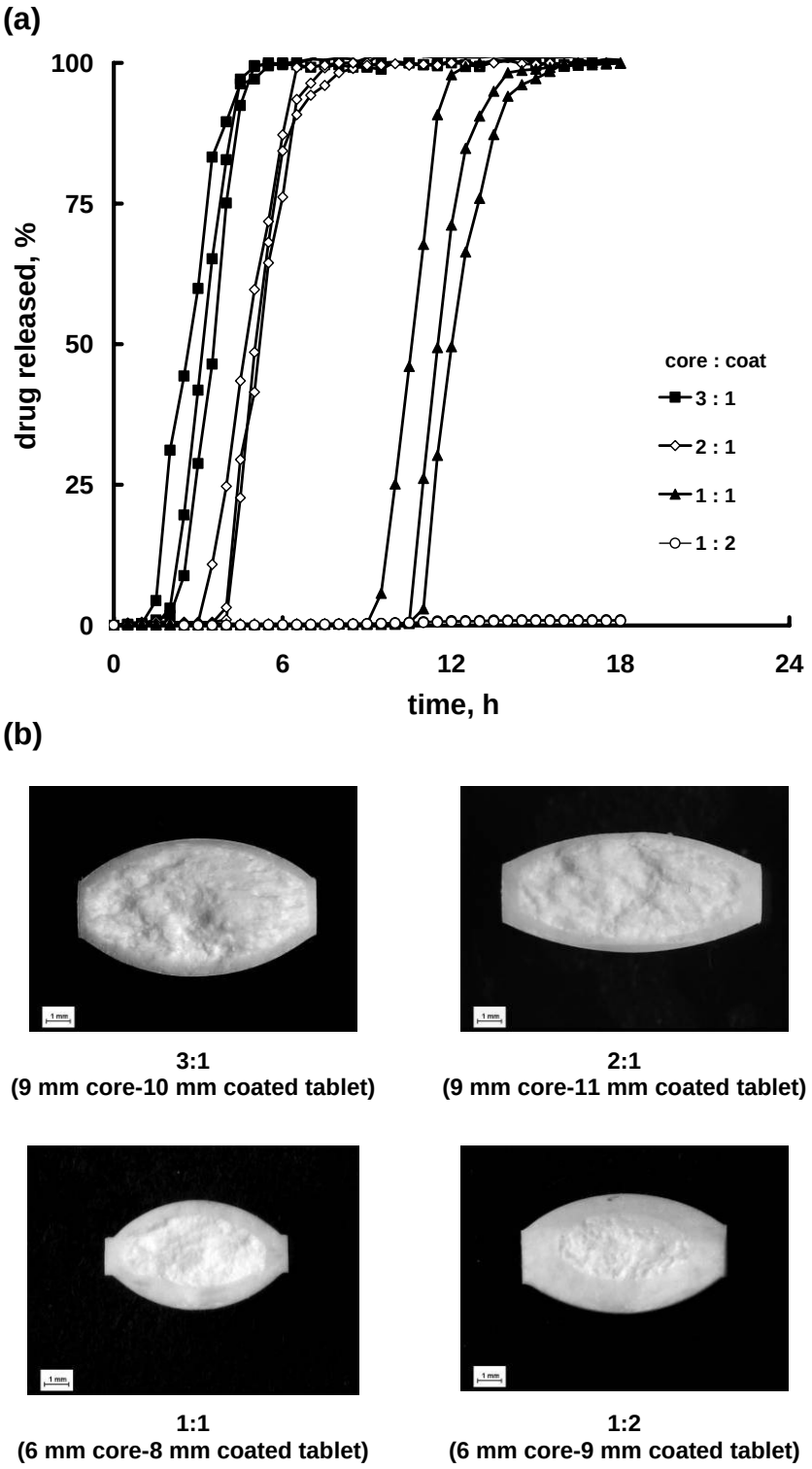


Fig. 23 Effect of tablet core:press-coat ratio on: (a) chlorpheniramine maleate release in pH 7.4 (n=3, individual release profiles shown); (b) cross sections of compression-coated tablets (Eudragit L:ethylcellulose, 75:25, 25 kN compression force)

3.2.3. Conclusion

The objective of this study was to develop pH-erosion controlled compression-coated tablets for potential colonic drug delivery with improved gastric resistance and pulsatile release based on compression-coatings of powder blends of the enteric polymer Eudragit® L 100-55 and the extended release polymer ethylcellulose. Tablet cores containing model drugs of varying solubilities (acetaminophen, carbamazepine and chlorpheniramine maleate) were compression-coated with different ratios of Eudragit® L100-55:ethylcellulose 10cP FP at different compression forces and tablet core:compression-coat ratios. The compression-coated tablets were characterized by drug release, acid uptake, erosion behaviour and wettability. All drugs were released in a pulsatile fashion in higher pH-media after a lag time, which was controlled by the erosion properties of the Eudragit L:ethylcellulose compression-coating. The addition of ethylcellulose avoided premature drug release in lower pH-media and significantly increased the lag time in higher pH-media because of a reduction in wettability, media uptake and erosion of the compression-coatings. Importantly, ethylcellulose also reduced the pH-dependency of the erosion process between pH 5.5 and 7.4. The lag time could also be increased by increasing the compression force and decreasing the core:compression-coat ratio. In conclusion, tablets compression-coated with blends of Eudragit L and ethylcellulose resulted in excellent release properties for potential targeting to the lower intestinal tract with no release in lower pH-media and rapid release after a controllable lag time in higher pH-media.

3.3 Modified release system from hydroxypropyl methylcellulose compression-coated tablets

3.3.1 Introduction

Time-controlled or pulsatile drug delivery systems are often based on rupturable (Bussemer et al., 2003; Sungthongjeen et al., 2004) or erodible coatings/matrices (Gazzaniga et al. 1994, Krögel and Bodmeier, 1998). A time-controlled delivery system named Chronotopic® system (Gazzaniga et al. 1994; Sangalli et al., 2001) is based on a drug-containing core spray-coated with the water-soluble polymer hydroxypropyl methylcellulose (HPMC). Upon contact with gastrointestinal fluids, the coating underwent swelling and lipophilic drugs were released after erosion of the gel layer. Pulsatile release profile can not be obtained with water-soluble drugs, because they are released already prior to erosion of the gel by diffusion through the gel layer. However, coating with high molecular weight HPMC presents some challenges. Spray-coating of the viscous and low concentrated coating solution requires long processing time; hydro-alcoholic HPMC solutions were used to reduce this problem (Maffion et al., 1993).

Compression-coating presents an attractive alternative to spray-coating techniques for high molecular weight polymers. Thick coatings can be applied rapidly and it is a solvent-free coating process (Bose and Bogner, 2007). Compression-coating has been used in the pharmaceutical field for different purposes: (1) to protect hygroscopic, light-sensitive, oxygen-labile or acid-labile drugs (Picker, 2002); (2) to combine and separate different therapeutic drugs (Maggi et al., 1993; Waterman and Fergione, 2003); (3) to modify a drug release pattern (delayed, pulsatile and programmable release of different drugs in one tablet) (Halsas et al., 2001; Lopes et al., 2007).

Various materials have been investigated as compression-coatings to obtain time-controlled release: HPMC (Conte et al., 1993; Sirkiä et al., 1994; Wu et al., 2007), Hydroxypropyl cellulose (Fukui et al., 2000), polyethylene oxide (Sawada et al., 2004), micronized ethyl cellulose (Lin et al., 2001, 2002), Eudragit® RS (González-Rodríguez et al., 2003), behenic acid (Peerapattana et al., 2004). Bimodal drug release

usually obtained with multi-layered matrix tablets (Streubel et al., 2000) can also be obtained with compression-coated tablets (Sirkiä et al., 1994; Lopes et al., 2007).

In this study, HPMC-compression-coated tablets were investigated to obtain flexible modified release profiles for model drugs covering a wide range in solubility. One objective was to obtain a pulsatile release with this system also for water-soluble drugs by inhibiting the drug release through the gelled layer prior to erosion.

3.2.2. Results and discussion

The goal of this study was to obtain flexible extended drug release profiles (e.g., sigmoidal, pulsatile, increasing release rate with time) with HPMC compression-coated tablets. Drugs of varying solubility (solubilities of carbamazepine, acetaminophen, propranolol HCl and chlorpheniramine maleate are 0.2, 20, 253 and 562 mg/ml, respectively) were incorporated into the core in order to evaluate the flexibility/limitations of the compression-coated system with regard to different drug candidates.

All tablet cores (without compression-coating) resulted in complete drug release within 15 min (data not shown). The HPMC-compression-coating resulted in release profiles with a distinct lag time followed by a complete release with different release rates (Fig. 24). The HPMC compression-coating hydrated and swelled around the drug cores. Depending on their solubility, drugs are released from HPMC matrix tablets by diffusion through and/or erosion of the gelled HPMC matrix (Siepmann et al., 2002). Carbamazepine, the least water-soluble drug, was released in a pulsatile fashion after a long lag time. It was thus released after erosion of the HPMC compression-coating and not by diffusion through the gel. The release of the other, more water-soluble drugs started after a shorter but similar lag-time for these drugs. The drug release then increased with increasing drug solubility (chlorpheniramine maleate > propranolol HCl > acetaminophen), pointing to an increasing diffusional release component with increasing drug solubility.

Next, the effect of various changes in the HPMC compression-coating on the drug release was investigated.

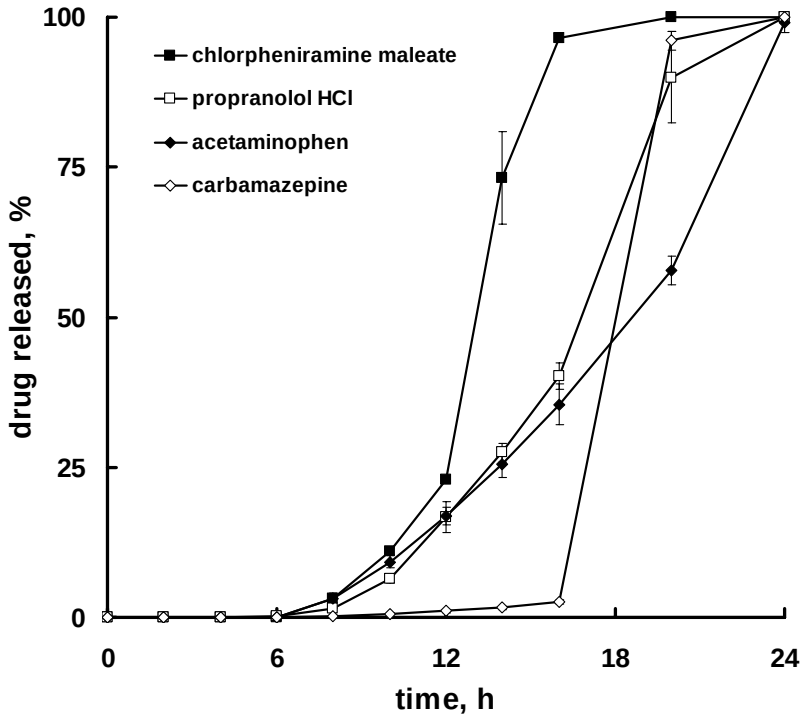


Fig. 24 Effect of type of drug on the drug release from HPMC 400 compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force)

With the water-insoluble carbamazepine, increasing the molecular weight of HPMC significantly increased the lag time because of the erosion-based release mechanism and the stronger gel and slower erosion with the higher molecular weight HPMC grades (Fig. 25a). In contrast, increasing the viscosity grade (molecular weight) of HPMC in the compression-coating did not affect the release of the more soluble acetaminophen much (Fig. 25b). The initial release phase was the same with the different HPMC grades because of a release mechanism of diffusion through the gel. Only at the later stages did the lower viscosity grade HPMC E50 erode faster and thus resulted in an earlier completeness in release.

