Oral Controlled-Release Solid Dosage Forms, Use of Novel Polymer and Unconventional Polymer Blends

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To my wife (Langa), children (Elia & Elian) and parents,

with love and gratitude

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Contents

INTRODUCTION

1. INTRODUCTION

1.1. Oral controlled-release dosage forms

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact that gastrointestinal (GI) physiology offers more flexibility in dosage form design than most of the other routes (Chen et al., 2010; Maderuelo et al., 2011; Tongwen and Binglin, 1998).

Among the various novel drug-delivery systems available in the market, per oral controlled-release systems hold the major market share because of their obvious advantages of ease of administration and better patient compliance (Verma and Garg, 2001). Controlled-release delivery systems provide desired concentration of drug to the absorption site allowing maintenance of plasma concentrations within the therapeutic range and therefore, reducing the dosing frequency. These products typically provide significant benefits over immediate-release formulations, including greater effectiveness for the treatment of chronic conditions, reduced side effects, and greater patient convenience due to a simplified dosing schedule.

A number of design options are available to control or to modulate the drug release from a dosage form. In general, per oral controlled-release dosage forms fall into the category of single-unit systems like matrix, reservoir, and osmotic systems or multiple-unit systems like coated beads and minitablets. In matrix systems, the drug is embedded within a polymer matrix, and the release takes place by partitioning of drug between the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded/coated by a rate controlling membrane. Factors like pH, presence of food, and other physiological factors may affect the drug release from these controlled-release systems (matrix and reservoir). On the other hand, osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent, and it is possible to modulate the release characteristics by optimizing the properties of drug and system (Theeuwes et al., 1985).

1.2. Single-unit systems

1.2.1. Reservoir or membrane-controlled systems

Tablet coating may be used simply for aesthetic reasons to improve the appearance of a tablet, or may be functional in order to mask an unpleasant taste or odor, or to protect the ingredient(s) from decomposition during storage.

Thin films of water soluble polymers are often applied for taste or odor masking, to improve the stability of moisture sensitive products or for better mechanical resistance to the product during handling (Lehmann et al., 1994). Such protective coatings need to remain intact for the short time of swallowing the dosage form. Thereafter, they should dissolve instantaneously to ensure the immediate drug release without retardation. Polymers employed for that purpose are cellulose ethers, e.g. hydroxypropylmethylcellulose, polyvinyl acetate or polyvinylpyrrolidon (Porter and Bruno, 1990). Eudragit® E is a methacrylic copolymer especially designed to be insoluble in the saliva, but should rapidly dissolve in the acidic pH of the stomach. Sometimes also enteric polymers, e.g. shellac are applied at a very low coating level. In that case, the film thickness is not sufficient to provide gastric resistance and disintegrates in the stomach within 30 min (Lehmann et al., 1994).

Another type of film coat is enteric-coated tablets, in which the coating barrier controls the site of release of orally administered drug. An enteric coat is designed to resist the low pH of gastric fluids but to disrupt or dissolve when the tablet enters the higher pH of the duodenum. The most effective enteric polymers contain many carboxylic acid groups with a pKa value of 3-5 (Lehmann et al., 1994). Shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, Eudragit® L and Eudragit® S are used as enteric polymer.

Polymers for extended release are in general insoluble in water over the entire pH-range (Sakellariou and Rowe, 1995); In this case, medium penetration and drug diffusion through the coating are limited (Ozturk et al., 1990) (**Fig. 1**). The drug release is thus controlled by diffusion through the hydrated polymer or through cracks or water-filled pores (Lecomte et al., 2005). Furthermore, the release of the drug is a function of its solubility, the number, and size of the pores formed in the membrane and the membrane thickness (Källstrand and Ekman, 1983).

Despite commercial availability of many extended release polymers like cellulose acetate, ethylcellulose, polyvinyl acetate and the methacrylic acid copolymers Eudragit® RS, RL and

NE, there are few publications regarding their use for preparation of single-unit reservoir tablets, for example, Marini et al. used ethylcellulose and polyethylene glycol 3350 for this purpose (Marini et al., 1991).

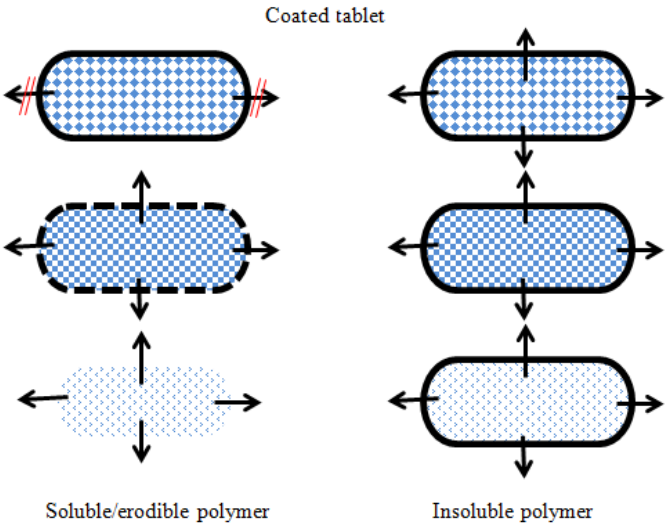

Fig. 1 Release behavior of coated tablets with soluble/erodible or insoluble polymers.

1.2.2. Matrix systems

Formulation and manufacturing of matrix tablets are well-known and established processes resulting in highly reproducible drug release, and *in vitro-in vivo* correlation of drug release has been evaluated (Dalton et al., 2001). Furthermore, the development of innovative functional excipients (entirely new substances as well as derivatives or co-processed existing materials) and evaluation of the drug-delivery potential of these systems have made matrix tablets an interesting field of research recently (Colombo et al., 2009).

According to the nature of the carrier material, lipid and polymer matrices can be distinguished. In case of lipid matrices' waxes and lipids embed the active compounds and have been classified with regard to their interaction with aqueous media. These interactions govern the release mechanism of lipid matrices being either diffusion or erosion controlled (Khan and Craig, 2003; Pivette et al., 2012).

The polymeric carriers further subdivided into groups considering the solubility and swelling characteristics of the carrier materials (water soluble/erodible - water insoluble and swellable - non-swellable polymers). A few examples are summarized in **Table 1**.

Table 1 List of common polymers for matrix preparation (examples)

Polymer properties		Examples
Soluble/ Erodible	Swellable	Hydroxypropylmethylcellulose, Sodium carboxymethylcellulose, Poly(ethylene oxide) Pectin, Alginate, Xanthan gum
	Non-swellable	Polyvinylpyrrolidon Hydroxypropylcellulose
Insoluble	Non-swellable	Ethyl cellulose Cellulose acetate
	Swellable	Kollidon® SR Eudragit® RS

Generally, the dissolution medium penetration into the matrix tablets more or less is hindered by the functional excipients that form the carrier. The tablets deliver the drug in a sustained fashion due to their barrier-free structure.

The swellable soluble/erodible polymers hydrated instead of disintegrated when get in contact with water. Entry of the solvent hydrates and swells the polymer, consequently, relaxes the polymer chains, and decreases the glass transition temperature (T_g). This leads to the formation of a zone in which the polymer passes from the crystalline state to a "rubbery" state known as a gel layer.

Thus, penetration of the medium into the matrix is accompanied by the formation of series of fronts (**Fig. 2**), which later disappear during the process of matrix dissolution (Colombo et al., 2000; Colombo et al., 1999). Soluble drugs are released via diffusion through the gel front, whereas in case of insoluble drugs, the diffusion front falls together with the erosion front, and the drug is liberated via erosion of the surrounding matrix structure (Maderuelo et al., 2011).

Generally, the gel strength is the key parameter affecting drug release and can be influenced, for example, by the polymer itself, its molecular weight and content, the substitution type, the interactions with the dissolution medium, the drug and other excipients (Maderuelo et al., 2011).

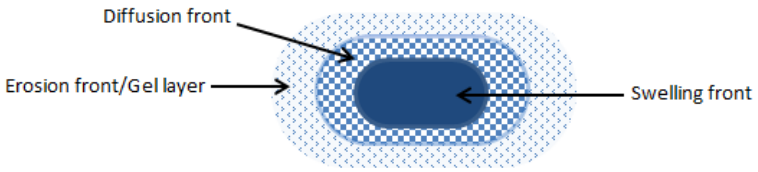

Fig. 2 Scheme of the hydrophilic matrix after entry of the dissolution medium.

On the other hand, for non-swellable soluble/erodible polymers, the erosion front falls together with the wetting front, and the drug particles are solely released by erosion of the tablet surface. Here, the tablet dimensions' decrease over time (**Fig. 3**) (Grund, 2013).

In case of insoluble polymers, the matrices ideally stay intact during drug release experiments. The medium penetrates the tablet dissolving the drug on its way, so that the molecules can diffuse through the polymer network. The matrix dimensions will increase with time in case of swellable polymers, while they stay the same for non-swellable polymers.

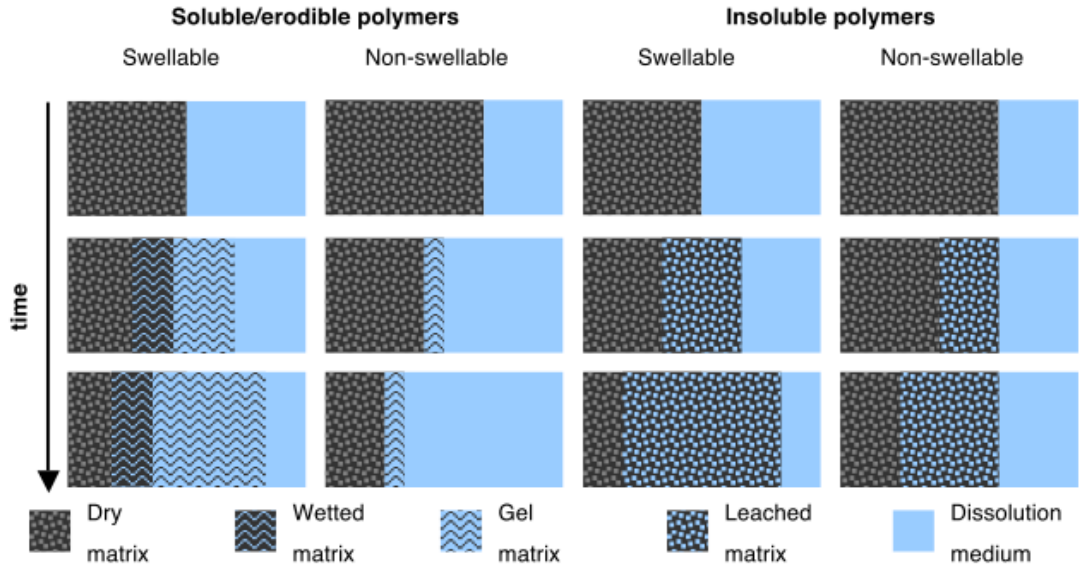

Fig. 3 Schematic representation of fronts' movement in different types of matrices.

1.2.3. Osmotic systems

Osmotic systems utilize osmotic pressure as a driving force for controlled delivery of drugs **Fig. 4**. In its simplest design, elementary osmotic pump consists of an osmotic core (containing drug with or without an osmagent) coated with a semipermeable membrane (Fig. 4a). After coming in contact with the aqueous fluids, the dosage form imbibes water at a rate determined by the membrane permeability and osmotic pressure of core formulation (Theeuwes, 1975). This imbibition of water results in formation of a saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane. Though 60%–80% of drug is released at a constant rate from the osmotic tablet, a lag time of 30–60 min is observed in most of the cases as the system hydrates before the zero-order delivery begins (Jerzewski and Chien, 1992). These systems are suitable for delivery of drugs having moderate water solubility.