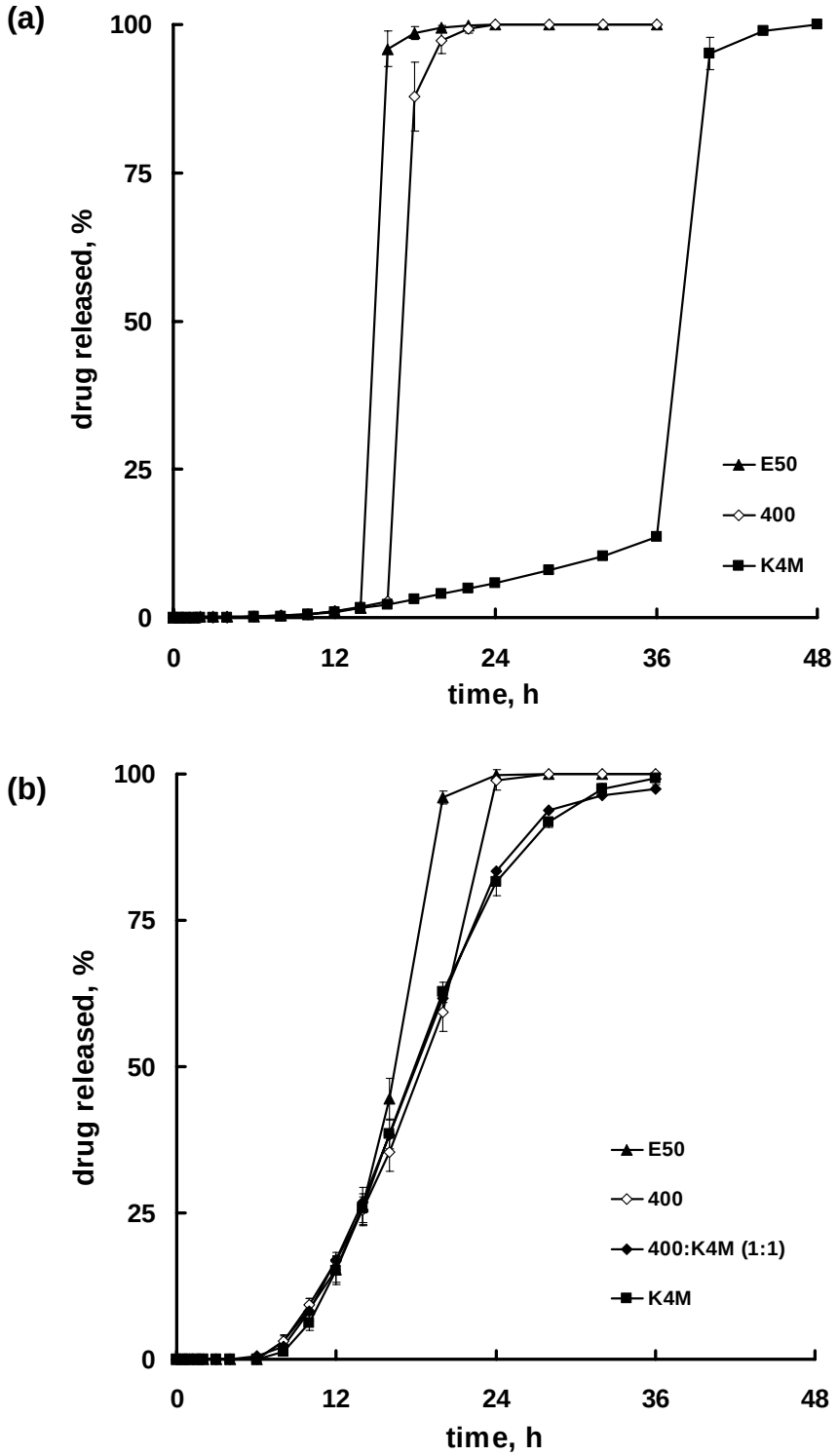


Fig. 25 Effect of HPMC-type on drug release from HPMC compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) carbamazepine; (b) acetaminophen

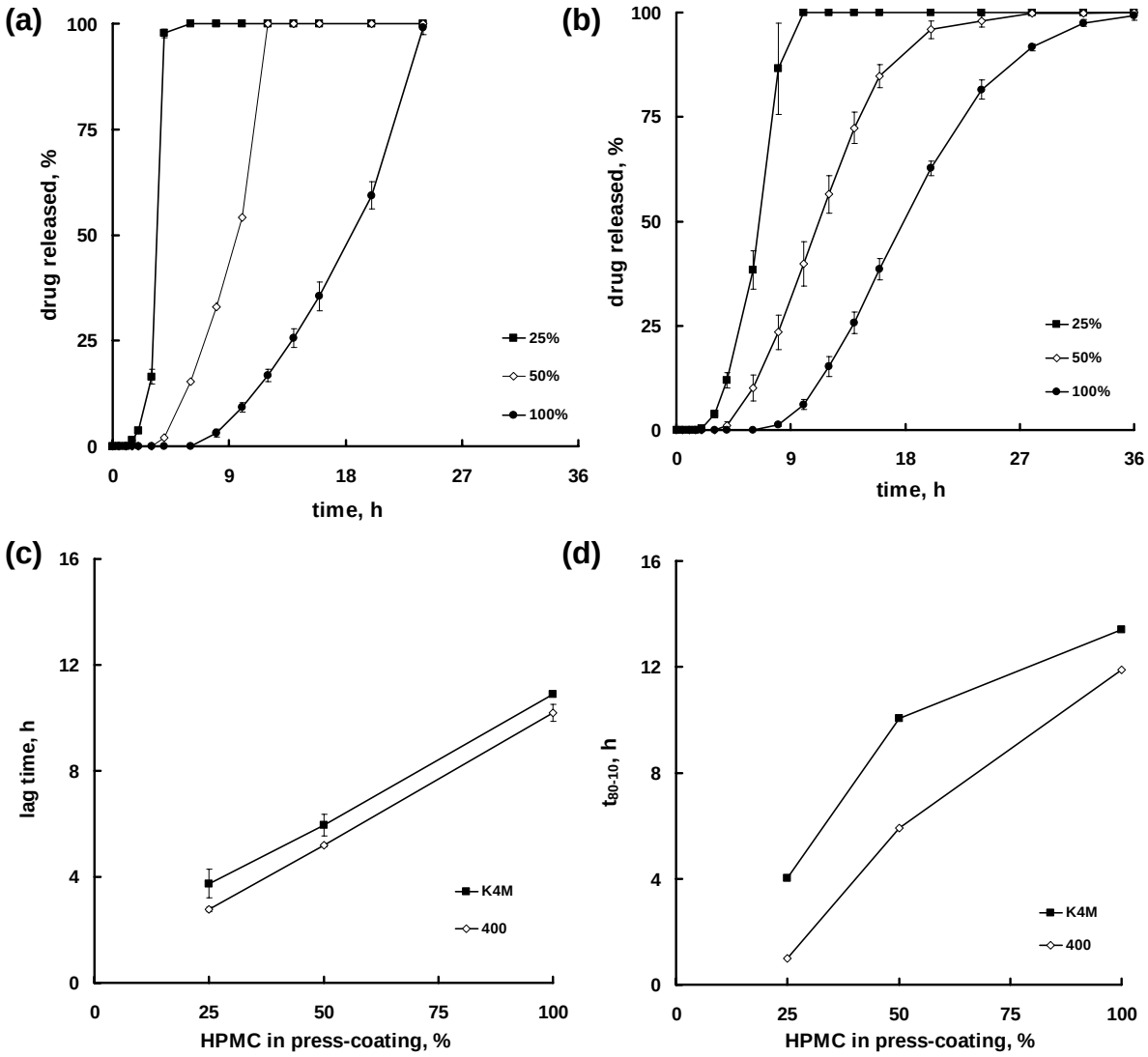


Fig. 26 Effect of HPMC content in compression-coating on acetaminophen release (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force): (a) HPMC 400; (b) HPMC K4M and (c) lag time (d) release time (t_{80-10})

The lag-time and the release rate could also be well controlled by varying the composition (ratio HPMC/lactose-Ludipress®) and the amount (thickness) of the compression-coating (Figs. 26 and 27). Increasing the HPMC amount prolonged the lag time and extended the release phase (less steep profiles) because of a higher gel strength (slower erosion) and a higher diffusional resistance (Fig. 26a-b). Slight differences in lag

time between HPMC 400 and K4M were observed (Fig. 26c); however, larger differences with regard to the steepness of the release phase (t_{80-10}) were observed because of the faster erosion of the lower molecular weight HPMC 400 (Fig. 26d). As expected, increasing the amount of the compression-coating (decreasing core:coat ratio) resulted in an increasing lag time and decreasing release rate (Fig. 27) because of an increase in gel thickness and thus diffusional path length.

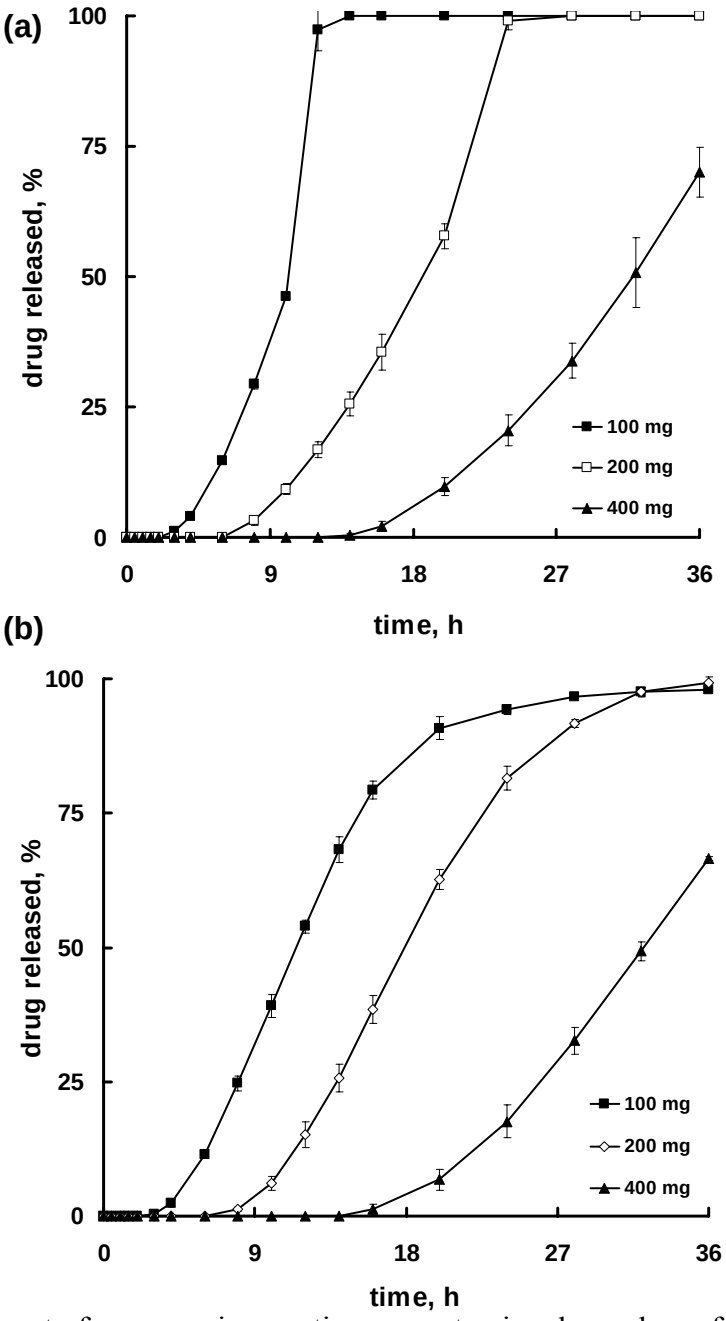


Fig. 27 Effect of amount of compression-coating on acetaminophen release from HPMC compression-coated tablets: (a) HPMC 400; (b) HPMC K4M

The compression-coating compression force did not affect the drug release in the range investigated (15 – 25kN) (Fig. 28). HPMC quickly formed a gel layer on the surface, thus eliminating the potential effect of minor differences in densities obtained with different compression forces. This confirms findings of previous studies with HPMC matrix tablets (Hiremath and Saha, 2008) and pectin-HPMC compression-coatings (Turkoglu et al., 2002).

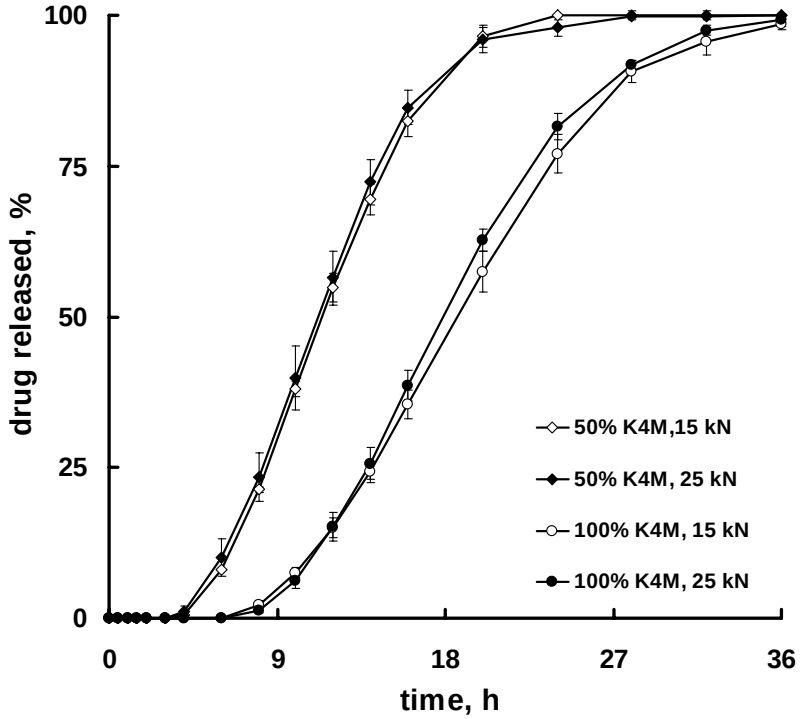


Fig. 28 Effect of compression-coating compression force on acetaminophen release from HPMC K4M compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets)

A pulsatile release from HPMC compression-coated tablets, as obtained with the water-insoluble carbamazepine (Fig. 24) would also be desirable for water-soluble drugs. This could be achieved by introducing an enteric polymer layer of Eudragit L between the drug core and the HPMC compression-coating (Fig. 29). The Eudragit L subcoating eliminated drug diffusion into the gelled HPMC layer prior to erosion of the layer; the enteric polymer completely dissolved after erosion of the HPMC compression-coating in intestinal pH-ranges/regions. The lag time increased with increasing Eudragit L coating level because of a slower dissolution of the thicker Eudragit L coating (Fig. 29).

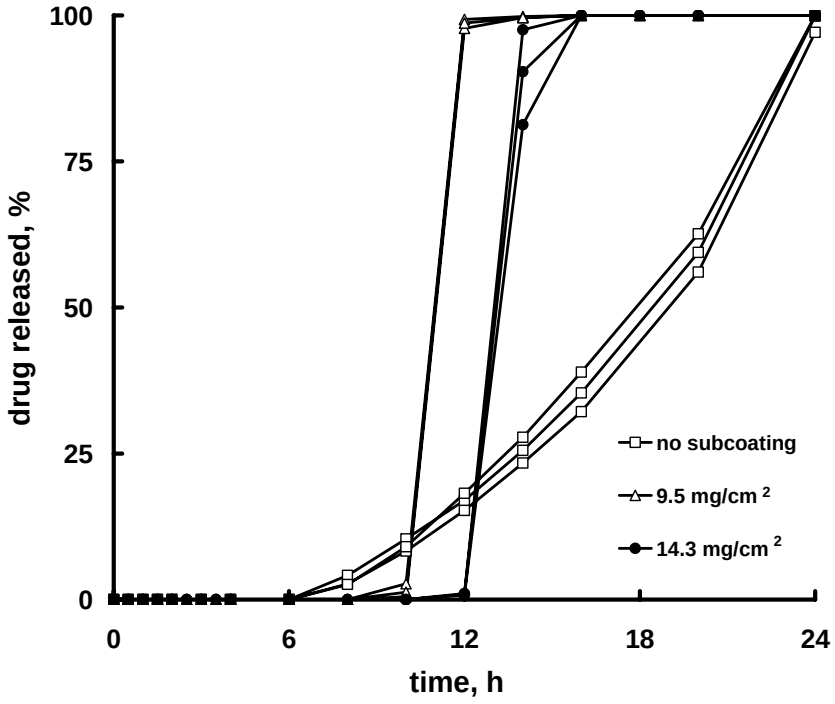


Fig. 29 Effect of Eudragit L subcoating level (mg/cm^2) on acetaminophen release from HPMC 400 compression-coated tablets (core:coat, 1:2, 6 mm Eudragit L sub-coated tablets cores in 9 mm compression-coated tablets, 25 kN compression force) (n=3, individual release profiles shown)

The HPMC type in the compression-coating also affected the drug release from Eudragit L subcoated cores. Pulsatile release was obtained with the lower molecular weight HPMC E50 and 400, but extended release with longer lag time with from HPMC K4M (Fig. 30a). Extended release from HPMC K4M compression-coated tablets was explained by drug diffusion through the partially dissolved Eudragit L subcoat and swollen HPMC K4M compression-coating having higher gel strength compared with HPMC E50 and 400. Pulsatile release from HPMC compression-coated tablets with Eudragit L subcoating was also obtained with the highly water-soluble chlorpheniramine maleate (Fig. 30b).

To further gain flexibility in the drug release profile, drug was also incorporated in the compression-coating in addition to the tablet core (Fig. 31). A constant zero-order drug release profile was obtained with 50% drug each in the core and compression-coating. The individual release curves from drug present in the compression-coating only resulted in a typical matrix-type release profile with a decreasing release rate, while the drug present in the core only resulted in a profile with an increasing release rate. The decreasing and increasing release rates of the compression-coating and the core then summed up to a constant release rate. Increasing the drug loading in compression-coating resulted in an increased drug release due to a decreased HPMC amount in the compression-coating (Fig. 32). The drug release rate changed from increasing release rates to decreasing release rates with increasing drug loadings in the compression-coating.

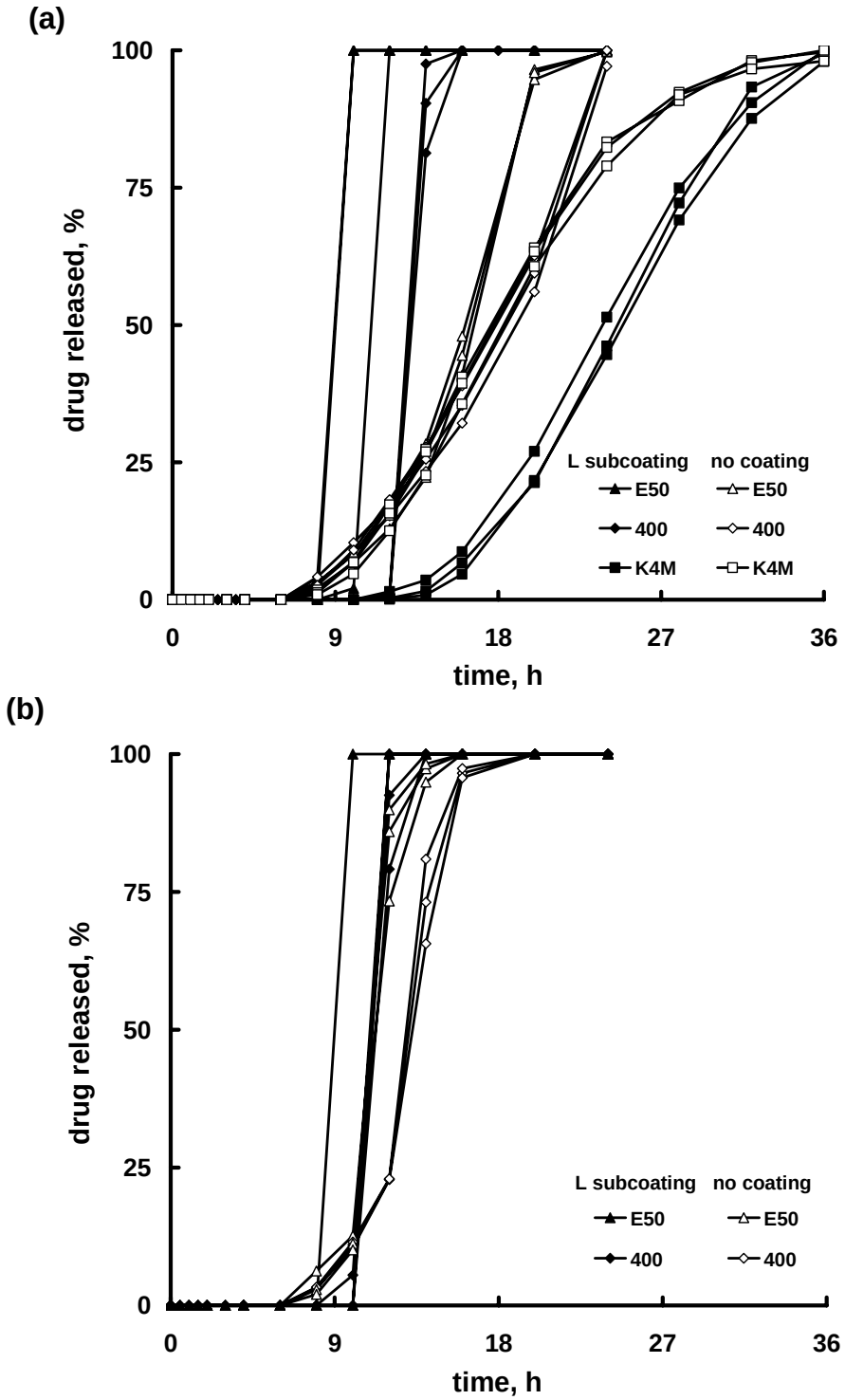


Fig. 30 Effect of HPMC type and Eudragit L subcoating on drug release from compression-coated tablets (core:coat, 1:2, 6 mm tablets cores in 9 mm compression-coated tablets, 25 kN compression force) (n=3, individual release profiles shown): (a) acetaminophen; (b) chlorpheniramine maleate