Push–pull osmotic pump can be used for delivery of drugs having extremes of water solubility. As shown in Fig. 4b, it is a bilayer tablet coated with a semipermeable membrane. Drug with osmagents is present in the upper compartment whereas lower compartment consists of polymeric material (Cortese and Theeuwes, 1982).

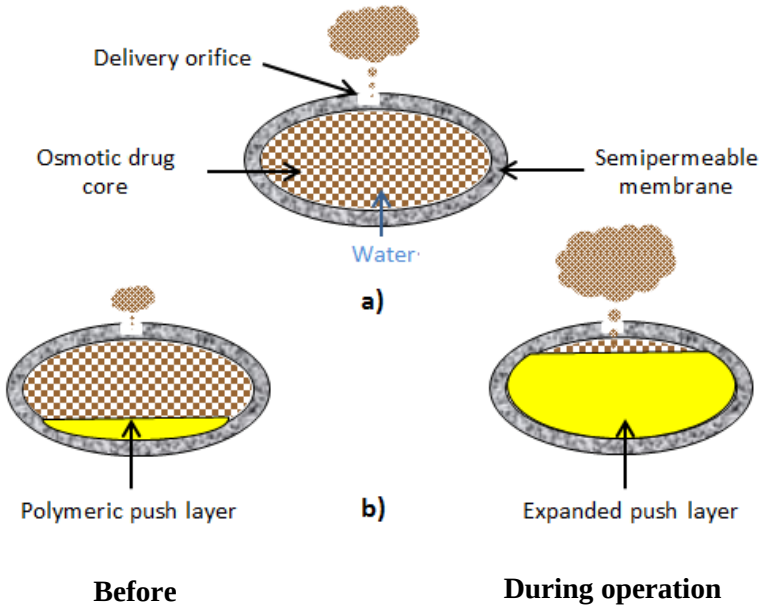

Fig. 4 Schematic of: **a)** elementary osmotic pump system and **b)** push-pull osmotic pump system.

Water influx into osmotic tablets can be described by the following equation (Theeuwes, 1975):

$$\frac{\mathrm{d}v}{\mathrm{d}t} = \frac{A}{h} Lp(\sigma \Delta\pi - \Delta\rho)$$

Where *dv/dt* is water influx, *A* and *h* are the membrane area and membrane thickness, respectively; *Lp* is the membrane mechanical permeability; σ is the reflection coefficient (in case of a perfectly semipermeable membrane, σ is close to unity); and $\Delta\pi$ and Δp are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system. The general expression for the solute delivery rate, d*M*/d*t*, obtained by pumping through the orifice is given by:

$$\frac{dM}{dt} = \frac{dv}{dt} . C$$

As size of the delivery orifice increases, hydrostatic pressure inside the system is minimized and $\Delta\pi >> \Delta p$. Since, osmotic pressure of the GI fluids is negligible as compared to that of the core, π can be safely substituted for $\Delta\pi$; replacing the product $Lp\sigma$ by a constant *K* the following equation is obtained:

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{A}{h} K\pi C$$

The best possible way to achieve a constant release from osmotic systems is through proper selection and optimization of the semipermeable membrane.

1.2.3.1. Membrane types

The choice of a rate-controlling membrane is an important aspect for the formulation development of oral osmotic systems. Drug release from osmotic systems is independent on the pH and agitation intensity of the GI tract to a large extent. This is because of selectively water permeable membrane and effective isolation of the dissolution process from the gut environment (Theeuwes et al., 1985; Theeuwes, 1975).

Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate

butyrate, etc. (Guittard et al., 1987); cellulose ethers like ethyl cellulose (Seminoff and Zentner, 1992); and Eudragit® (Jensen et al., 1995).

Cellulose acetate (CA) was one of the first materials used for manufacturing semipermeable membrane in elementary osmotic pumps developed by ALZA Corporation. The water permeability of CA membrane is relatively high and can be easily adjusted by varying the degree of acetylation. As the acetyl content in the CA increases, the CA film permeability decreases, and solvent resistance increases. In addition to CA (CA-398-10 and CA-320S), cellulose acetate butyrate CAB 171-15PG was used as semi-permeable film-forming materials (Shanbhag et al., 2007).

Both CA and CAB 171-15PG are insoluble in water; hence, they were applied from organic solutions like acetone. The biggest disadvantage of this process is explosion and flammability hazards, as well as environmental considerations, and the high viscosity of polymer solutions.

1.3. Multiple-unit systems

In the past three decades, multiple units drug-delivery systems like pellets have gained increasing attention due to numerous advantages (Bechgaard and Gyda, 1978; Ghebre-Sellassie, 1989; Roy and Shahiwala, 2009). One reason may be commercial benefits like extended patent protection and market expansion. However, more important are the formulation advantages and therapeutic benefits. Due to their multitude, pellets of different, potentially incompatible drugs or pellets with different release profiles can be combined in just one final dosage form, thus allowing a greater flexibility during formulation development (Ghebre-Sellassie, 1989).

The spherical shape, narrow size distribution and excellent flow properties of pellets result in uniform and reproducible application of drug and polymer layers as well as accurate volumetric dosing on tablet presses or capsule filling machines (Gryczová et al., 2008). Drug release from pellets is controlled by a multitude of particles rather than just one device as in case of single units, e.g. coated tablets. This reduces the variability in release profiles and prevents the risk of dose dumping. The gastric residence time of pellets is shorter and more predictable compared to single units and pellets spread more homogeneously throughout the GI tract, thus causing fewer local irritations of the mucosa and potentially leading to higher bioavailability.

In order to keep the easy administration of oral single unit systems, coated pellets can be either filled into hard gelatin capsules or compressed into tablets (Lehmann et al., 1994; Dashevsky et al., 2004). However, in contrast to coated single units, which must not be divided by any means, the pellets can be re-obtained easily by opening the capsule or dispersing the tablet in water. This allows easier swallowing for children and elderly people or even administration via naso-gastric feeding tubes.

The term 'pelletization' originally described the agglomeration of fine powders of drugs and excipients into small, free-flowing, and more or less spherical beads, which were referred to as pellets. However, the potential of sugar seeds (so-called called nonpareils) as starter cores for the formulation of layered/coated pellet dosage forms has been recognized as early as 1949 (Ghebre-Sellassie, 1989). Various designs have been developed for coated pellets (**Fig. 5**). High-dose drugs are often incorporated in matrix pellets via extrusion and spheronization with microcrystalline cellulose (MCC), lactose or blend of the two (Wesseling and Bodmeier, 2001). This technique allows sufficiently high drug loading levels. However, these matrix pellets alone would disintegrate quickly in contact with medium (Chambin et al., 2004) and thus require an outer polymer film coating in order to obtain the controlled release (Fig. 5a). Potent low dose drugs, on the other hand, can be formulated easier by spraying them onto inert starter cores in a fluidized bed coater. The release-controlling polymer can be co-applied with the drug from the same solution or dispersion, yielding so-called matrix-coated pellets (Fig. 5b). At the same time, this approach has several disadvantages like higher risk of drug polymer interactions, fast initial release and incomplete release (Mota, 2010). Therefore, a separate polymer coating step, subsequent to the drug layering, is more common (Fig. 5c), the term 'reservoir pellets' typically refers to the latter system.

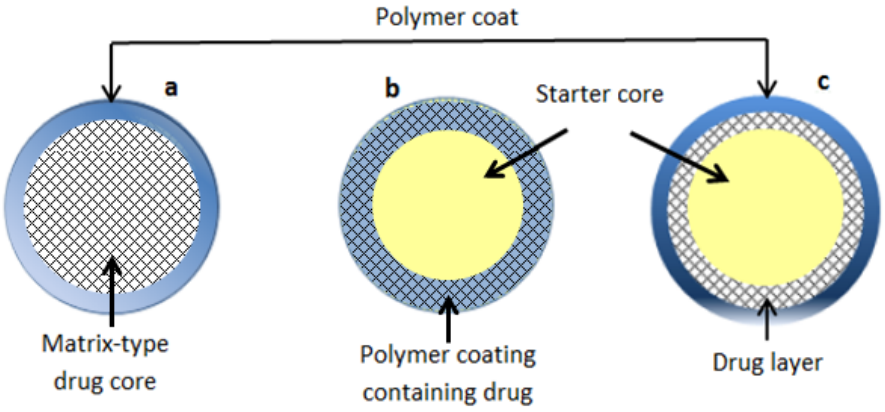

Fig. 5 Schematic presentation of: **a)** coated matrix pellets, **b)** matrix-coated pellets and **c)** reservoir pellets (black: drug; blue: release-controlling polymer; white: other excipients).

1.3.1. Mechanisms of drug release

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

For pellets coated with an insoluble film, different passage ways have been described (Ozturk et al., 1990) (**Fig. 6)**. Following concentration gradients, the drug diffuses either through a) the intact coating, b) through channels made by plasticizers and c) through medium filled channels / pores (**Fig. 6**a-c). There is also the osmotically driven release (**Fig. 6**d) which has been described by Ozturk et al. (Ozturk et al., 1990).

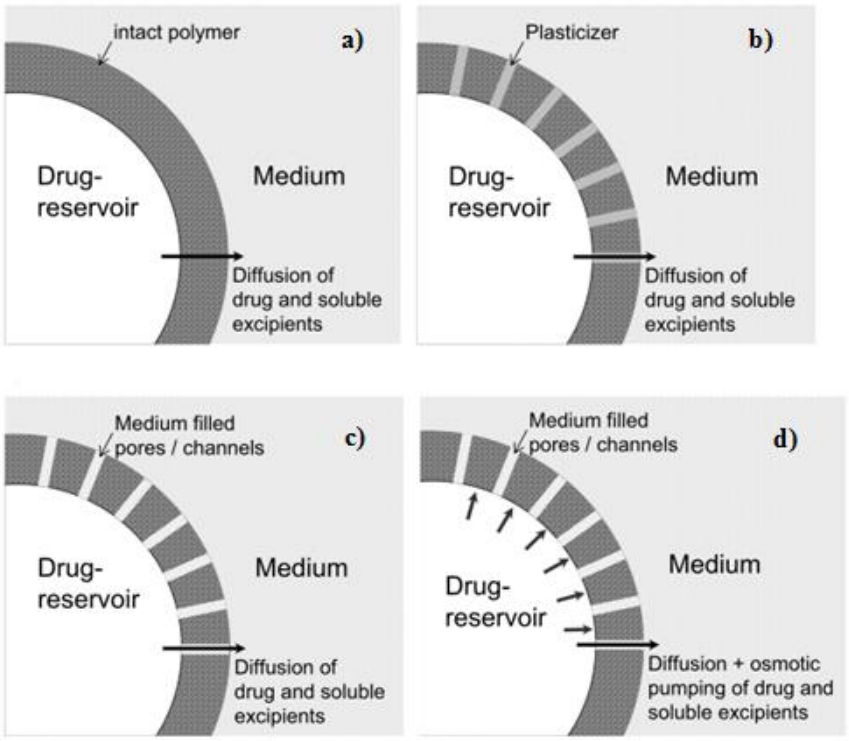

Fig. 6 Schematic representation of typical release mechanisms of coated pellets through **a)** intact coating, **b)** channels made by plasticizers and **c)** medium filled channels/pores and **d)** osmotically driven release (for reasons of simplicity, channels / pores / cracks are depicted interconnected and without any tortuosity).

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

$$\frac{dm}{dt} = \frac{D.A.Cs}{h}$$

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

In contrast to matrix systems (where the length of diffusional pathway's increases during drug releases unless the matrix erodes), the diffusional path length (coating thickness) is assumed to be rather constant for reservoir systems. Hence, zero-order release is possible for coated systems in a steady state, as long as there is still un-dissolved drug left inside the reservoir to allow for

saturation. Once the drug is dissolved, the concentration gradient and in consequence, the driving force of diffusional release decrease. The fraction of drug which is potentially released in zero-order can be estimated from its solubility and its volume fraction inside the core (Theeuwes, 1975; Zentner et al., 1985).