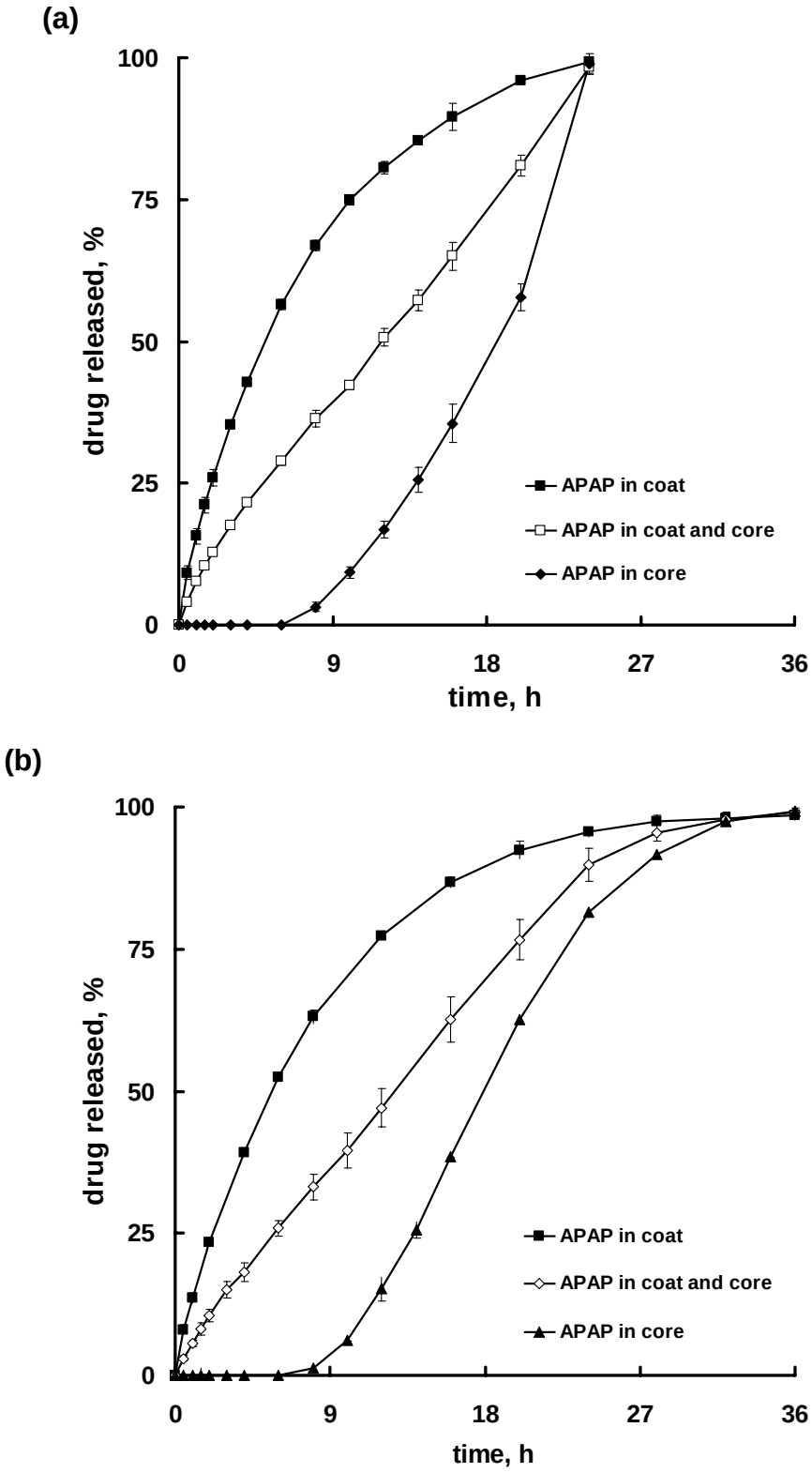


Fig. 31 Acetaminophen release from (a) HPMC 400 and (b) HPMC K4M compression-coated tablets with acetaminophen (APAP) amount in core:coat, 1:1 (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force)

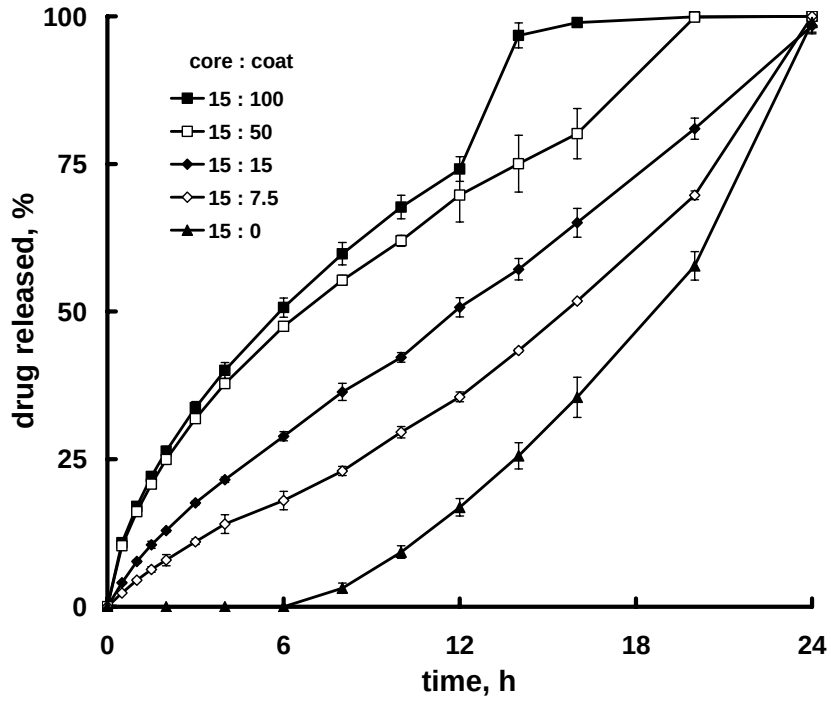


Fig. 32 Effect of drug distribution in the core:coat on acetaminophen release from HPMC 400 compression-coated tablets (core:coat, 1:2, 6 mm tablet cores in 9 mm compression-coated tablets, 25 kN compression force)

3.3.3. Conclusion

The goal of this study was to obtain flexible extended drug release profiles (e.g., sigmoidal, pulsatile, increasing/decreasing release rates with time) with hydroxypropyl methylcellulose (HPMC) compression-coated tablets. Drugs of varying solubility (carbamazepine, acetaminophen, propranolol HCl and chlorpheniramine maleate) were incorporated into the tablet core in order to evaluate the flexibility/limitations of the compression-coated system. The HPMC-compression-coating resulted in release profiles with a distinct lag time followed by different release phases primarily determined by the drug solubility. Carbamazepine, a water-insoluble drug, was released in a pulsatile fashion after a lag time only after erosion of the HPMC compression-coat, while the more soluble drugs were released in a sigmoidal fashion by diffusion through the gel prior to erosion. With carbamazepine, increasing the molecular weight of HPMC significantly increased the lag time because of the erosion-based release mechanism, while, in contrast, molecular weight did not affect the release of the more soluble drugs. The lag-time and the release rate could also be well controlled by varying the HPMC amount in and the thickness of the compression-coating. A pulsatile release could also be achieved for water-soluble drugs by introducing an enteric polymer coating between the drug core and the HPMC compression-coating. This novel concept of introducing an enteric subcoating eliminated drug diffusion through the gelled HPMC layer prior to its erosion. Incorporating drug in the compression-coating in addition to the tablet core in varying ratios resulted in release profiles with increasing, decreasing or constant release rates. In conclusion, a versatile single-unit delivery system for a wide range of drugs with great flexibility in release profiles was presented.

4. SUMMARY

4.1 Moisture plasticization for enteric Eudragit® L30D-55-coated pellets prior to compression into tablets

Oral modified release pellet-based drug delivery systems are either filled into capsules or compressed into tablets. To achieve compression of polymer-coated pellets into tablets, good flexibility of the polymeric coating is crucial in order not to rupture and to loose the modified release properties. Enteric polymers such as cellulose esters (cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate) and methacrylic acid–acrylate copolymers (Eudragit® L100-55 and S100) are quite brittle in the dry state and thus not suitable as pellet coatings for compression into tablets. The objective of this study was to investigate the role of humidity treatment prior to compression and thus the role of moisture as potent plasticizer for the successful compression of enterically coated pellets. Based on previous studies on the mechanical properties of wet polymeric films and the plasticization effect of water, the polymer films were stored at elevated humidity (84%RH) in order to investigate possible plasticization effects of adsorbed moisture and to obtain an increase in flexibility of the polymer films sufficient for compression. The mechanical properties of Eudragit® L100-55 improved dramatically, while the properties of the other enteric polymers showed only minor changes after storage at higher humidity. The significant increase in flexibility of the Eudragit® L film was caused by hydration/plasticization; its elongation value changed from approx. 3% in the dry state to approx. 140% at the higher storage humidity. Therefore, Eudragit® L100-55 was further evaluated as a potential moisture-plasticized enteric polymer candidate for the compression of coated pellets. To avoid organic solvents during coating, the aqueous dispersion Eudragit® L30D-55 was used in the following studies.

Eudragit® L30D-55 coated pellets were stored at different humidities for different time periods and then compressed and evaluated for changes in acetaminophen release (model drug). The damage to the Eudragit® L-coated pellets decreased with increasing storage humidity and storage time, as indicated by a lower increase in release upon compression. Storage at 84% relative humidity resulted in comparable release profiles of compressed and uncompressed pellets. A higher storage humidity resulted in an increased water content and plasticization effect of the films as indicated by a decrease in the glass transition temperature of films. The glass transition temperature decreased

below the compression temperature (room temperature) at storage humidities between 75% and 84%. The glass transition relative humidity leading to a change from the glassy to the rubbery state was determined by dynamic vapor sorption to be 76.8%. Moisture was also a much more effective plasticizer for Eudragit® L than the conventionally used plasticizer triethyl citrate. The improved compressibility of moisture-treated Eudragit® L-coated pellets was also shown with single pellet compression data as indicated by an increased crushing force and deformation.

In conclusion, moisture plasticization was a highly effective tool to enable the successful compression of pellets coated with the brittle enteric polymer Eudragit® L.

4.2 Improved drug delivery to the lower intestinal tract with tablets compression-coated with enteric/nonenteric polymer powder blends

The objective of this study was to develop pH-erosion controlled compression-coated tablets for potential colonic drug delivery with improved gastric resistance and pulsatile release based on compression-coatings of powder blends of the enteric polymer Eudragit® L 100-55 and the extended release polymer ethylcellulose. Tablet cores containing model drugs of varying solubilities (acetaminophen, carbamazepine and chlorpheniramine maleate) were compression-coated with different ratios of Eudragit® L100-55:ethylcellulose 10cP FP at different compression forces and tablet core:compression-coat ratios. The compression-coated tablets were characterized by drug release, acid uptake, erosion behaviour and wettability. All drugs were released in a pulsatile fashion in higher pH-media after a lag time, which was controlled by the erosion properties of the Eudragit L:ethylcellulose compression-coating. The addition of ethylcellulose avoided premature drug release in lower pH-media and significantly increased the lag time in higher pH-media because of a reduction in wettability, media uptake and erosion of the compression-coatings. Importantly, ethylcellulose also reduced the pH-dependency of the erosion process between pH 5.5 and 7.4. The lag time could also be increased by increasing the compression force and decreasing the core:compression-coat ratio. In order to maximize the potential drug loading, different tablet core:compression-coat ratios of 3:1, 2:1, 1:1 and 1:2 were investigated. All formulations had no release in pH 1.0 for 20 h and a pulsatile release in pH 7.4 after a

distinct lag time, which decreased with increasing core:coat ratio because of the thinner compression-coating and thus faster erosion.

In conclusion, tablets compression-coated with blends of Eudragit® L and ethylcellulose resulted in excellent release properties for potential targeting to the lower intestinal tract with no release in lower pH-media and rapid release after a controllable lag time in higher pH-media.

4.3 Modified release from hydroxypropyl methylcellulose compression-coated tablets

The goal of this study was to obtain flexible extended drug release profiles (e.g., sigmoidal, pulsatile, increasing/decreasing release rates with time) with hydroxypropyl methylcellulose (HPMC) compression-coated tablets. Drugs of varying solubility (carbamazepine, acetaminophen, propranolol HCl and chlorpheniramine maleate) were incorporated into the tablet core in order to evaluate the flexibility/limitations of the compression-coated system. The HPMC-compression-coating resulted in release profiles with a distinct lag time followed by different release phases primarily determined by the drug solubility. Carbamazepine, a water-insoluble drug, was released in a pulsatile fashion after a lag time only after erosion of the HPMC compression-coat, while the more soluble drugs were released in a sigmoidal fashion by diffusion through the gel prior to erosion. With carbamazepine, increasing the molecular weight of HPMC significantly increased the lag time because of the erosion-based release mechanism, while, in contrast, molecular weight did not affect the release of the more soluble drugs. The lag-time and the release rate could also be well controlled by varying the HPMC amount in and the thickness of the compression-coating.

A pulsatile release could also be achieved for water-soluble drugs by introducing an enteric polymer coating between the drug core and the HPMC compression-coating. This novel concept of introducing an enteric subcoating eliminated drug diffusion through the gelled HPMC layer prior to its erosion. The lag time increased with increasing Eudragit L coating level because of a slower dissolution of the thicker Eudragit L coating. The HPMC type in the compression-coating also affected the drug release from Eudragit L subcoated cores. Pulsatile release was obtained with the lower

molecular weight HPMC E50 and 400, but extended release with longer lag time with from HPMC K4M.

Incorporating drug in the compression-coating in addition to the tablet core in varying ratios resulted in release profiles with increasing, decreasing or constant release rates. The individual release curves from drug present in the compression-coating only resulted in a typical matrix-type release profile with a decreasing release rate, while the drug present in the core only resulted in a profile with an increasing release rate. The decreasing and increasing release rates of the compression-coating and the core then summed up to a constant release rate.

In conclusion, a versatile single-unit delivery system for a wide range of drugs with great flexibility in release profiles was presented.

5. ZUSAMMENFASSUNG

4.1. Feuchtigkeit als Weichmacher für Pellets mit Magensaftresistenten Eudragit® L30D-55 Filmüberzügen zur Kompression zu Tabletten

Modifizierte Pellet basierende Arzneistofffreisetzungssysteme zu oralen Gabe werden entweder in Kapseln abgefüllt oder zu Tabletten verpresst. Zur Tablettierung von Filmüberzogenen Pellets eine gute Flexibilität des Polymerüberzüge entscheidend um Risse im Film zu vermeiden und dementsprechend die Freisetzungseigenschaften nicht zu verändern. Magensaftresistente Polymere wie Cellulose-Ester (Celluloseacetatphtalat, Hydroxypropyl-methylcellulose Acetat-Succinat) und Methacrylsäure-Acrylat-Copolymere (Eudragit® L100-55 und S100) sind sehr spröde in trockenem Zustand und sind daher als Filmüberzüge für Pellets zur Verpressung in Tabletten nicht geeignet. Das Ziel dieser Studie war es Feuchtigkeit als potenten Weichmacher zu untersuchen um magensaftresistent überzogene Pellets erfolgreich zu verpressen. Basierend auf vorangegangenen Studien der mechanischen Eigenschaften von feuchten Polymerfilmen und den Weichmacher Eigenschaften von Wasser wurden Polymerfilme bei erhöhter Luftfeuchtigkeit (84% relative Luftfeuchtigkeit) gelagert, um mögliche weichmachende Eigenschaften von adsorbierter Feuchtigkeit zu bestimmen und um die Flexibilität der Polymerfilme zu erhöhen damit eine Tablettierung möglich wird. Nachdem die Filme bei erhöhter Luftfeuchtigkeit gelagert worden waren, verbesserten sich die mechanischen Eigenschaften von Eudragit® L100-55 Filmen dramatisch, während sich die Eigenschaften von Filmen des anderen magensaftresistenten Polymers nur gering veränderten. Der signifikante Anstieg der Flexibilität von Eudragit® L100-55 Filmen wurden durch Hydratation / Plastifizierung hervorgerufen. Dabei stieg der Dehnungswert von etwa 3% im trockenen Zustand auf etwa 140% nach der Lagerung bei erhöhter Luftfeuchtigkeit. Daher wurde Eudragit® L100-55 als ein potentieller Kandidat eines feuchtigkeit-plastifizierendes magensaftresistentes Filmüberzugspolymer, geeignet für die Pellettablettierung, weiter untersucht. Um organische Lösungsmittel während des Übeziehens zu vermeiden, wurde die wässrige Dispersion Eudragit® L30D-55 für die folgenden Studien verwendet.

Eudragit® L30D-55 überzogene Pellets mit dem Wirkstoff Acetaminophen wurden bei verschiedenen Luftfeuchten für unterschiedliche Zeiträume gelagert und zu Tabletten verpresst. Anschließend wurden mögliche Veränderungen des Freisetzungsverhaltens bestimmt. Die Beschädigung der Eudragit® L haltigen Filme

verringerte sich mit ansteigender Lagerungsfeuchtigkeit und ansteigender Lagerungszeit was durch eine langsamere Freisetzung angezeigt wurde. Die Lagerung bei 84% relativer Luftfeuchtigkeit führte zu vergleichbaren Freisetzungprofilen von komprimierten und unkomprimierten Pellets. Die Lagerung bei höherer Luftfeuchtigkeit führte zu einem erhöhten Wassergehalt in den Filmen welcher zu einer verbesserten Plastifizierung führte. Dies wurde durch eine Verringerung der Glasübergangstemperatur der Polymerfilme angezeigt. Die Glasübergangstemperatur wurde bis unter die Kompressionstemperatur (Raumtemperatur) erniedrigt, wenn die Pellets bei relativen Luftfeuchtigkeiten zwischen 75% und 84% gelagert wurden. Die relative Luftfeuchtigkeit bei der das Polymer vom glasartigen in den gummiartigen Zustand bei Raumtemperatur übergeht wurde mit Dynamischer Wasserdampf Sorption auf 76.8% bestimmt. Feuchtigkeit zeigte bessere Weichmachereigenschaften als der herkömmlich verwendete Weichmacher Triethylcitrat. Die verbesserte Tablettierbarkeit von Feuchtigkeitsbehandelten Eudragit® L-überzogenen Pellets wurde auch durch einen Härtetest der einzelnen Pellets nachgewiesen, wobei diese eine gestiegene Bruchfestigkeit und eine bessere Verformbarkeit zeigten.

Zusammenfassend zeigten die Untersuchungen, daß die Benutzung von Feuchtigkeit als Weichmacher eine hocheffektive Möglichkeit darstellt, um Pellets mit spröden magensaftresistenten Eudragit® L Filmüberzügen erfolgreich in Tabetten zu verpressen.

4.2 Verbesserte Wirkstofffreisetzung in tieferen Darmabschnitten durch Manteltabletten mit Misch-Überzügen aus magensaftresistenten und wasserunlöslichen Polymerpulvern

Das Ziel dieser Studie war es, Manteltabletten mit verbesserter Magensaftresistenz zur potentiellen Arzneistoffapplikation im Dickdarm zu entwickeln, basierend auf Polymerpulver-Mischungen aus magensaftresistentem Eudragit® L 100-55 und retardierender, wasserunlöslicher Ethylcellulose. Die pulsatile Freisetzung dieser Tabletten sollte durch pH-Wert und Erosion kontrolliert werden.

Die Tablettenkerne mit Modell-Arzneistoffen unterschiedlicher Löslichkeiten (Paracetamol, Carbamazepin und Chlorpheniraminmaleat) wurden mit Mischungen der beiden Polymere ummantelt; dabei wurden das Polymer-Verhältnis von Eudragit® L100-55 zu Ethylcellulose 10cp FP, von Tablettenkern zum Mantel sowie die

Pressdrücke variiert . Die erhaltenen Manteltabletten wurden bezüglich ihrer Wirkstofffreisetzung, Säure-Aufnahme, Erosion und Benetzbarkeit charakterisiert. Bei höheren pH-Werten wurden alle Wirkstoffe nach einer lag-Zeit pulsatil freigesetzt; wobei die lag-Zeit durch die Erosions-Eigenschaften des Eudragit L / Ethylcellulose Mantels gesteuert wurde. Der Zusatz von Ethylcellulose verhinderte eine vorzeitige Wirkstofffreisetzung bei niedrigeren pH-Werten und erhöhte bei höheren pH-Werten signifikant die lag-Zeit aufgrund verringerter Benetzbarkeit, Flüssigkeitsaufnahme und Erosion des Mantels. Ethylcellulose reduzierte gleichzeitig auch die pH-Abhängigkeit des Erosions-Prozesses zwischen pH 5,5 und 7,4. Eine zusätzliche Verlängerung der lag-Zeit konnte auch durch eine höhere Pressdrücke und niedrige Kern : Mantel Verhältnisse erreicht werden.

Um die mögliche Arzneistoff-Beladung der Manteltabletten zu maximieren wurden Kern: Mantel Verhältnisse von 3:1, 2:1, 1:1 und 1:2 untersucht. Alle Formulierungen zeigten keinerlei Freisetzung in pH 1,0 für 20 h und eine pulsatile Freisetzung in pH 7.4 nach einer deutlichen lag-Zeit, wobei dünnere Ummantelungen erwartungsgemäß kürzere lag-Zeiten aufwiesen aufgrund der schnelleren Erosion.

4.3 Modifizierte Freisetzug aus Hydroxypropylmethylcellulose Manteltabletten

Das Ziel dieser Studie war es, flexibel steuerbare Freisetzungsprofile für Wirkstoffe (z.Bsp. sigmoidal, pulsatil, hohe / niedrige Freisetzungsraten) mit Hydroxypropylmethylcellulose (HPMC) Manteltabletten zu erhalten. Um die Möglichkeiten bzw. Grenzen des Systems zu evaluieren, wurden Arzneistoffe mit unterschiedlicher Löslichkeit (Carbamazepin, Paracetamol, Propranolol HCl und Chlorpheniraminmaleat) in den Tablettenkern eingearbeitet. Der HPMC-Mantel führte zu Freisetzungen mit einer deutlichen lag-Zeit gefolgt von verschiedenen Freisetzungsphasen, welche in erster Linie durch die Arzneistofflöslichkeit bestimmt wurden. Carbamazepin, ein schwer löslicher Arzneistoff, wurde erst nach vollständiger Erosion des HPMC-Mantels pulsatil freigesetzt, während die besser löslichen Arzneistoffe schon vorher durch Diffusion durch das Gel und somit eher sigmoidal freigesetzt wurden. Aufgrund des erosions-basierten Freisetzungsmechanismus konnte für Carbamazepin auch festgestellt werden, dass eine Erhöhung des Molekülgewichts der

HPMC die lag-Zeit signifikant verlängerte, während im Gegensatz dazu das Molekülgewicht keine Auswirkungen auf die Freisetzung der besser löslichen Substanzen zeigte. Die Lag-Zeit und die Freisetzungsrate konnten durch den HPMC-Anteil und die Schichtdicke des Mantels gut gesteuert werden.

Eine pulsatile Freisetzung konnte auch für wasserlösliche Arzneistoffe erreicht werden durch die Einführung einer magensaftresistenten Polymerschicht zwischen dem Tablettenkern und dem HPMC-Mantel. Dieses neuartige Konzept der Einführung einer magensaftresistenten Zwischenschicht verhinderte eine Arzneistoff-Diffusion durch die gequollene HPMC-Schicht vor deren Erosion. Mit zunehmender Schichtdicke von Eudragit® L verlängerte sich die lag-Zeit aufgrund der langsameren Auflösung der Eudragit-Schicht. Der HPMC-Typ im Mantel hatte auch einen Einfluss auf die Freisetzung von Eudragit® L überzogenen Kernen. Mit den niedrigeren Molekulargewichten HPMC E50 und 400 wurde pulsatile Freisetzung erhalten, während HPMC K4M zu retardierter Freisetzung und längeren lag-Zeiten führte.

Eine zusätzliche Einbettung von Arzneistoffen in den Mantel in unterschiedlichen Anteilen führte zu Profilen mit zunehmenden, abnehmenden oder konstante Freisetzungsraten. Die einzelnen Freisetzungskurven von Arzneistoffen aus dem Mantel resultierte lediglich in einem typischen Matrix-Freisetzungsprofil mit abnehmender Freisetzungsrate, während der Arzneistoff im Kern zu einem Profil mit einer zunehmenden Freisetzungsrate führte. Die beiden Freisetzungsraten von Mantel und Kern zusammen allerdings ergaben eine konstante Freisetzungsrate.

Abschließend kann man feststellen, dass hier eine vielseitig anwendbare einzeln-dosierte Arzneiform vorgestellt wurde, zur Verabreichung einer breiten Arzneistoff-Palette mit großer Flexibilität in den Freisetzungsprofilen.

6. REFERENCES

Abbaspour, M.R., Sadeghi, F., Garekani, H.A., 2007. Thermal treating as a tool to produce plastic pellets based on Eudragit® RS PO and RL PO aimed for tableting. Eur. J. Pharm. Biopharm. 67 (1), 260-267.

Abdul, S., Poddar, S.S., 2004. A flexible technology for modified release of drugs: multi layered tablets. J. Control. Release 97(3), 393-405.

Ahrabi, S., Sande, S., Waaler, T., Graffner, C., 1999. Effects of thermal neutron irradiation on some potential excipients for colonic delivery systems. Drug Dev. Ind. Pharm. 25(4), 453-462.

Akhgari, A., Sadeghi, F., Garekani, H.A., 2006. Combination of time-dependent and pH-dependent polymethacrylates as a single coating formulation for colonic delivery of indomethacin pellets. Int. J. Pharm. 320(1-2), 137-142

Altaf, S.A., Hoag, S.W., Ayres, J.W., 1999. Bead compacts. II. evaluation of rapidly disintegrating nonsegregating compressed bead formulations. Drug Dev. Ind. Pharm. 25(5), 635-42.