1.3.2. Tableting of multiparticulates

Multiparticulates systems such as pellets can be administered orally either filled into hard capsules or compressed into rapidly disintegrating tablets. The advantages of tableting multiparticulates include a reduced risk of tampering and fewer difficulties in esophageal transport when compared with capsules. Large-volume tablets generally have a higher patient compliance than capsules; higher dose strength could be administered with tablets. Tablets from pellets can be prepared at lower cost when compared to pellet-filled capsules because of the higher production rate of tablet presses. The expensive control of capsule integrity after filling is also eliminated. In addition, tablets containing multiparticulates could be scored without losing the controlled-release properties (Chambin et al., 2005).

However, compaction of coated multiparticulates into tablets could result either in disintegrating tablets providing a multiparticulate system during GI transit or in intact tablets due to the fusion of the multiparticulates in a larger compact. Ideally, the compacted pellets should disintegrate rapidly in the individual pellets in GI fluids. The pellets should not fuse into a non-disintegrating matrix during compaction, since the slower release due to retarded tablet disintegration could occur (Dashevsky et al., 2004a). The compaction process should not affect the drug release. The challenges of formulating pellets into tablets are evident. With reservoir-type coated pellet dosage forms, the polymeric coating must be able to withstand the compression force; be able to deform, but should not rupture. Without sufficient elasticity of the film, the coating could rupture during compression, and the extended release properties would be lost (Altaf et al., 1998). In addition, the bead core should also have some degree of plasticity, which can accommodate changes in shape and deformation during tableting (Bodmeier, 1997).

Due to their flexibility, acrylic polymers are more suitable for compression of coated pellets (Bodmeier and Paeratakul, 1994a) rather than ethylcellulose. Pellets coated with acrylic polymers were compressed without damage to the coating (Lehmann et al., 1993). However, the

drug release from compressed pellets coated with the aqueous ethylcellulose dispersion was much faster when compared to the release of the uncompressed pellets (Bansal et al., 1993). Hosseini et al. layered standard tableting excipients (microcrystalline cellulose, lactose, or sorbitol) onto ethylcellulose-coated pellets to form a cushion layer in order to protect the integrity of the brittle ethylcellulose coating during compression (Hosseini et al., 2013).

One of the important parameters, which characterizes whether the tablet is sufficiently strong is the tensile strength, which is the maximum tensile stress that can be tolerated in the tablet before it breaks. Various inert excipients have to be used to assist the compaction process and to prevent the rupture and damage of the coated pellets. Theoretically, 29% of excipients are needed to fill the void space between densely packed spheres. The excipients should result in hard and rapidly disintegrating tablets at low compression forces and should not affect the drug release (Bodmeier, 1997). The hardness of compacts decreased with increasing amounts of pellets (Beckert, 1995) and the maximum content of pellets that give tablets, which are strong enough, was found to be 40% w/w (Lundqvist and Podczeck, 1997).

1.4. Polymers for oral drug delivery systems

Polymers are chains of covalently bound monomers. They are used throughout the pharmaceutical industry and in relation to oral drug-delivery systems, they are used as carriers for the drug (Colombo et al., 2000). Polymers are used as a backbone in conventional and controlled-release formulations. For controlled-release formulations, the polymers need to have certain characteristics to control and maintain the rigidity of the matrix over a prolonged period (Kim, 2000).

According to the interesting aspect for the specific use, the polymer may be classified as protective or functional coating. Based on their origin or preparation, natural, semi-synthetic or synthetic polymers are distinguished. Semi-synthetic polymers are derived from a natural substance, receiving its specific property after certain chemical modifications. The cellulose derivatives used for coating are one example of such materials. Synthetic polymers in contrast are fully chemically synthesized, as for example the methacrylic acid copolymers.

Hydroxypropylmethylcellulose (HPMC)

HPMC is a semisynthetic derivative of cellulose, it is the most common hydrophilic carrier material used for the preparation of oral controlled drug-delivery systems (Colombo, 1993). It's nontoxic property, ease of handling, ease of compression, ability to accommodate a large percent of drug, and relatively simple tablet manufacturing technology make it an excellent carrier material (Alderman, 1984). It is nonionic, thus, interaction problems when it is used in acidic, basic, or other electrolytic systems are minimized, and it forms a gel when get in contact with water. It is stable at a pH between 3.0 and 11.0 and resists enzyme attack (Rogers, 2009). HPMC works well with soluble and insoluble drugs at high and low dosage levels (DOW, 2000).

One of the most important characteristics of HPMC is high swellability, which has a significant effect on the release kinetics of an incorporated drug. Upon contact with water or biological fluid the latter diffuses into the system, resulting in polymer chain relaxation with volume expansion (Brannon-Peppas, 1990; Brannon-Peppas and Peppas, 1990). As the outer gel layer of the tablet fully hydrates and dissolves, a new inner layer must replace it and be cohesive and continuous enough to retard the influx of water and control drug diffusion. Although gel strength is controlled by polymer viscosity and concentration, polymer chemistry also plays a significant role. Evidence suggests that the chemistry of HPMC encourages a strong, tight gel formation compared to other cellulose. As a result, drug release rates have been sustained longer with HPMC than with equivalent levels of methylcellulose, hydroxyethylcellulose, or carboxymethylcellulose (DOW, 2000).

Among the dissolution test conditions, hydrodynamic properties (agitation intensity) and mechanical destructive force are important factors, which affect the dissolution behavior of the dosage form. Orally administered dosage forms receive stress by the peristaltic movement of the GI wall. In hydrogel-type tablets, *in vivo* drug release was much faster than that expected from *in vitro* dissolution tests due to the peristalsis of the GI tract (Shameem et al., 1995). Ghimire et al. showed that both *in vitro* and *in vivo* erosion profiles for matrix tablets were dependent upon the concentration of HPMC, and erosion was faster for tablets containing 20% w/w HPMC than those containing 40% w/w HPMC (Ghimire et al., 2010). Abrahamsson compared hydrophilic matrix tablets and considered that factors affecting swelling, and erosion of these polymers may account for differences between *in vitro* dissolution results and subsequent *in vivo* performance

(Abrahamsson et al., 1999). The erosion rate was seen to increase with a decrease in polymer molecular weight, with a decrease in ionic strength and increasing agitation rate (Kavanagh and Corrigan, 2004).

Cellulose acetate butyrate (CAB-553-0.4)

There is a wide range of butyryl, acetyl, and hydroxyl levels available in Eastman CABs and, consequently, a broad range of properties. CAB-553-0.4 is a member of the series of Eastman's cellulose acetate butyrate esters. High-hydroxyl content (4.8 wt.%, average) contributes to its solubility in low molecular weight alcohols as well as other organic solvents. Films of CAB-553-0.4 are colorless and unmodified films of CAB-553-0.4 have high-tensile strength (352 kg/cm^2) (Eastman, 2006). Cellulose acetate butyrate exhibited good solubility in organic solvents, while being more hydrophobic than CA (Eastman, 2005).

In industry, CAB is used in certain fields like, coatings for automotive and plastics, lacquers for paper and wood and nail care; however, the use of this polymer in the pharmaceutical field, to our knowledge has not been described yet. The characterization of this polymer and its feasibility in pharmaceutical field and oral drug delivery will be studied in this work.

Eudragit® RL and RS

Eudragit® RL and RS (ammonio methacrylate copolymer type A and B) are methacrylate copolymers with cationic quaternary trimethylammonio groups, which determine their hydrophilicity. Next to ethylcellulose, RS and RL are the most common polymers for extended release applications. In addition, RS and RL have low T_g of ~ 63 ± 5 °C. They are water-insoluble over the physiological pH-range but swell upon contact with aqueous media (Bodmeier et al., 1996). The extent of this swelling is controlled by the content of quaternary ammonium groups in the polymer. RL has a higher ratio of 1:20 (ammonio groups to neutral esters), while in RS, it is only 1:40. Hence, RL swells easier and becomes more permeable than RS.

Due to the quaternary ammonium groups, the ionization of RL/RS (and in consequence, the hydration of the polymer) is not expected to be affected by pH within the physiological range.

However, pseudo-pH-dependent release profiles have been observed due to ion-exchange processes with the counter ions of the release medium (Bodmeier et al., 1996; Okor, 1990).

Kollicoat® SR 30 D

Kollicoat® SR 30 D is a new aqueous colloidal dispersion based on polyvinyl acetate (27% w/v), polyvinylpyrrolidon (2.7% w/v) and sodium dodecyl sulfate (0.3% w/v), which is prepared by an emulsification polymerization method. Kollicoat® SR 30 D has a low minimum film formation temperature, which is 18 °C. A low minimum film formation temperature is preferred for coating process; it results in easier coalescence of the colloidal polymer particles during coating at product temperatures between 30 °C and 40 °C. In addition, may also eliminate the need for the addition of plasticizers, which have to be added in concentrations of 20–30% (based on the polymer weight) to the other dispersions for a reduction of the minimum film formation temperature.

The Kollicoat® SR 30 D dispersion can be used for pH-independent extended release formulations (Dashevsky et al., 2004b), as well as in blended films, for the development of particular kinds of drug release systems, e.g. colon targeting (Rock et al., 2000).

Ethylcellulose (EC)

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

The viscosity of ethylcellulose solutions and the mechanical properties of the resulting coating, depend on the molecular weight (chain length) of the polymer. Viscosity of the solution and tensile strength of the films increases at higher molecular weights, thus reducing the incidence of film cracking and decreasing drug release (Rowe, 1992). However, with a T_g of ~133 °C (EC

10 cP) films made from the pure polymer are very brittle and thus commonly require plasticizers (Terebesi and Bodmeier, 2010).

Ethylcellulose is generally considered non-toxic, non-allergenic and stable under physiological conditions. Its water-insoluble and pH-independent properties have made ethylcellulose one of the most important polymers for controlled-release applications, moisture protection, and taste masking purposes (Marucci et al., 2009). Pure ethylcellulose exhibits a very low water permeability; only ~1/10 of cellulose acetate (Lindstedt et al., 1989). Therefore, it is often combined with more permeable polymers, like the enteric Eudragit® L or the water-soluble Kollicoat® IR (Lecomte et al., 2005; Muschert et al., 2009).

Hydroxypropyl methyl cellulose phthalate (HPMCP)

HPMCP is cellulose in which some of the hydroxyl groups are replaced with methyl ethers, 2-hydroxypropyl ethers, or phthalyl esters. Several different types of HPMCP are commercially available with molecular weights in the range 20 000–200 000. HPMCP is insoluble in gastric fluid but will swell and dissolve rapidly in the upper intestine. HPMCP is widely used in oral pharmaceutical formulations as an enteric coating material for tablets or granules (Stafford, 1982); it is applied without the addition of a plasticizer or other film formers, using established coating techniques. However, the addition of a small amount of plasticizer or water can avoid film-cracking problems. Since HPMCP is tasteless and insoluble in saliva, it can also be used as a coating to mask the unpleasant taste of some tablet formulations. HPMCP has also been co-precipitated with a poorly soluble drug to improve dissolution characteristics (Sertsou et al., 2002). Various grades of HPMCP are available with differing degrees of substitution and physical properties, e.g. grades HP-50 HP-55, and HP-55S (Shin-Etsu Chemical Co. Ltd). The number following ‘HP’ in each grade designation refers to the pH value (×10) at which the polymer dissolves in aqueous buffer solutions. The designation ‘S’ in HP-55S indicates a higher molecular weight grade, which produces films with a greater resistance to cracking.

Eudragit® L and S

Eudragit® L and S, also referred to as methacrylic acid copolymers in the USP32–NF27 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in Eudragit® L (Type A) and nearly 1:2 in Eudragit® S (Type B). Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. They are available as a 12.5% solution in propan-2-ol without plasticizer (Eudragit® L 12.5 and S 12.5); and as a 12.5% ready-to-use solution in propan-2-ol with 1.25% dibutyl phthalate as plasticizer (Eudragit® L 12.5 P and S 12.5 P). Solutions are colorless, with the characteristic odor of the solvent. Eudragit® L -100 and Eudragit® S-100 are white free-flowing powders with at least 95% of dry polymers.