Alvarez-Fuentes, J., Fernández-Arévalo, M., González-Rodríguez, M.L., Cirri, M., Mura, P., 2004. Development of enteric-coated timed-release matrix tablets for colon targeting. J. Drug Target. 12(9-10), 607-612.

Amighi, K., Moës, A.J., 1995. Evaluation of thermal and film forming properties of acrylic aqueous polymer dispersion blends: application to the formulation of sustained-release Film Coated Theophylline Pellets. Drug Dev. Ind. Pharm. 21(20), 2355-2369.

Ando, M., Ito, R., Ozeki, Y., Nakayama, Y., Nabeshima, T., 2007a. Evaluation of a novel sugar coating method for moisture protective tablets. Int. J. Pharm. 336(2), 319-328.

Ando, M., Kojima, S., Ozeki, Y., Nakayama, Y., Nabeshima, T., 2007b. Development and evaluation of a novel dry-coated tablet technology for pellets as a substitute for the conventional encapsulation technology. Int. J. Pharm. 336(1), 99-107

Ashford, M., Fell, J., Attwood, D., Sharma, H., Woodhead, P., 1993. An evaluation of pectin as a carrier for drug targeting to the colon. J. Control. Release 26(3), 213-220.

Aulton, M.E., Dyer, A.M., Khan, K.A., 1994. The strength and compaction of millispheres:

the design of a controlled-release drug delivery system for ibuprofen in the form of a tablet comprising compacted polymer-coated millispheres. Drug Dev. Ind. Pharm. 20(20), 3069-3104.

Bando, H., McGinity, J.W., 2006a. Relationship between drug dissolution and leaching of plasticizer for pellets coated with an aqueous Eudragit® S100:L100 dispersion. Int. J. Pharm. 323(1-2), 11-17.

Bando, H., McGinity, J.W., 2006b. Physicochemical properties of enteric films prepared from aqueous dispersions and organic solutions. Int. J. Pharm. 313(1-2), 43-48.

Basit, A.W., 2005. Advances in Colonic Drug Delivery. Drugs 65(14), 1991-2007.

Beckert, T.E., Lehmann, K., Schmidt, P.C., 1996. Compression of enteric-coated pellets to disintegrating tablets, Int. J. Pharm. 143(1), 13-23.

Beckert, T.E., Lehmann, K., Schmidt, P.C., 1998. Compression of enteric-coated pellets to disintegrating tablets: uniformity of dosage units, Powder Technol. 96(3), 248–254.

Berggren, J., Alderborn, G., 2001. Effect of drying rate on porosity and tabletting behaviour of cellulose pellets, International Journal of Pharmaceutics, 227 (1-2), 81-96.

Bley, O., Siepmann, J. and Bodmeier, R., 2009. Characterization of moisture-protective polymer coatings using differential scanning calorimetry and dynamic vapor sorption, J. Pharm. Sci. 98 (2), 651-664.

Bodmeier, R., 1997. Tableting of coated pellets, Eur. J. Pharm. Biopharm. 43(1), 1-8.

Bodmeier, R., Paeratakul, O., 1994a. Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage forms. Pharm. Res. 11(6), 882-888.

Bodmeier, R., Paeratakul, O., 1994b. The distribution of plasticizers between aqueous and polymer phases in aqueous colloidal polymer dispersions. Int. J. Pharm. 103(1), 47-54.

Bogdanova, S., Pajeva, I., Nikolova, P., Tsakovska, I., Müller, B., 2005. Interactions of Poly(vinylpyrrolidone) with Ibuprofen and Naproxen: Experimental and Modeling Studies. Pharm. Res. 22(5), 806-815.

Bose, S. and Bogner, R.H., 2007. Solventless pharmaceutical coating processess: a review, Pharm. Dev. Technol. 12(2), 115-131.

Bravo-Osuna, I., Ferrero, C., Jiménez-Castellanos, M.R., 2007. Influence of moisture content on the mechanical properties of methyl methacrylate-starch copolymers. Eur. J. Pharm. Biopharm. 66(1), 63-72.

Bussemer, T., Dashevsky, A., Bodmeier, R., 2003. A pulsatile drug delivery system based on rupturable coated hard gelatin capsules. J. Control. Release 93(3), 331-339.

Calinescu, C, Mateescu, M.A., 2008. Carboxymethyl high amylose starch: Chitosan self-stabilized matrix for probiotic colon delivery, Eur. J. Pharm. Biopharm. 70(2), 582-589.

Casas, M., Strusi, O.L., Jiménez-Castellanos, M.R., Colombo, P., 2010. Tapioca starch graft copolymers and Dome Matrix® modules assembling technology. I. Effect of module shape on drug release. Eur. J. Pharm. Biopharm. 75(1), 42-47.

Chambin, O., Rota, A., Rochat-Gonthier, M., Pourcelot, Y., 2005. Performance of multilayered particles: influence of a thin cushioning layer. Drug Dev. Ind. Pharm. 31 (8), 739-746.

Chan, E.S., Zhang, Z., 2005. Bioencapsulation by compression coating of probiotic bacteria for their protection in an acidic medium. Proc. Biochem. 40 (10), 3346–3351.

Chan, H.K., Doelker, E., 1985. Polymorphic Transformation of Some Drugs Under Compression. Drug Dev. Ind. Pharm. 11, 315-332.

Chang, R.K., Rudnic, E.M., 1991. The effect of various polymeric coating systems on the dissolution and tableting properties of potassium chloride microcapsules. Int. J. Pharm. 70 (3) 261-270.

Chen, P., Zhang, L., Cao, F., 2005. Effects of moisture on glass transition and microstructure of glycerol-plasticized soy protein. Macromol. Biosci. 5(9), 872-880.

Cheng, W.T., Lin, S.Y., Wang, S.L., 2008. Differential scanning calorimetry with curve-fitting program used to quantitatively analyze the polymorphic transformation of famotidine in the compressed compact. Drug Dev. Ind. Pharm. 34(12), 1368-1375.

Chidambaram, N., Porter, W., Flood, K., Qiu, Y., 1998. Formulation and characterization of new layered diffusional matrices for zero-order sustained release. J. Control. Release 52(1-2), 149-158.

Conte, U., Maggi, L., 1996. Modulation of the dissolution profiles from Geomatrix® multi-

layer matrix tablets containing drugs of different solubility. Biomaterials 17(9), 889-896.

Conte, U., Maggi, L., 2000. A flexible technology for the linear, pulsatile and delayed release of drugs, allowing for easy accommodation of difficult in vitro targets. J. Control. Release 64(1-3), 263-268.

Conte, U., Maggi, L., Torre, M.L., Giunchedi, P., Manna, A.L., 1993. Press-coated tablets for time-programmed release of drugs. Biomaterials 14(13), 1017-1023.

Dashevsky, A., Kolter, K., Bodmeier, R., 2004. Compression of pellets coated with various aqueous polymer dispersions. Int. J. Pharm. 279 (1-2), 19-26.

Dashevsky, A., Wagner, K., Kolter, K., Bodmeier, R., 2005. Physicochemical and release properties of pellets coated with Kollicoat® SR 30 D, a new aqueous polyvinyl acetate dispersion for extended release. Int. J. Pharm. 290 (1-2), 15-23.

Davis, S.S., Hardy, J.G., Fara, J.W., 1986. Transit of pharmaceutical dosage forms through the small intestine. Gut 27(8), 886-892.

Di Gioia, L., Guilbert, S., 1999. Corn protein-based thermoplastic resins: effect of some polar and amphiphilic plasticizers. J. Agric. Food. Chem. 47(3), 1254-1261.

Eeckman, F., Moës, A.J., Amighi, K., 2002. Evaluation of a new controlled-drug delivery concept based on the use of thermoresponsive polymers. Int. J. Pharm. 241(1), 113-125.

Eeckman, F., Moës, A.J., Amighi, K., 2003. Surfactant induced drug delivery based on the use of thermosensitive polymers. J. Control. Release 88(1), 105-116.

Efentakis, M., Koligliati, S., Vlachou, M., 2006a. Design and evaluation of a dry coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release. Int. J. Pharm. 311(1-2), 147-156.

Efentakis, M., Politis, S., 2006b. Comparative evaluation of various structures in polymer controlled drug delivery systems and the effect of their morphology and characteristics on drug release. Eur. Polym. J. 42(5), 1183-1195.

Egorov, V.I., Schastlivtsev, I.V., Prut, E.V., Baranov, A.O., Turusov, R.A., 2002. Mechanical properties of the human gastrointestinal tract. J. Biomech. 35(10), 1417-1425.

El-Malah, Y., Nazzal, S., 2008. Novel use of Eudragit® NE 30D/Eudragit® L 30D-55 blends as functional coating materials in time-delayed drug release applications. Int. J. Pharm. 357 (1-2), 219-227.

Felton, L.A., 2007. Film coating of oral solid dosage forms. In: Swarbrick, J. (Ed.), Encyclopedia of pharmaceutical technology, Third Edition. Informa Healthcare USA, Inc., New York, 1729-1744.

Fukui, E., Miyamura, N., Kobayashi, M., 2001a. Effect of magnesium stearate or calcium stearate as additives on dissolution profiles of diltiazem hydrochloride from press-coated tablets with hydroxypropylmethyl- cellulose acetate succinate in the outer shell. Int. J. Pharm. 216(1-2), 137-146.

Fukui, E., Miyamura, N., Kobayashi, M., 2001b. An in vitro investigation of the suitability of press-coated tablets with hydroxypropylmethylcellulose acetate succinate (HPMCAS) and hydrophobic additives in the outer shell for colon targeting. J. Control. Release 70(1-2), 97-107.

Fukui, E., Miyamura, N., Uemura, K., Kobayashi, M., 2000b. Preparation of enteric coated timed-release press-coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting. Int. J. Pharm. 204(1-2), 7-15.

Fukui, E., Uemura, K., Kobayashi, M., 2000a. Studies on applicability of press-coated tablets using hydroxypropylcellulose (HPC) in the outer shell for timed-release preparations. J. Control. Release 68(2), 215-223.

Fukui, E., Uemura, K., Kobayashi, M., 2000c. Studies on applicability of press-coated tablets using hydroxyl -propylcellulose (HPC) in the outer shell for timed-release preparations. J. Control. Release 68(2), 215-223.

Fürst, T., 2009. Multiparticulate Sustained Release Formulations with EUDRAGIT® Range of Polymers. 64th EUDRAGIT® Workshop (6th International Controlled Release Workshop). Evonik Röhm GmbH, Darmstadt, Coatings & Additives/ Pharma Polymers.

Garcia, R.A., Onwulata, C.I., Ashby, R.D., 2004. Water plasticization of extruded material made from meat and bone meal and sodium caseinate. J. Agric. Food. Chem. 52(12), 3776-3779.

Gazzaniga, A., Iamartino, P., Maffione, G., Sangalli, M.E., 1994. Oral delayed-release system for colonic specific delivery. Int. J. Pharm. 108(1), 77–83.

Ghanam, D., Hassan, I., Kleinebudde, P., 2010. Compression behaviour of [kappa]-carrageenan pellets. Int. J. Pharm. 390(2), 117-127.

Ghebremeskel, A.N., Vemavarapu, C., Lodaya, M., 2007. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: selection of polymer–surfactant combinations using solubility parameters and testing the processability. Int. J. Pharm. 328(2), 119-129.

Gohel, M.C., Parikh, R.K., Nagori, S.A., Dabhi, M.R., 2008. Design of a potential colonic drug delivery system of mesalamine. Pharm. Dev. Technol. 13(5), 447-456.

González-Rodríguez, M., Pérez-Martínez, J., Merino, S. Fini, A., Rabasco, A., 2001. Channeling agent and drug release from a central core matrix tablet. Drug Dev. Ind. Pharm. 27(5), 439-446.

González-Rodríguez, M.L., Maestrelli, F., Mura, P., Rabasco, A.M., 2003. In vitro release of sodium diclofenac from a central core matrix tablet aimed for colonic drug delivery. Eur. J. Pharm. Sci. 20(1), 125-131.

Guo, H.X., Shi, Y.P., 2009. A novel zein-based dry coating tablet design for zero-order release. Int. J. Pharm. 370(1-2), 81-86.