Eudragit® L 100-55 (prepared by spray-drying Eudragit® L 30 D-55) is a white, free-flowing powder that could be dispersed in water to form a latex that has properties similar to those of Eudragit® L 30 D-55.

1.4.1. Polymers blends for oral drug delivery

Polymeric film coatings are frequently used to control drug release from solid pharmaceutical dosage forms (Ghebre-Sellassie, 1994; Cole et al., 1995; Vansavage and Rhodes, 1995). Several natural and synthetic macromolecules have proven to be suitable coating materials, providing different types of drug release behavior, e.g. zero order kinetics, pulsatile and sigmoidal patterns (Vansavage and Rhodes, 1995; Narisawa et al., 1994; Bussemer et al., 2003). To obtain a particular, desired release profile, different formulation and processing parameters can be varied, such as the coating level, type of polymer and type and amount of added plasticizer (Frohoff-Hülsmann et al., 1999; Okarter and Singla, 2000; Shao et al., 2002). However, the variation of these parameters is generally restricted, and it is sometimes difficult to adjust optimized release kinetics. For instance, too low and too high coating levels must be avoided to prevent accidental film rupturing (and subsequent dose dumping) and too long processing times. The type of polymer used should be known to be non-toxic; otherwise, time- and cost- intensive toxicity

studies are required. Too high amounts of added plasticizers lead to intense sticking of the coated dosage forms, whereas too low amounts result in too brittle films.

An interesting possibility to overcome these restrictions is based on the use of blends of two types of polymers, which are known to be non-toxic and exhibit different physicochemical characteristics (e.g., water and drug permeability, mechanical stability and solubility along the GI tract (Khan et al., 1999; Dashevsky et al., 2004; Strübing et al., 2007). By simply varying the polymer blends ratio; the resulting film coating properties can effectively be altered, and broad ranges of drug release patterns be provided (Lecomte et al., 2003). Interestingly, not only the slope of the release curves can be varied, but also their shape, due to changes in the underlying drug release mechanisms (Lecomte et al., 2004). The presence of a second type of macromolecules can also help to improve film formation in the case of aqueous polymer dispersions and to provide appropriate mechanical film coating stability when osmotically active pellet/capsule/tablet cores generate considerable hydrostatic pressure within the systems during drug release (Lecomte et al., 2005).

Amighi and Moes investigated the effects of the Eudragit® RL:Eudragit® RS blends ratio on the resulting drug release kinetics from coated theophylline matrix pellets (Amighi and Moes, 1995). Broad ranges of drug release rates were achieved by varying the polymer blend ratio. Theophylline release was slightly delayed in the case of pure Eudragit® RL-based coatings compared to uncoated pellets. Importantly, the release rate significantly decreased with increasing Eudragit® RS content. Thus, desired drug release profile was easily achieved by adjusting the polymer blends ratio.

The addition of a second polymer to a controlled-release film coating does not always aim at adjusting desired drug permeability within the release barriers; it can also serve to improve other coating properties, such as mechanical stability and degree of film formation. For instance, Eudragit® NE (a neutral ethylacrylate:methylmethacrylate copolymer) being highly flexible and can be added to Eudragit® RL to improve the mechanical stability of the film coatings. Deshpande et al. prepared a controlled-release tablet exhibiting gastro-retentive properties used this combination (Deshpande et al., 1997).

Importantly, not only polymers with similar chemical backbones can be blended in controlled-release film coatings, but also macromolecules with very different chemical structures. For

example, Phuapradit et al. added Eudragit® RL (an acrylic polymer) to cellulose derivatives (ethylcellulose and cellulose acetate). The permeability and mechanical properties of the resulting films were measured. In both cases, an increase in the Eudragit® RL content led to an increase in the theophylline diffusivity within the system (Phuapradit et al., 1995).

1.4.2. Curing

The process in which coated dosage forms are stored at elevated temperatures to promote further gradual coalescence of the film is known as curing. It can also be defined as the input of energy into a system after the desired film coat level is applied (Hamed and Sakr, 2003). Curing of film-coated dosage forms is an important step in the film-formation mechanism from aqueous latexes. During the coating process, the curing takes place, to a certain extent, itself. However, this is inadequate; to assure the completion of coalescence, the dosage form is generally exposed to elevated temperature after the coating. This can be done in the coating machine using a process known as post-coating fluidization (Harris et al., 1986) or by placing the coated dosage forms in an oven (Goodhart et al., 1984; Lippold et al., 1989).

The film formation process from the aqueous polymeric dispersions is highly influenced by the amount of water in the polymeric film and environmental temperature. The increased temperature and amount of water in the polymeric films decrease the T_g of colloidal particles, resulting in an increased mobility of the polymer chains, which in turn enhances the further gradual coalescence of the latex particles; as a result, better film formation takes place.

On the other hand, decreased temperature and reduced amount of water in polymeric film will not produce enough forces to bring together and deform latex particles, which in turn results in incomplete film formation. Therefore, in order to achieve complete film formation, which facilitates having stable release profile, the proper curing conditions are required, which is known as “conventional curing." This conventional curing is most commonly recommended for the aqueous polymers, which have high T_g and high minimum film forming temperature. Heating of the films above T_g facilitates polymer movement and relaxation. For example, the manufacturer (FMC, the USA) recommended curing at 60 °C for at least one hour for Aquacoat® ECD and it has also reported in literature (Bodmeier and Paeratakul, 1991; Gilligan and Li Wan Po, 1991).

The curing process is dependent on both the time and temperature used during the curing process. The curing rates can be accelerated by increasing the storage temperature and relative humidity because of fast kinetic factors responsible for coalescence (Körber et al., 2010; Bianchini et al., 1993).

Drug release from Kollicoat® SR 30 D coated pellets was unchanged by increasing the curing time (Dashevsky et al., 2005). This was attributed to complete film formation during the coating process due to a low minimum film formation temperature of plasticized Kollicoat® SR 30 D coatings. In contrast, a strong curing effect depending on the plasticizer type and curing conditions was reported with Kollicoat® SR 30 D coated pellets (Shao et al., 2002).

Curing at 60 °C for 8 h was found to be sufficient to form complete film with Aquacoat® ECD coated pellets (Wesseling and Bodmeier, 2001) which could be further minimized by increasing the plasticizer concentrations (Bodmeier and Paeratakul, 1994b). The type of plasticizer and coating level can also affect the extent of curing effect. For example, drug release decreased with increasing harshness (time, temperature and relative humidity) of curing conditions, when using triethyl citrate as a plasticizer, whereas with dibutyl sebacate this relationship was only seen at low coating levels (Yang et al., 2010).

Additionally, the controlled humidity can accelerate the curing step significantly. This happens because water facilitates polymer particle coalescence, and it acts as plasticizer for many polymers (Liu and Williams, 2002; Williams and Liu, 2000).

Furthermore, the drug migration into the coatings can also occur during the curing step which results an increase in drug release rather than decrease. In order to overcome this problem, a sub-coating was applied between drug layer and polymer coating (Hamed and Sakr, 2003).

1.5. Objectives

- Use of unconventional polymer blends of Kollicoat® SR 30 D and Eudragit® RL 30 D:
  - To increase robustness of hydroxypropylmethylcellulose matrix tablet against agitation and mechanical forces
  - To prepare and characterize single-unit reservoir tablets

- Use of CAB-553-0.4 as a novel polymer in controlled-release drug delivery field:
  - Preparation and characterization of osmotic tablets
  - Preparation and characterization of multiparticulate pellets
  - Preparation and characterization of matrix tablet

- Increase tablettability of pellets through Eudragit® RL top coating

- Eudragit® matrix system:
  - Preparation and characterization of high ibuprofen loaded controlled-release matrix tablet
  - Use of Eudragit® RL PO as a carrier for preparation of controlled-release matrix tablets; role of curing conditions

MATERIALS AND METHODS

2. MATERIALS AND METHODS

2.1. Materials

Cores

Sucrose nonpareils 355-425 µm and 710-850 µm (NP, Suglets®, NP Pharm S.A., Bazainville, France); microcrystalline cellulose 350 µm and 780 µm (MCC, Cellets®, Harke Pharma GmbH, Mühlheim an der Ruhr, Germany).

Drugs

Metoprolol tartrate, propranolol HCl, diprophylline, caffeine, theophylline, ibuprofen, and carbamazepine (BASF AG, Ludwigshafen, Germany).

Polymers

Kollicoat® SR 30 D (BASF AG, Ludwigshafen, Germany); Eudragit® RL 30 D, Eudragit® RL PO, Eudragit® RS PO and Eudragit® L 100-55 (Evonik Röhm GmbH, Darmstadt, Germany); hydroxypropylmethylcellulose, Methocel® K100M premium and E5 premium LV and ethylcellulose, Ethocel® std. 100 premium standard and 10 cP FP premium (Colorcon Ltd, Dartford, Kent, UK); hydroxypropylcellulose, HPC (Klucel LF-pharm, Ashland, Wilmington, USA); cellulose acetate butyrate, (CAB-553-0.4, Krahn Chemie GmbH, Hamburg, Germany); hydroxypropyl methylcellulose phthalate (HPMCP HP-55, hypromellose phthalate, Shin-Etsu Co. Ltd., Japan).

Fillers

Lactose monohydrate, FlowLac® 100 (Meggle Wasserburg GmbH & Co. KG, Wasserburg, Germany); microcrystalline cellulose, Avicel® PH 101 and Avicel® PH 200 (FMC Biopolymer, Philadelphia, PA, USA).

Plasticizer

Triethylcitrate, TEC (Citroflex®, Morflex Inc., Greensboro, NC, USA).

Others

Sodium lauryl sulfate, SLS (Roth GmbH & Co. KG., Karlsruhe, Germany); magnesium stearate (Pharma veg®, Baerlocher, Germany); colloidal silica (Aerosil® 200, Degussa GmbH, Hanau, Germany).

2.2. Methods

2.2.1. Kollicoat® SR 30 D and Eudragit® RL 30 D polymer blends: Increase mechanical robustness of HPMC matrix tablets

2.2.1.1. Preparation of polymeric films

Casting and spraying techniques were used for films' preparation followed by studying water uptake and mechanical properties, respectively. Polymer blends (10% w/w) of Kollicoat® SR 30 D:Eudragit® RL 30 D containing plasticizer (5% w/w, TEC) were cast (or sprayed) onto self-made teflon plates, 14 cm × 14 cm, dried for 24 h at 40 °C and carefully removed by hand and equilibrate at ambient conditions at least for 4 h. The film thickness was measured at three points with a thickness gauge Minitest 600 (Erichsen, Hemer, Germany).

2.2.1.2. Water uptake and dry mass loss measurement

Thin, polymeric films were cut into pieces of 2 cm × 2 cm, each piece was weighed (dry mass (0)) then separately placed into 60 mL plastic container filled with 40 mL 0.1 N HCl (n = 3), followed by horizontally shaking for 6 h (37 °C, 80 rpm; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time intervals, samples were withdrawn, accurately weighed (wet mass (t)), and dried to constant weight at 40 °C (dry mass (t)). The water content (%) and film dry mass loss at the time t was calculated as follows:

$$\text{Water content (\%) (t)} = \frac{\text{wet mass (t)} - \text{dry mass (t)}}{\text{wet mass (t)}} \times 100$$

$$\text{Film dry mass loss (\%) (t)} = \frac{\text{dry mass (0)} - \text{dry mass (t)}}{\text{dry mass (0)}} \times 100$$

The same equations were used for the swollen tablets which were withdrawn from the dissolution medium accurately weighed (wet mass (t)) and dried to constant weight at 40 °C (dry mass (t)).

2.2.1.3. Mechanical properties

Films (9.0 cm × 6.5 cm) were fixed in a self-designed Teflon holder with 18 holes (diameter 10 mm). The mechanical properties of films were measured with a texture analyzer (TA.XT. Plus texture analyzer, Stable Micro Systems Ltd., UK). A metal probe with a hemispherical end (diameter 0.5 cm, length 15 cm) was driven through the dry film at a speed of 0.1 mm/sec. Force (N) versus displacement (mm) curves were recorded with a 50 kg load cell, n = 3. Then the holder with fixed film was immersed into 0.1 N HCl at 37 °C for 2 h and puncture tests were performed as described above on the wet film.

Same procedure used for measuring wet tablet strength, using a metal probe with a flat end (diameter 2 cm)

The following parameters were calculated:

$$\text{Tensile strength (N/cm}^2\text{)} = \frac{F_{max}}{A}$$

Where F_{max} is the maximum applied force at film break, A is the area of the edge of film located in the path of the cylindrical hole of film holder ($A = 2\ (\pi\ r^2) + h\ (2\pi\ r)$, where r is the radius of the hole, h is the thickness of film).

$$\text{Elongation at break (\%)} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

$$= \frac{\sqrt{r^2 + d^2} - r}{r} \times 100$$

Where d is the displacement of the punch

Young's modulus (E), a measure of intrinsic film stiffness (García et al., 2009), can be calculated by using the following equation (Martin et al., 1993):

$$\text{Young's modulus (N/cm}^2\text{)} = \frac{\text{Tensile strength (N/cm}^2\text{)}}{\text{Elongation at break}}$$

2.2.1.4. Preparation of HPMC matrix tablets

Tablets were prepared by direct compression process. Powder blends containing 10% w/w propranolol HCl, 10% w/w HPMC (Methocel® K100M), 80% w/w FlowLac® 100 and 1% w/w magnesium stearate and Aerosil® 200 were directly compressed into 10 mm diameter, round, convex-faced tablets (500 ± 25 mg) at the hardness of 90 ± 10 N using single punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany).

2.2.1.5. Tablet coating

Tablet cores were coated with 10% w/w aqueous dispersion of polymer blends. The coating was carried out in perforated coating pan (Glatt lab-coater, GC300, Switzerland). Core tablets were sprayed with a coating dispersion at following parameters: batch size: 1.5 kg, pan rotation: 15 rpm, airflow: 100 m^3/h, product temperature: 26-32 ^oC, atomization pressure: 1.3 bar, spraying rate: 6-9 g/min. The coating was continued until the desired weight gain on core tablets was achieved. Coated tablets were cured at 40 ^oC/ 75% RH for 24 h.

2.2.2. Kollicoat® SR 30 D and Eudragit® RL 30 D polymer blends: Preparation and characterization of reservoir tablets

2.2.2.1. Preparation of tablet cores

Powder blends containing diprophylline (50% w/w) and excipient(s) (50% w/w) were manually granulated with water. Magnesium stearate (1% w/w) was added to dried granules (0.5 mm- 1.0 mm), then compressed at 100 ± 10 N into 9 mm diameter, round, convex-faced tablets (250 ± 10 mg) using single punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany).

2.2.2.2. Tablet coating

Tablet cores were coated with 11%, 12%, and 13% w/w aqueous dispersion of polymer blends (70:30. 75:25 and 80:20 Kollicoat® SR:Eudragit® RL, respectively) at the same coating conditions described in section 2.2.1.5.

2.2.2.3. Mechanical properties

A metal probe with a flat end (diameter 2 cm, length 15 cm) was driven to the tablets at a speed of 0.1 mm/sec., as described in section 2.2.1.3.

2.2.2.4. Fourier transform infrared (FT-IR) spectroscopy analysis

FTIR-spectra were generated with an Excalibur 3100 FTIR spectrophotometer (Varian Inc., Palo Alto, USA). The spectra were collected using a horizontal ATR accessory with a single reflection diamond crystal (Pike MIRacle, Pike Technologies, Madison, USA). 500 scans at 2 cm^{-1} resolution were averaged and spectral contributions coming from water vapor in the light pass were subtracted using Varian software (Resolution Pro 4.0). Finally, the spectra was treated with a 64 point smoothing function.

2.2.2.5. Differential scanning calorimetric (DSC) analysis

To determine the drug/excipient interaction in tablets under accelerated stability conditions, DSC studies were performed using a differential scanning calorimeter (DSC-822e Mettler-Toledo, Switzerland). Tablets were grinded, then samples (5 mg to 10 mg) were placed in sealed aluminum pans with a perforated lid, and an empty pan was used as a reference. The samples were heated at a rate of 10 °C/min from 25 °C to 250 °C (purged with gaseous nitrogen 50 mL/min) and standard DSC scans were recorded.

2.2.2.6. Physical interaction (adsorption) analysis

To study physical interaction (adsorption); tablets that exposed to accelerated stability condition for one month were grinded and dissolved in 0.05 N HCl to make a concentration of 0.03% w/v (theoretically contain 15 mg diprophylline) and left for 48 h with continuous stirring. The drug concentration was measured by UV-spectrophotometer.

2.2.3. Cellulose acetate butyrate as controlled-release polymer: Osmotic tablets

2.2.3.1. Preparation of polymeric films

Ethanol (96%) was used as a solvent for the polymer film's preparation. The polymer solutions of CAB:Eudragit® RL PO or ethylcellulose:Eudragit® RL PO (10% w/w polymer content) containing 20% w/w TEC as plasticizer were cast onto Teflon plates (14 cm × 14 cm). The solutions dried for 24 h at 40 °C and carefully removed by hand, and then equilibrate at ambient conditions for at least 4 h. The film thickness (n = 3) was measured with a thickness gauge (Minitest 600; Erichsen, Hemer, Germany) (Moebus et al., 2012).

2.2.3.2. Film's water uptake, dry mass loss and mechanical properties

Described in section 2.2.1.2, and 2.2.1.3.

The rupture force of the tablets was measured with the texture analyzer (TA.XT. Plus texture analyzer, Stable Micro Systems Ltd., UK). A metal probe with a flat end (diameter 2 cm, length 15 cm) pressed the tablet after 24 h incubations in the dissolution medium at a speed of 0.1 mm/sec. The force at which the tablet ruptured was recorded.

2.2.3.3. Preparation of tablet cores

Powder blends containing 30% caffeine, 3% Methocel® E5 and 67% w/w of FlowLac® 100 were manually granulated using water as a granulating fluid. Magnesium stearate (1% w/w) was added to dried granules (0.45 mm-1.00 mm) then compressed at 13 ± 1 kN into 8 mm diameter, round, convex-faced tablets (200 ± 10) mg using single punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany). The tablet hardness was 90 ± 10 N.

2.2.3.4. Tablet coating

Tablet cores were coated with ethanol solution of CAB:Eudragit® RL (15% w/w) and ethylcellulose: Eudragit® RL (10% w/w) containing plasticizer (TEC, 20% w/w depending on polymer weight). The coating was carried out in drum coater (Glatt lab-coater, GC300, Switzerland). Core tablets were sprayed with a coating solution at following parameters: batch size: 1.5 kg, pan rotation: 15 rpm, airflow: 100 m^3/h, product temperature: 20-23 °C, atomization pressure: 1.0 bar, spraying rate: 6-9 g/min. The coating was continued until the desired coating level was achieved. The residual

solvent removed by further rotation of the coated tablets for 30 min at 30 °C. Finally, a hot needle was used for making the delivery orifice (1 ± 0.2 mm).

2.2.4. Cellulose acetate butyrate as controlled-release polymer: Multiparticulates

2.2.4.1. Drug layering

The diprophylline (10% w/w) were layered on NP or MCC starter core using an isopropanol:water (88:12, w:w) solution of HPMC (20% w/w of drug) as a binder in a fluidized bed coater (Aeromatic Strea-I, Binzen, Germany) to achieve 15% w/w drug content. The layering conditions were: batch size = 900 g, product temperature ~40 °C, air flow = 60-70 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 1.2 bar, spray rate = 6-10 g/min, final drying for 15 min.

2.2.4.2. Coating of drug-layered pellets

The diprophylline- or caffeine-layered pellets were coated with 10% w/w solid content of the cellulose acetate butyrate solution (7.5% w/w for carbamazepine) in the fluidized bed coater (Mini-Glatt 4, Glatt GmbH, Binzen, Germany) to achieve a coating level of 15% w/w (based on final pellets weight) using isopropanol/water (85:15, w/w). For carbamazepine pellets, HPC (20% - 40%) w/w was used as a pore-former. The coating conditions were: batch size = 80 g, nozzle diameter = 0.5 mm, airflow = 0.2 bar, spray pressure = 0.9 bar, product temperature = ~35 °C, spray rate = 0.5-1 g/min final drying at ~35 °C for 10 min.

2.2.4.3. Tableting

The blends of 50% w/w coated pellets and 50% w/w Avicel® PH-200 were compressed at 10 kN to 20 kN into 10 mm diameter, flat faced tablets (400 ± 20 mg) using single punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany).

2.2.5. Increase tablettability of pellets through Eudragit® RL top coating

2.2.5.1. Drug layering

Described in section 2.2.4.1.

2.2.5.2. Coating of drug-layered pellets

The diprophylline-layered pellets were coated with hydroxypropyl methylcellulose phthalate and ethylcellulose organic solution, cellulose acetate butyrate and Eudragit® L organic solution, and Kollicoat® SR aqueous dispersion with solid content 7%, 10% and 15% w/w, in the fluidized bed coater (Mini-Glatt 4, Glatt GmbH, Binzen, Germany). Isopropanol:water (85:15, 88:12, 85:15, and 100:0) were used as solvents for organic solutions and coating level (cl) of 20% w/w (15% w/w cellulose acetate butyrate) were achieved based on final pellet's weight. The coating conditions were; batch size = 80 g, nozzle diameter = 0.5 mm, airflow = 0.2 bar, spray pressure = 0.9 bar, product temperature = ~30 °C, spray rate = 0.5-1 g/min final drying at ~35 °C for 10 min.

2.2.5.3. Top-coating of coated pellets

The coated pellets were top-coated with 10% w/w solid content of Eudragit® RL aqueous dispersion or organic solution (Isopropanol:water / 97:3) containing 20% TEC in fluidized bed coater (Mini-Glatt 4, Glatt GmbH, Binzen, Germany) to achieve the coating level of 5% w/w at same coating conditions as described in 2.2.5.2.

2.2.5.4. Tableting

The blends of 70% w/w coated pellets and 30% w/w Avicel® PH-200 were compressed at 5 kN into 10 mm diameter, flat-faced tablets (400 ± 20 mg) using single-punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany).

The tablets were characterized for their dimension and hardness (Multicheck, Erweka GmbH, Heusen-stamm, Germany). The radial tensile strength (σ_t) was calculated according to this equation (Fell and Newton, 1970): $\sigma_t = \frac{2H}{\pi d h}$

Where H is the tablet crushing force, d is tablet diameter, and h is tablet thickness.

2.2.6. Cellulose acetate butyrate as controlled-release polymer: Matrix tablets

2.2.6.1. Preparation of the tablets

Powder blends containing drug, cellulose acetate butyrate and lactose monohydrate were manually granulated (0.5 mm - 1.0 mm) using isopropanol as a granulating solvent. Magnesium stearate (1% w/w) was added to the blends (granulated and un-granulated) followed by compression at 15 ± 1 kN into 8 mm diameter, flat faced tablets (120 ± 10 mg) using single punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany). The tablet's dimensions and hardness were characterized (Multicheck, Erweka GmbH, Heusen-stamm, Germany).