Gupta, V.K., Beckert, T.E., Price, J.C., 2001. A novel pH- and time-based multi-unit potential colonic drug delivery system. I. development. Int. J. Pharm. 213(1-2), 83-91.

Halsas, M., Pentinen, P., Veski, H., Jürjenson, H., Marvola, M., 2001. Time controlled release pseudoephedrine tablets: bioavailability and in vitro/ in vivo correlations. Pharmazie. 56(9), 718-723.

Hancock, B.C., Zografi, G., 1994. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res. 11(4), 471-477.

Hiremath, P.S., Saha, R.N., 2008. Oral controlled release formulations of rifampicin. part II: effect of formulation variables and process parameters on in vitro release. Drug Delivery 15(3), 159–168.

Hodge, R.M., Bastow, T.J., Edward, G.H., Simon, G.P., Hill, A.J., 1996. Free volume and the

mechanism of plasticization in water-swollen poly (vinyl alcohol), Macromolecules 29(25), 8137-8143.

Ibekwe, V.C., Khela, M.K., Evans, D.F., Basit, A.W., 2008. A new concept in colonic drug targeting: a combined pH-responsive and bacterially-triggered drug delivery technology. Aliment. Pharmacol. Ther. 28(7), 911-916.

Iloañusi, N.O., Schwartz, J.B., 1998. The Effect of wax on compaction of microcrystalline cellulose beads made by extrusion and spheronization. Drug Dev. Ind. Pharm. 24(1), 37-44.

Johansson, B., Wikberg, M., Ek, R., Alderborn, G., 1995. Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties, Int. J. Pharm. 117 (1), 57-73.

Kangarlou, S., Haririan, I., Gholipour, Y., 2008. Physico-mechanical analysis of free ethyl cellulose films comprised with novel plasticizers of vitamin resources. Int. J. Pharm. 356(1-2), 153-166.

Kenyon, C.J., Cole, E.T., Wilding, I.R., 1994. The effect of food on the in vivo behaviour of enteric coated starch capsules. Int. J. Pharm. 112(3), 207-213.

Kern Sears, J., Darby, J.R., 1982. Mechanism of plasticizers action. In: Technology of plasticizers. John Wiley & Sons, New York. 35-55.

Kohlrausch, A., 2005. Multilayer tablet. US Patent No. 2005/0186274.

Kojima, M., Nakagami, H., 2002. Development of controlled release matrix pellets by annealing with micronized water-insoluble or enteric polymers. J. Control. Release 82(2), 335-343.

Krishnaiah, Y.S.R., Satyanarayana, V., Dinesh Kumar, B., Karthikeyan, R.S., 2002. In vitro drug release studies on guar gum-based colon targeted oral drug delivery systems of 5-fluorouracil. Eur. J. Pharm. Sci. 16(3), 185-192.

Krögel, I., Bodmeier, R., 1998. Pulsatile drug release from an insoluble capsule body controlled by the properties of an erodible plug. Pharm. Res. 15(3), 474-481.

Kuzuya, M., Ito, K., Kondo, S., Makita, Y., 2001b. A new drug delivery system using plasma-irradiated pharmaceutical aids. VIII. Delayed-release of theophylline from

double-compressed tablet composed of Eudragit as wall material. Chem. Pharm. Bull. 49(1-2), 1586-1592.

Kuzuya, M., Kondo, S, Sasai, Y., 2001a. Plasma Techniques for Preparation of Controlled Drug Release System. Plasmas Polym. 6(3), 145-162.

Law, D., Zhang, Z., 2007. Stabilization and target delivery of Nattokinase using compression coating. Drug Dev. Ind. Pharm. 33(5), 495-503.

Lecomte, F., Siepmann, J., Walther, M., MacRae, R.J., Bodmeier, R., 2003. Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns, J. Control. Release 89(3) 457-471.

Lecomte, F., Siepmann, J., Walther, M., MacRae, R.J., Bodmeier, R., 2005. pH-sensitive polymer blends used as coating materials to control drug release from spherical beads: elucidation of the underlying mass transport mechanisms. Pharm. Res. 22(7), 1129-1141.

Lehmann, K., Petereit, H.U., Dreher, D., 1994. Fast disintegrating controlled release tablets from coated particles. Drugs Made Ger. 37(2), 53-60.

Lin, K.H., Lin, S.Y., Li, M.J., 2001a. Compression forces and amount of outer coating layer affecting the time-controlled disintegration of the compression-coated tablets prepared by direct compression with micronized ethylcellulose. J. Pharm. Sci. 90(12), 2005-2009.

Lin, S.Y., Li, M.J., Lin, K.H., 2004a. Hydrophilic excipients modulate the time lag of time-controlled disintegrating press-coated tablets. AAPS PharmSciTech 5(4).

Lin, S.Y., Lin, K.H., Li, M.J., 2001b. Micronized ethylcellulose used for designing a directly compressed time-controlled disintegration tablet. J. Control. Release 70(3), 321-328.

Lin, S.Y., Lin, K.H., Li, M.J., 2002. Influence of excipients, drugs, and osmotic agent in the inner core on the time-controlled disintegration of compression-coated ethylcellulose tablets. J. Pharm. Sci. 91(9), 2040-2046.

Lin, S.Y., Lin, K.H., Li, M.J., 2004b. Formulation design of double-layer in the outer shell of dry-coated tablet to modulate lag time and time-controlled dissolution function: studies

on micronized ethylcellulose for dosage form design (VII). AAPS J. 6(3) Article 17, 1-6.

Liu, J., Williams III, R.O., 2002. Properties of heat-humidity cured cellulose acetate phthalate free films. Eur. J. Pharm. Sci. 17(1-2), 31-41.

Lopes, C.M., Lobo, J.M., Pinto, J.F., Costa, P.C., 2007. Compressed matrix core tablet as a quick/slow dual-component delivery system containing ibuprofen, AAPS PharmSciTech 8, E76.

Losi, E., Bettini, R., Santi, P., Sonvico, F., Colombo, G., Lofthus, K., Colombo, P., Peppas, N.A., 2006. Assemblage of novel release modules for the development of adaptable drug delivery systems. J. Control. Release 111(1-2), 212-218.

Lourdin, D., Bizot, H., Colonna, P., 1997. "Antiplasticization" in starch-glycerol films? J. Appl. Polym. Sci. Symp. 63, 1047-1053.

Lundqvist, Å.E.K., Podczeck, F., Newton, J.M., 1998. Compaction of, and drug release from, coated drug pellets mixed with other pellets. Eur. J. Pharm. Biopharm. 46(3), 369-379.

Maffion, G., Iamartino, P., Guglielmini, G., Gazzaniga, A., 1993. High-viscosity HPMC as a film-coating agent. Drug Dev. Ind. Pharm. 19(16), 2043-2053.

Maggi, L., Conte, U., Giunchedi, P., Colombo, P., 1993. Press-coated tablets for the sequential pulsed administration of two different drugs. Int. J. Pharm. 99(2-3), 173-179.

Maggi, L., Massolini, G., De Lorenzi, E., Conte, U., Caccialanza, G., 1996. Evaluation of stereoselective dissolution of verapamil hydrochloride from matrix tablets press-coated with chiral excipients. Int. J. Pharm. 136(1-2), 43-51.

Marcilla, A., Beltrán, M., 2004. Mechanisms of plasticizers action. In: Wypych, G.(Ed.), Handbook of Plasticizers. William Andrew Inc, Toronto, 107-120.

Matsuo, M., Arimori, K., Nakamura, C., Nakano, M., 1996. Delayed-release tablets using hydroxyethyl- cellulose as a gel-forming matrix. Int. J. Pharm. 138(2), 225-235.

Miller, R.A., Leung, E.M., Oates, R.J., 1999. The compression of spheres coated with an aqueous ethylcellulose dispersion. Drug Dev. Ind. Pharm. 25(4), 503-511.

Moussa, I.S., Cartilier, L.H., 1997. Evaluation of cross-linked amylose press-coated tablets for sustained drug delivery. Int. J. Pharm. 149(2), 139-149.

Nair, R., Nyamweya, N., Gönen, S., Martínez-Miranda, L.J., Hoag, S.W., 2001. Influence of various drugs on the glass transition temperature of poly(vinylpyrrolidone): a thermodynamic and spectroscopic investigation. Int. J. Pharm. 225(1-2), 83-96.

Nakagawa, T., Kondo, S.-i., Sasai, Y., Kuzuya, M., 2006. Preparation of Floating Drug Delivery System by Plasma Technique. Chem. Pharm. Bull. 54(4), 514-518.

Nicklasson, F., Alderborn, G., 1999a. Modulation of the tabletting behaviour of microcrystalline cellulose pellets by the incorporation of polyethylene glycol. Eur. J. Pharm. Sci. 9(1), 57-65.

Nicklasson, F., Johansson, B., Alderborn, G., 1999b. Tabletting behaviour of pellets of a series of porosities-a comparison between pellets of two different compositions, Eur. J. Pharm. Sci. 8(1), 11-17.

Nunthanid, J., Huanbutta, K., Luangtana-anan, M., Sriamornsak, P., Limmatvapirat, S., Puttipipatkhacorn, S., 2009b. Development of time-, pH-, and enzyme-controlled colonic drug delivery using spray-dried chitosan acetate and hydroxypropyl methylcellulose. Eur. J. Pharm. Biopharm. 68(2), 253-259.

Nunthanid, J., Luangtana-anan, M., Sriamornsak, P., Limmatvapirat, S., Huanbutta, K., Puttipipatkhacorn, S., 2009a. Use of spray-dried chitosan acetate and ethylcellulose as compression coats for colonic drug delivery: Effect of swelling on triggering in vitro drug release. Eur. J. Pharm. Biopharm. 71(2), 356-361.

Obara, S., McGinity, J.W., 1995. Influence of processing variables on the properties of free films prepared from aqueous polymeric dispersions by a spray technique. Int. J. Pharm. 126(1-2), 1-10.

Otsuka, M., Matsuda, Y., 1995. Programmable drug release of highly water-soluble pentoxifylline from dry-coated Wax Matrix Tablets. J. Pharm. Sci. 90(4), 443-447.

Otsuka, M., Matsumoto, T., Kaneniwa, N., 1989. Effects of the mechanical energy of multi-tableting compression on the polymorphic transformations of chlorpropamide. J. Pharm. Pharmacol. 41(10), 665-669.

Ozeki, Y., Ando. M., Watanabe,Y., Danjo, K., 2004. Evaluation of novel one-step dry coated tablets as a platform for delayed –release tablets. J. Control. Release 95(1), 51-60.

Ozeki, Y., Watanabe, Y., Inoue, S., Danjo, K., 2003a. Comparison of the compression characteristics between new one-step dry-coated tablets (OSDRC) and dry-coated tablets (DC). Int. J. Pharm. 259(1-2), 69-77.

Ozeki, Y., Watanabe, Y., Inoue, S., Danjo, K., 2003b. Evaluation of the compression characteristics and physical properties of the newly invented one-step dry-coated tablets. Int. J. Pharm. 267(1-2), 69-78

Ozeki, Y., Watanabe,Y., Okamoto, H., Danjo, K., 2004. Development of dividable one-step dry-coated tablets (dividable-OSDRC) and their evaluation as a new platform for controlled drug release. Pharm. Res. 21(7), 1177-1183.

Pan, X., Chen, M., Han, K., Peng, X., Wen, X., Chen, B., Wang, J., Li, G., Wu, C., 2010. Novel compaction techniques with pellet-containing granules. Eur. J. Pharm. Sci. In Press, Uncorrected Proof.

Pearnchob, N., Bodmeier, R., 2003a. Dry powder coating of pellets with micronized Eudragit® RS for extended drug release. Pharm. Res. 20(12), 1970-1976.

Pearnchob, N., Bodmeier, R., 2003b. Coating of pellets with micronized ethylcellulose particles by a dry powder coating technique. Int. J. Pharm. 268(1-2), 1-11.

Peerapattana, J., Otsuka, K., Otsuka, M., 2004. Time-controlled pulse-drug release from dry-coated wax matrix tablets for colon drug delivery. Biomed. Mater. Eng. 14(3), 293–301.