2.2.6.2. Powder X-ray diffraction measurement (PXRD)

Cellulose acetate butyrate, caffeine, physical mixtures and tablet (after grinding) were measured by wide-angle x-ray diffractometry on a Philips PW 1830 x-ray generator with a copper anode (Cu Kα radiation, λ=0.15418 nm, 40 kV), fixed with a Philips PW 1710 diffraction control unit (Philips Industrial and Electro-acoustic Systems Divisions, Almelo, Netherlands). The radiation scattered in the crystalline regions of the samples was measured with a vertical goniometer (Philips PW 1820, Philips Industrial and Electro acoustic Systems Division, Almelo, The Netherlands). Patterns were obtained using a step width of 0.02^{o} with a detector resolution in 2θ (diffraction angle) between 4^{o} and 40^{o} at the ambient.

2.2.7. Preparation and characterization of high ibuprofen loaded matrix tablets

2.2.7.1. Preparation of tablets

Powder blends containing ibuprofen, and polymer carrier were manually granulated using ethanol:water mixture as a granulation fluid. Magnesium stearate (1% w/w) were added to dried granules then compressed into 8 mm diameter, flat-faced tablets (120 ± 10 mg) at 15 ± 1 kN using single punch tablet press as described in section 2.2.6.1.

2.2.7.2. Fourier transform infrared (FT-IR) spectroscopy analysis

Described in section 2.2.2.4.

2.2.8. Preparation and characterization of an oral controlled-release tablet of a water-insoluble drug, using Eudragit® RL PO as a water-insoluble permeable carrier: role of curing conditions

2.2.8.1. Preparation of tablets

Tables prepared by both direct compression and wet granulation compression method (0.71 mm – 1.0 mm). Powder blends containing 30% w/w carbamazepine, 67% w/w polymer and 3% Methocel® E5 as a binder were granulated using ethanol:water as a granulating fluid (granules were dried at room temperature). Then 1% w/w magnesium stearate was added to dried granules or power blends then compressed into 8 mm diameter, flat-faced tablets (120 ± 10 mg) at 15 ± 1 kN using single punch tablet press (section 2.2.6.1).

2.2.8.2. Powder X-ray diffraction measurement (PXRD)

Described in section 2.2.6.2

2.2.9. Drug release

The drug release from the matrix tablets was investigated in a USP type II (paddle) apparatus (Vankel VK 300, Vankel Industries, Edison, NJ, USA) (900 mL 0.1N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8 (PBS) Pharm. Eur., 37 °C, n=3). Pellets coated with delayed release polymers were tested at 100 rpm, 37 °C, 750 mL 0.1 N HCl for 2 h. Then 250 mL 0.2 N tribasic sodium phosphate were added and the pH was adjusted using 2 N NaOH or HCl to a pH of 6.80 ± 0.05. Samples were withdrawn at predetermined time points, and drug concentrations measured by UV-spectrophotometer (metoprolol λ = 221 nm, propranolol HCl λ = 290 nm, diprophylline λ = 272 nm, caffeine λ = 274 nm, theophylline λ = 274 nm, ibuprofen λ = 222 nm and carbamazepine λ = 284 nm).

The similarity factor (f_2) was used to establish similarity of two dissolution profiles (Polli et al., 1997):

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

n = number of pull points for tested samples, R_t = reference assay at time points t, T_t = test assay at time points t.

f_2 values higher than 50 (50–100) shows the similarity of the dissolution profiles.

2.2.10. Stability tests

Samples were subjected to the accelerated stability test. Samples were maintained for one to three months in an accelerated stability chamber (Sanyo Gallenkamp PLC, Leicester, UK) at 40 ± 2 °C and 75 ± 5% relative humidity.

RESULTS AND DISCUSSION

3. RESULTS AND DISCUSSION

3.1. Kollicoat® SR 30 D and Eudragit® RL 30 D polymer blends: Increase mechanical robustness of HPMC matrix tablets

Background

Hydrophilic matrices are compressed powder mixtures of drug and excipients, including one, or more, water-swellable hydrophilic polymers in which the formation of a viscous hydrated polymer layer at the matrix surface provides a diffusion barrier that retards drug release and prolongs its therapeutic effect. Hydroxypropylmethylcellulose is the most widely used polymer in this application (Li et al., 2005). Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion (Brannon-Peppas, 1990; Brannon-Peppas and Peppas, 1990). Then, the incorporated drug diffuses out of the system.

Among the dissolution test conditions, hydrodynamic properties (agitation rate) and mechanical destructive force are important factors, which affect the dissolution behavior of the dosage form. Orally administered dosage forms receive stress by the peristaltic movement of the GI wall. In hydrogel-type tablets, *in vivo* drug release was much faster than that expected from *in vitro* dissolution tests due to the peristalsis of the GI tract (Shameem et al., 1995).

Both *in vitro* and *in vivo* erosion profiles for matrix tablets were dependent upon the concentration of HPMC, and erosion was faster for tablets containing 20% w/w HPMC than those containing 40% w/w HPMC (Ghimire et al., 2010). Abrahamsson et al. compared hydrophilic matrix tablets and considered that factors affecting swelling, and erosion of these polymers may account for differences between *in vitro* dissolution results and subsequent *in vivo* performance (Abrahamsson et al., 1999).

The aim of this study was to coat the HPMC matrix tablets with unconventional polymer blends of flexible Kollicoat® SR 30 D with permeable Eudragit® RL 30 D, to enhance its robustness toward agitation and to increase mechanical stability of the tablet.

Results and discussion

HPMC is a polymer, which is widely used in the manufacture of matrices for extended release of drugs. In this study, HPMC matrix tablets were coated with polymer blends to increase mechanical robustness of the tablets.

When the polymer blends are applied from aqueous dispersions, special care has to be taken when preparing the coating formulations. Colloidal polymer dispersions can be very sensitive to external factors (e.g., pH, temperature, presence of a second polymer) and might be destabilized, resulting in flocculation.

Kollicoat® SR 30 D, which is stabilized with the anionic surfactant SLS, is incompatible with the Eudragit® RL 30 D that has cationic quaternary ammonium group. Wong reported that the positive charge of Eudragit® RL can be changed to a negative charge if the dispersion is diluted to 6% w/w and added into concentrated SLS solution (Wong, 1994). Concentrated SLS solution (~ 10% w/v) was prepared by dissolving required amount of SLS (2.5% w/w, depending on the diluted Eudragit® RL) in the rest of free water required for final polymer dispersion. The diluted Eudragit® RL dispersion (6% w/w) was added slowly into the concentrated SLS solution under continuous stirring. The undiluted Kollicoat® SR 30 D was added slowly in to the Eudragit® RL-SLS mixture with continuous mixing. Finally, TEC was added {10% and 5% w/w for Kollicoat® SR:Eudragit® RL 60:40 and (70:30 and 80:20), respectively} and dispersions were stirred for an overnight.

Polymer blends of Kollicoat® SR 30 D:Eudragit® RL 30 D at ratios of 80:20, 70:30, and 60:40 were prepared. The results of centrifugation study confirmed that blends of all ratios were stable (data is not shown here); the most important step in blends preparation is changing positive charge of Eudragit® RL to be negative, otherwise, the blended aggregate and make a lump.

Due of its high permeability, increased Eudragit® RL content (20%, 30%, and 40% w/w), film medium uptake and dry mass loss was increased after incubation in the dissolution medium **(Fig. 7)**.

Increased dry mass loss was due to dissolved stabilizer (SLS), which increased with Eudragit® RL proportionally. Moreover, because it is less flexible than Kollicoat® SR, with increased the

Eudragit® RL content, the film elongation percent was decreased and the films' stiffness was increased (Young's modulus increase) **(Table 2**).

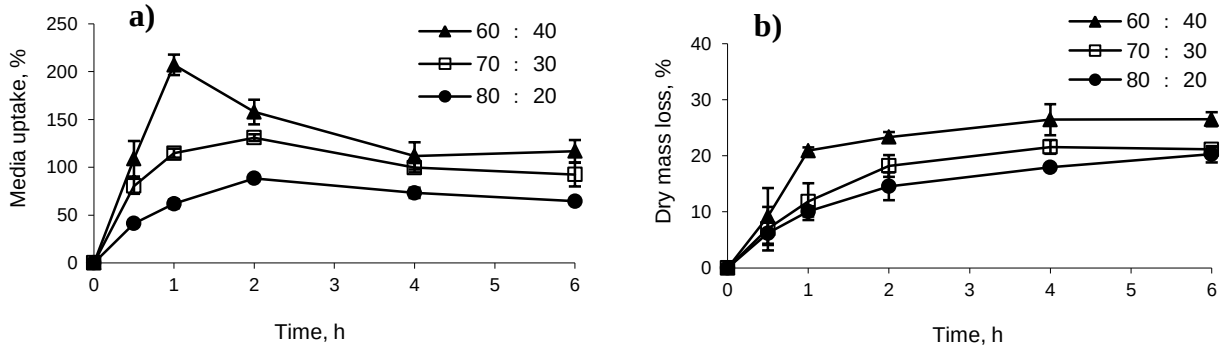

Fig. 7 Effect of the polymer ratio (Kollicoat® SR:Eudragit® RL) on: **a)** film water uptake and **b)** dry mass loss (5% w/w TEC, 0.1 N HCl).

Table 2 Effect of polymer ratio (Kollicoat® SR:Eudragit® RL) on film elongation percent and Young's modulus, 5% TEC (film thickness 110±15 μm)

Polymer Blends	**Film dry state**		**Film wet state**	
Kollicoat® SR 30D:Eudragit® RL 30D %	Elongation %	Young's Modulus N/cm^2	Elongation %	Young's Modulus N/cm^2
80:20	119 ± 24	7.1 ± 1.2	962 ± 173	0.20 ± 0.03
70:30	63 ± 5	14.7 ± 1.5	726 ± 45	0.30 ± 0.02
60:40	23 ± 1	46.8 ± 4.3	334 ± 26	0.32 ± 0.07

A simple change in polymer blend ratio; the resulting film coating properties can effectively be altered, and broad ranges of drug release patterns are provided (Lecomte et al., 2003). **Fig. 8** shows the effect of Kollicoat® SR 30 D:Eudragit® RL 30 D polymer blends at ratios 80:20, 70:30 and 60:40 on propranolol HCl release. After a well-defined short lag time, the drug release profile is almost linear ($R^2 = 0.995$). The short lag time was probably caused by the time required for water soluble ingredient {2.7% polyvinylpyrrolidon of Kollicoat® SR 30 D and stabilizer (SLS)} of the film to be dissolved and the dissolution medium to diffuse through the coating and for the drug concentration gradient across the film coating to be established. In addition, with increased Eudragit® RL ratio, the drug release was faster; this is due to: a) high permeability of this polymer, which increases medium uptake by the film as mentioned above and b) with

increased Eudragit® RL content, more SLS was required for the blend stabilization, which probably acts as a wetting agent and pore-former at the same time.

In general, the high solubility of some drugs in water leads to rapid release, and the burst effect appears, which involves a very rapid initial release of an amount of drug in a short period as soon as it enters into contact with the medium before it starts to be released at the desired rate (Huang and Brazel, 2001). The drug release (t_{80}) for uncoated tablets (without HPMC), uncoated HPMC matrix, coated tablets (without HPMC), and coated HPMC matrix tablets was < 0.5 h, 2.5 h, 6 h, and 15 h, respectively (**Fig. 9**). This result confirms that the coat plays a role in controlling drug release also.

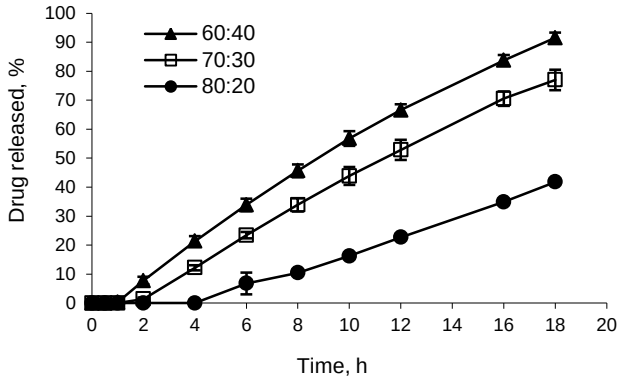

Fig. 8 Effect of the polymer ratio (Kollicoat® SR:Eudragit® RL) on the propranolol HCl release from coated HPMC matrix in 0.1 N HCl (cl 10% w/w).

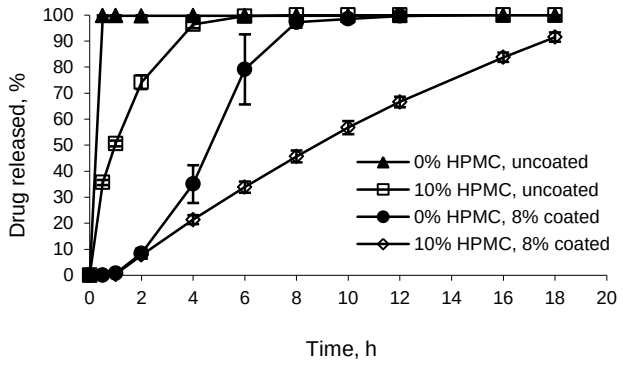

Fig. 9 Effect of the HPMC as a matrix former and the polymer coat on propranolol HCl release in 0.1 N HCl (Kollicoat® SR:Eudragit® RL 60:40, cl 8% w/w).

Most of the solid oral dosage forms lose their mechanical strength by their immersion in water. After 4 h dissolution test, the mechanical strength of hydrogel-type tablets decreased from more than 20 N to 0.5 N (Sako et al., 1996), and a similar decrease was observed in insoluble film-coated tablets (Hirasima et al., 1990). Hence, effect of incubation time in the dissolution medium on the force that ruptures the tablet's coat was investigated (**Fig. 10**). The rupture force of coated HPMC matrix tablet was decreased (58, 34, 3, and 1 N) with increased incubation time of the coated HPMC tablets in the release medium (4, 8, 16, and 24 h, respectively). This is due to increased swelling of the tablet and thinning of the polymer coat with time (**Fig. 11**). The mechanical destructive force of human's stomach under fed conditions is 1.9 N, and it is 1.5 N under fasting condition (Kamba et al., 2000), and intestinal destructive force is 1.2 N (Kamba et al., 2002). Accordingly, the coated HPMC matrix probably would stay intact *in vivo* at least for 16 h.

Fig. 12 shows effect of the agitation rate of the dissolution medium on the drug release from uncoated and coated HPMC matrix tablets. For the uncoated HPMC matrix tablet (Fig. 12a), the drug release was increased with increased agitation rate (50 rpm to 150 rpm), due to increase erosion rate of the HPMC matrix tablet (Kavanagh and Corrigan, 2004). However, release of propranolol HCl from coated HPMC tablet was unaffected by agitation rate form 6% to 10% w/w coating level (Fig. 12b and 12c). It is conclude that, the coated HPMC matrix tablet may withstand the hydrodynamic condition *in vivo*.

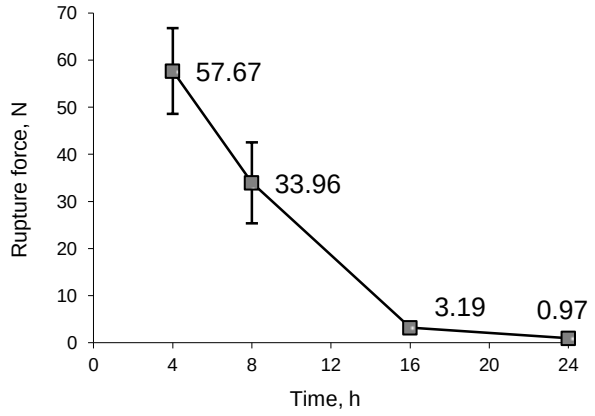

Fig. 10 Effect of incubation time on the force that rupture the coat of HMPC matrix tablet (Kollicoat® SR:Eudragit® RL 60:40, cl 8% w/w).

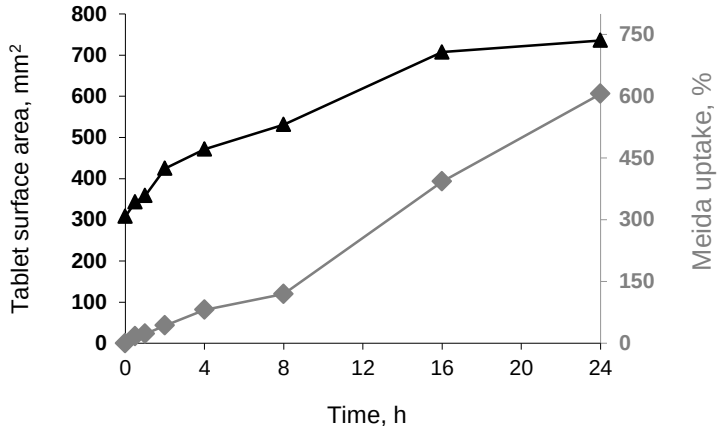

Fig. 11 Effect of incubation time on the tablet surface area and medium uptake (Kollicoat® SR:Eudragit® RL 60:40, cl 8% w/w).

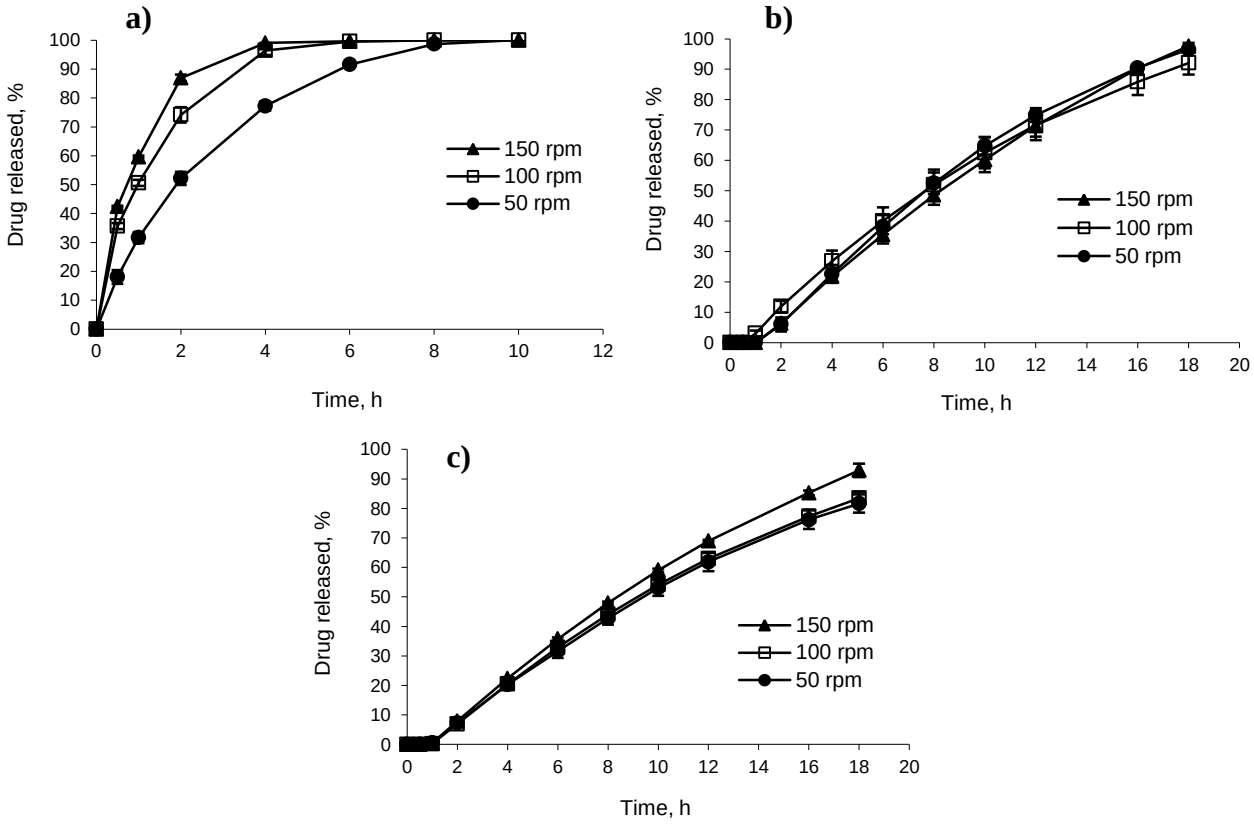

Fig. 12 Effect of agitation rate on propranolol HCl release from **a)** uncoated HPMC matrix tablet, **b)** coated HPMC matrix tablet (cl 6% w/w) and **c)** coated HPMC matrix tablet (cl 10% w/w) in 0.1 N HCl (Kollicoat® SR:Eudragit® RL 60:40).

Gao et al. reported that the drug solubility affected the release rate (Gao et al., 1996). The release rate of drug with different solubility from coated HPMC matrix tablet was in order of caffeine ≥ propranolol HCl > carbamazepine (**Fig. 13**). In general, water-soluble drugs tend to follow a release mechanism based on diffusion through the gel layer, while water-insoluble drugs do so mainly through the mechanism of erosion (Skoug et al., 1993; Tahara et al., 1995). The film coat protected the HPMC matrix from erosion, hence, water-insoluble carbamazepine showed very slow release. Despite having a lower solubility (21.45 mg/mL; Wyttenbach et al., 2007), caffeine release rate was equal to propranolol HCl (130 mg/mL; Takka et al., 2001), probably due to the difference in molecular weight which are 194.19 g/mol and 295.80 g/mol for caffeine and propranolol HCl, respectively. Drugs with a low molecular weight tend to diffuse through the gel layer more easily than those of high molecular weight (Talukdar et al., 1996); furthermore, for water-soluble drug (>5 mg/mL), the dissolution rate is not very affected by the solubility but is similar to that of the entry of water into the system (Tahara et al., 1996).

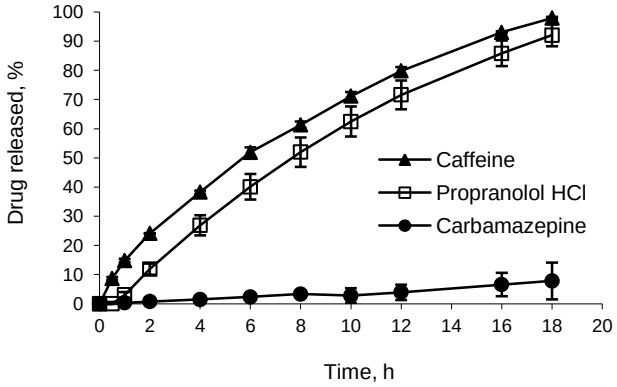

Fig. 13 Effect of drug solubility on the release from coated HPMC matrix in 0.1 N HCl (Kollicoat® SR:Eudragit® RL 60:40, cl 6% w/w).

As shown in (**Fig. 14**), drug release from coated HPMC matrix tablet was increased with increased drug content (10%, 30% and 50%) w/w, because the gel layer through which highly-soluble drugs readily diffuse will be weaker (Tiwari and Rajabi-Siahboomi, 2008). As the drug load increases with respect to the polymer in a matrix system based on HPMC, the system becomes more porous, leading to a faster release rate (Siepmann and Peppas, 2000).

Regardless of the physicochemical characteristics of the polymer, the drug release rate decreases with an increase in the percentage of polymer in the matrix. The greatest percentage of polymer

corresponds to a lower porosity of the matrix, which achieves slower drug release rates (Reza et al., 2003); hence, increased polymer content from 10% to 30% w/w caused a slower drug release (**Fig. 15**).