Picker, K.M., 2002. Influence of tableting on the enzymatic activity of different α-amylases using various excipients. Eur. J. Pharm. Biopharm. 53(2), 181-185.

Picker, K.M., 2004. "Soft Tableting": A new concept to tablet pressure sensitive materials. Pharm. Dev. Technol. 9(1):107-121.

Pinto, J.F., Podczeck, F., Newton, J.M., 1997. Investigations of tablets prepared from pellets produced by extrusion and spheronisation Part I: The application of canonical analysis to correlate the properties of the tablets to the factors studied in combination with principal component analysis to select the most relevant factors. Int. J. Pharm. 147(1), 79-93.

Qi, M., Wang, P. and Wu, D. 2003. A novel pH and time-dependent system for colonic drug delivery. Drug Dev. Ind. Pharm. 29(6), 661-667.

Ritschel, W.A., Sabouni, A., Gehrke, S.H., Hwang, S.T., 1990. Permeability of [3H] water across a porous polymer matrix used as rate-limiting shell in compression-coated tablets. J. Control. Release 31(1) 12, 97-102.

Sangalli, M.E., Maroni, A., Zema, L., Busetti, C., Giordano, F., Gazzaniga, A., 2001. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. J. Control. Release 73(1), 103–110.

Santosa, F.X.B., Padua, G.W., 1999. Tensile properties and water absorption of zein sheets plasticized with oleic and linoleic Acids. J. Agric. Food. Chem. 47, 2070-2074.

Sawada, T., Kondo, H., Nakashima, H., Sako, K., Hayashi, M., 2004. Time-release compression-coated core tablet containing nifedipine for chronopharmacotherapy. Int. J. Pharm. 280(1-2), 103-111.

Sawada, T., Sako, K., Fukui, M., Yokohama, S., Hayashi, M., 2003. A new index, the core erosion ratio, of compression-coated timed-release tablets predicts the bioavailability of acetaminophen. Int. J. Pharm. 265, 53-63.

Sawicki, W., Łunio, R., 2005. Compressibility of floating pellets with verapamil hydrochloride coated with dispersion Kollicoat SR 30 D. Eur. J. Pharm. Biopharm. 60 (1), 153-158.

Sawicki, W., Mazgalski, J., 2009. Hot tableting as a new method for obtaining tablets from slow release-coated pellets. Drug Dev. Ind. Pharm. 35(7):857-865.

Schaeffler, A., 2008. Delayed-release glucocorticoid treatment of rheumatoid disease. US Patent No. 0076743A1.

Schmid, W., Picker-Freyer, K.M., 2009. Tableting and tablet properties of alginates: characterisation and potential for Soft Tableting. Eur. J. Pharm. Biopharm. 72(1). 165-172.

Sebhatu, T., Ahlneck, C., Alderborn, G., 1997. The effect of moisture content on the compression and bond-formation properties of amorphous lactose particles, Int. J. Pharm. 146(1), 101-114.

Sekizaki, H., Danjo, K., Eguchi, H., Yonezawa, Y., Sunada, H., Otsuka, A., 1995. Solid-state interaction of ibuprofen with polyvinylpyrrolidone. Chem. Pharm. Bull. 43 (6), 988–

993.

Shimizu, T., Kameoka, N., Iki, H., Tabata, T., Hamaguchi, N., Igari, Y., 2003. Formulation study for lansoprazole fast-disintegrating tablet. II. Effect of triethyl citrate on the quality of the products. Chem. Pharm. Bull. 51(9), 1029—1035.

Shivanand, P. and Sprockel, O.L. 1998. A controlled porosity drug delivery system. Int. J. Pharm. 167(1-2), 83–96.

Siepe, S., Lueckel, B., Kramer, A., Ries, A. and Gurny, R., 2006. Strategies for the design of hydrophilic matrix tablets with controlled microenvironmental pH. Int. J. Pharm. 316 (1-2), 14-20.

Siepmann, J., Paeratakul, O., Bodmeier, R., 1998. Modeling plasticizer uptake in aqueous polymer dispersions. Int. J. Pharm. 165(2), 191-200.

Siepmann, J., Streubel, A., Peppas, N.A., 2002. Understanding and Predicting Drug Delivery from Hydrophilic Matrix Tablets Using the "Sequential Layer" Model. Pharm. Res. 19(3), 306-314.

Singh, B.N., 2007. Modified-Release Solid Formulations for Colonic Delivery. Recent Pat. Drug Deliv. Formul. 1(1), 53-63.

Sinha, V.R., Mittal, B.R., Bhutani, K.K., Kumria, R., 2004. Colonic drug delivery of 5-fluorouracil: an in vitro evaluation. Int. J. Pharm. 269(1), 101-108.

Sirkiä, T., Salonen, H., Veski, P., Jürjenson, H., Marvola, M., 1994. Biopharmaceutical evaluation of new prolonged-release press-coated ibuprofen tablets containing sodium alginate to adjust drug release. Int. J. Pharm. 107(3), 179-187.

Steendam, R., Eissens A.C.E., Frijlink, H.W. and Lerk, C.F., 2000. Plasticization of amylodextrin by moisture: Consequences for drug release from tablets. Int. J. Pharm. 204(1-2):23-33.

Streubel, A., Siepmann, J., Peppas, N.A., Bodmeier, R., 2000. Bimodal drug release achieved with multi-layer matrix tablets: transport mechanisms and device design. J. Control. Release 69(3), 455–468.

Sugisaki, M., Suga, H., Seki, S., 1968. Calorimetric study of the glassy state. 4. Heatcapacities of glassy water and cubic ice. Bull. Chem. Soc. Jpn. 41(11):2591-2599.

Sundy, E., Danckwerts, M.P., 2004. A novel compression-coated doughnut-shaped tablet design for zero-order sustained release. Eur. J. Pharm. Sci. 22(5), 477-485.

Sungthongjeen, S., Puttipipatkhachorn, S., Paeratakul, O., Dashevsky, A., Bodmeier, R., 2004. Development of pulsatile release tablets with swelling and rupturable layers. J. Control. Release 95(2), 147-159.

Suyatma, N.E., Tighzert, L., Copinet, A., Coma, V., 2005. Effects of hydrophilic plasticizers on mechanical, thermal, and surface properties of chitosan films. J. Agric. Food. Chem. 53(10), 3950-3957.

Tajiri, T., Morita, S., Ozaki, Y., 2009. Hydration mechanism on a poly (methacrylic acid) film studied by in situ attenuated total reflection infrared spectroscopy. Polymer 50(24), 5765-5770.

Takeuchi, H., Yasuji, T., Yamamoto, H., Kawashima, Y., 2000. Spray-dried lactose composite particles containing an ion complex of alginate-chitosan for designing a dry-coated tablet having a time-controlled releasing function. Pharm. Res. 17(1), 94-99.

Ting, R., Hsiao, C., 2002. Press-coated, pulsatile drug delivery system suitable for oral administration. US Patent No. 2002/0164371.

Tokudome, Y., Ohshima, H., Otsuka, M., 2009. Non-invasive and rapid analysis for observation of internal structure of press-coated tablet using X-ray computed tomography. Drug Dev. Ind. Pharm. 35(6), 678-682.

Tunón, Å., Börjesson, E., Frenning, G., Alderborn, G., 2003. Drug release from reservoir pellets compacted with some excipients of different physical properties. Eur. J. Pharm. Biopharm. 20(4-5), 469-479.

Turkoglu, M., Ugurlu, T., 2002. In vitro evaluation of pectin–HPMC compression coated 5-aminosalicylic acid tablets for colonic delivery. Eur. J. Pharm. Biopharm. 53(1), 65-73.

Ugurlu, T., Turkoglu, M., Gurer, U.S., Akarsu, B.G., 2007. Colonic delivery of compression coated niasin tablets using pectin/HPMC polymer mixture. Eur. J. Pharm. Biopharm. 67(1), 202-210.

Van den Mooter, G., 2006. Colon drug delivery. Expert Opin. Drug Deliv. 3(1), 111-125.

Vergote, G.J., Kiekens, F., Vervaet, C., Remon, J.P., 2002. Wax beads as cushioning agents

during the compression of coated diltiazem pellets. Eur. J. Pharm. Biopharm. 17(3), 145-151.

Vilkov, Z., 2004. Controlled release press-coated formulation of water-soluble active agents. US Patent No. 2004/0241234.

Wagner, K.G., Krumme, M., Beckert, T.E., Schmidt, P.C., 2000a. Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press. European Eur. J. Pharm. Biopharm. 50(2), 285-292.

Wagner, K.G., Krumme, M., Schmidt, P.C., 1999. Investigation of the pellet-distribution in single tablets via image analysis. Eur. J. Pharm. Biopharm. 47(1), 79-85.

Wagner, K.G., Krumme, M., Schmidt, P.C., 2000b. Pellet-containing tablets: examination of distribution and deformation behaviour. S.T.P. Pharma Sci. 10, 327–334.

Waterman, K.C., Fergione, M.B., 2003. Press-coating of immediate release powders onto coated controlled release tablets with adhesives. J. Control. Release 89(3), 387-395.

Wei, H., Li-Fang, F., Bai, X., Chun-Lei, L., Qing, D., Yong-Zhen, C., De-Ying, C., 2009. An investigation into the characteristics of chitosan/Kollicoat SR30D free films for colonic drug delivery, Eur. J. Pharm. Biopharm. 72(1), 266-274.

Winheuser, J., Cooper, J., 1956. The pharmaceutics of coating tablets by compression. J. Am. Pharm. Assoc. 45(8), 542-545.

Wu, B., Shun, N., Wei, X., Wu, W., 2007. Characterization of 5-fluorouracil release from hydroxypropyl-methylcellulose compression-coated tablets. Pharm. Dev. Technol. 12(2), 203-210.

Wu, C., McGinity, J.W., 1999. Non-traditional plasticization of polymeric film. Int. J. Pharm. 177(1), 15-27.

Wu, C., McGinity, J.W., 2001. Influence of ibuprofen as a solid-state plasticizer in Eudragit® RS 30 D on the physicochemical properties of coated beads. AAPS PharmSciTech 2, 35-43.

Wu, C., McGinity, J.W., 2003. Influence of methylparaben as a solid-state plasticizer on the physicochemical properties of Eudragit® RS PO hot-melt extrudates. Eur. J. Pharm. Biopharm. 56(1), 95-100.

Yang, L., Chu, J.S., Fix, J.A., 2002. Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation. Int. J. Pharm. 235(1-2), 1-15.

Zarrintan, M.H., Teng, C.D., Groves, M.J., 1990. The effect of compactional pressure on a wheat germ lipase preparation. Pharm. Res. 7(3), 247-250.

Zhu, Y., Navnit H. Shah, N.H., Malick, W., Infeld, M.H., McGinity, J.H., 2002. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. Int. J. Pharm. 241(2), 301-310.

Zografi, G., Kontny, M.J., 1986. The interactions of water with cellulose- and starch-derived pharmaceutical excipients. Pharm. Res. 3, 187-194.

Zou, H., Jiang, X., Kong, L., Gao, S., 2008. Design and evaluation of a dry coated drug delivery system with floating-pulsatile release. J. Pharm. Sci. 97, 263-273.

7. PUBLICATIONS & PRESENTATIONS

RESULTING FROM THIS WORK

7.1. Publications

Rujivipat, S**.,** Bodmeier, R. Moisture plasticization for enteric Eudragit® L30D-55-coated pellets prior to compression into tablets. (in preparation)

Rujivipat, S**.,** Bodmeier, R. Improved drug delivery to the lower intestinal tract with tablets compression-coated with enteric/nonenteric polymer powder blends. (in preparation)

Rujivipat, S**.,** Bodmeier, R. Modified release from hydroxypropyl methylcellulose compression-coated tablets. (in preparation)

7.2. Presentations

Rujivipat, S., Bodmeier, R. Time delayed drug delivery based on HPMC press-coated tablets, Annual Meeting of the American Association of Pharmaceutical Scientists, AAPS, San Antonio, USA, (2006).

Rujivipat, S., Bodmeier, R. Zero order drug release from HPMC press-coated tablets, Annual Meeting of the American Association of Pharmaceutical Scientists, AAPS, San Antonio, USA, (2006).

8. CURRICULUM VITAE

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