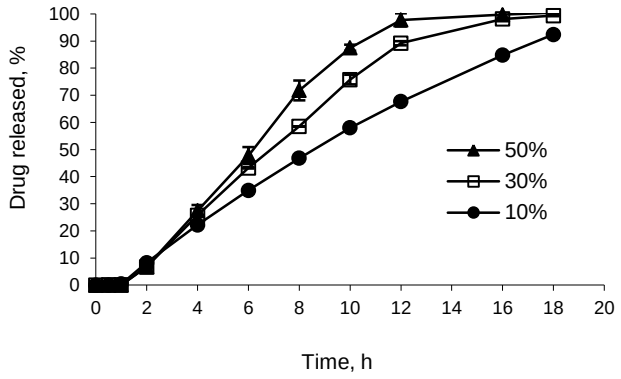

Fig. 14 Effect of drug content on the propranolol HCl release from coated HPMC matrix tablet release in 0.1 N HCl (Kollicoat® SR:Eudragit® RL 60:40, cl 8% w/w).

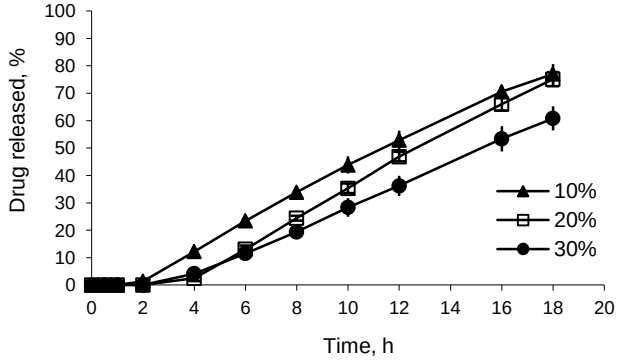

Fig. 15 Effect of HPMC content on propranolol HCl release from coated HPMC matrix tablet in 0.1 N HCl (Kollicoat® SR:Eudragit® RL 70:30, 10% w/w drug, cl 10% w/w).

With various aqueous polymer dispersions, film formation often was not complete after the coating process, and a thermal after-treatment (curing) at elevated temperatures was necessary to complete film formation and to avoid changes in the drug release profiles during storage because of further gradual coalescence (Gilligan and Li Wan Po, 1991). Curing at 40 ºC/ 75% RH for 24 h had no effect on drug release from uncoated HPMC matrix tablet. However, the propranolol HCl release from coated HPMC matrix tablets was curing dependent, the release rate was in

order coated/uncured ≥ coated/40 ºC cured > coated/40 ºC/75% RH cured (**Fig. 16**), furthermore, cured tablet (40 ˚C/ 75% RH) had highest flexibility (inspected manually).

Finally, the release of propranolol HCl was robust and did not influence by coating level from 6% to 10% w/w (**Fig. 17**).

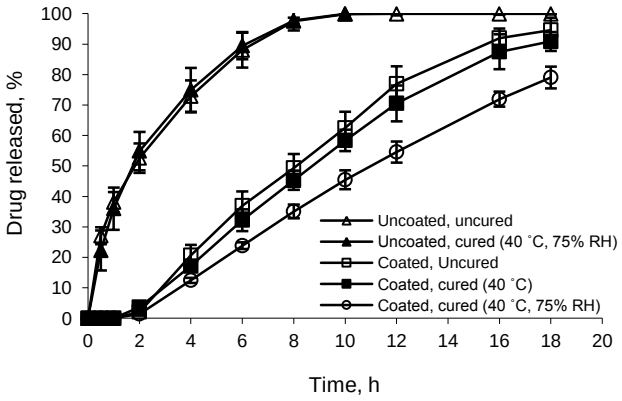

Fig. 16 Effect of curing conditions on propranolol HCl release from uncoated and Kollicoat® SR:Eudragit® RL (70:30) coated HPMC matrix tablet in 0.1 N HCl (cl 10% w/w).

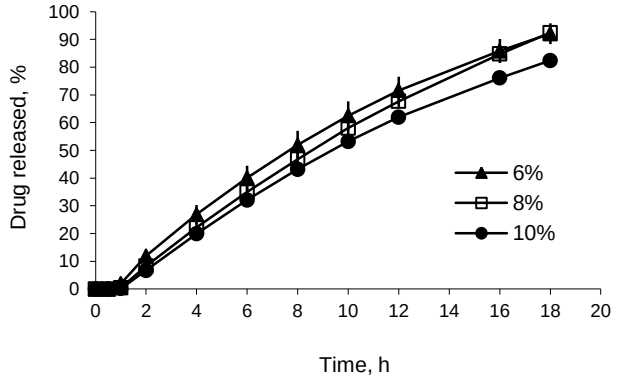

Fig. 17 Effect of coating level on propranolol HCl release from coated HPMC matrix tablet in 0.1 N HCl (Kollicoat® SR:Eudragit® RL, 60:40).

Conclusions

Kollicoat® SR 30 D and Eudragit® RL 30 D polymer blends is an interesting combination because of its flexibility and permeability. This makes it suitable for HPMC matrix coating. Polymer blends ratio had not only an impact on drug release, but also on mechanical properties of the film. The flexibility of the film increased as Kollicoat® SR increased and its water uptake increased as Eudragit® RL increased. The release from the coated tablet was independent of coating level and agitation. *In vitro* study showed that the coating film was strong enough to protect the HPMC matrix from gastric and intestinal force for at least 16 h. Curing (temperature and humidity) had an impact on polymer coalescence. Coating is useful for those drugs, which have diffusion-dependent rather than erosion-dependent release, because the coat prevents erosion of HPMC.

3.2. Kollicoat® SR 30 D and Eudragit® RL 30 D polymer blends: Preparation and characterization of reservoir tablets

Background

Controlled-release systems can be classified into matrix and reservoir system; matrix devices consist of drug dispersed homogenously throughout a continuous phase of polymer or lipid. However, a drug-containing core surrounded by release-rate controlling polymer characterizes reservoir systems.

Multiporous Oral Drug Absorption System (MODAS; Elan Corporation, Ireland) and Multipor technology (Ethical Holdings Plc., UK) are examples of reservoir system. The tablet core consists of a mixture of active drug and other excipients, subsequently coated with a solution of water-insoluble polymers and water-soluble excipients. Upon exposure to aqueous media, the surrounded coating is transformed into a permeable membrane through which the drug diffuses in a rate-limiting manner (Verma and Garg, 2001).

Despite of commercial availability of many extended release polymers like cellulose acetate, ethylcellulose, polyvinyl acetate and the methacrylic acid copolymers Eudragit® RS, RL and NE, there are few publication regarding their use for preparation of single-unit reservoir tablets, for example Marini et al. used ethylcellulose and polyethylene glycol 3350 (Marini et al., 1991).
Polymer blends are frequently used as excipients in controlled drug delivery systems. For example, they serve as matrix formers in tablets (Samani et al., 2003), micro- and nanoparticles (Beten and Moes, 1994) or as coating materials for solid dosage forms (Amighi and Moes, 1995)

The objective was to prepare reservoir tablets using unconventional polymer blends of a flexible polymer Kollicoat® SR 30 D, with a more permeable copolymer like Eudragit® RL 30 D and characterizing the factors which may affect drug release from this dosage form.

Results and discussion

The reservoir system is a type of controlled-release systems characterized by a drug-containing core surrounded by a release-rate controlling polymer(s). Kollicoat® SR 30 D, as a flexible polymer, and Eudragit® RL 30 D, as a permeable polymer, were selected as coating materials for preparation of single-unit reservoir system.

Kollicoat® SR 30 D, which is stabilized with the anionic surfactant SLS, is incompatible with the cationic Eudragit® RL 30 D (quaternary ammonium group). Wong reported that the positive charge of Eudragit® RL can be changed to a negative charge if the dispersion is diluted to 6% w/w and added into concentrated SLS solution (required SLS was 2.5% w/w, depending on weight of Eudragit® RL dispersion) (Wong, 1994). The process for preparation of stable dispersion was described above (3.1).

In contrast to polymer solutions, dispersed polymer particles need to deform and fuse together in order to form the film. Post-coating and drying at temperatures above the minimum film forming temperature (curing) provides sufficient coalescence. Curing changed the film's structure, influenced mechanical properties of the free film and the dissolution profiles of the coated dosage form (Bhattacharjya and Wurster, 2008; Hutchings et al., 1994; Wesseling and Bodmeier, 2001). Curing of the coated tablets at 40 °C had no effect on the drug release and the film strength. However, with 75% relative humidity significantly decreased the drug release and increased the film strength (inspected manually) (**Fig. 18**). High relative humidity attained adequate capillary pressure and facilitate polymer coalescence (Carlin et al., 2008); it also increased polymer chain inter-diffusion (Haley et al., 2008). This result confirmed the crucial role of the curing condition on complete film formation.

Increased Eudragit® RL content in the Kollicoat® SR:Eudragit® RL blends (20%, 25%, and 30%), accelerated the diprophylline release (**Fig. 19**) due to an increase in film permeability. In addition, as Eudragit® RL content increased, higher amount of SLS was required for dispersion stabilization, which further increased film permeability.

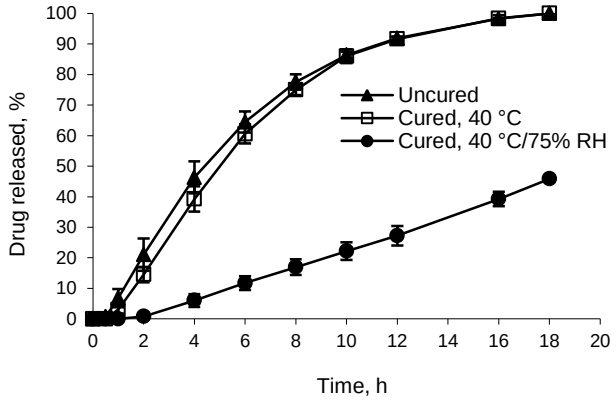

Fig. 18 Effect of the curing conditions on diprophylline release from coated tablets in 0.1 N HCl (drug 50% w/w, Avicel® 50% w/w, Kollicoat® SR:Eudragit® RL 80:20, cl 6% w/w).

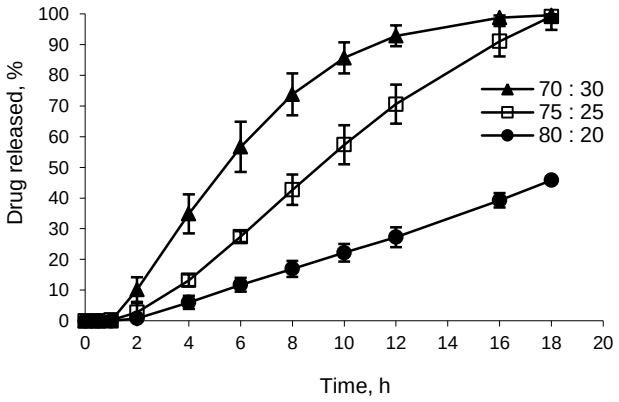

Fig. 19 Effect of Kollicoat® SR:Eudragit® RL ratios on diprophylline release in 0.1 N HCl (drug 50% w/w, Avicel® 50% w/w, cl 6% w/w).

Ionic strength, pH, and mixing intensity of the GI fluids are variables that affect the rate at which a drug is released from extended-release dosage forms. The ionic strength of GI fluids in the human under both fasted and fed states and various physiological pH conditions varies from 0 to 0.4 M (Johnson et al., 1993). In order to investigate the effect of the ionic strength, NaCl was added into the dissolution medium. Increased ionic strength of the release medium had no effect on the diprophylline release from coated tablets (**Fig. 20**).

In order to study the effect of pH on drug release, dissolution of the tablets was conducted in different pH medium. Diprophylline release was faster in the order of pH 6.8 PBS ≥ pH 4.5 acetate buffer > pH 1 (0.1 N) HCl (**Fig. 21**). This is due to exchange of chloride counter ion of

the cationic quaternary ammonium group of Eudragit® RL to anionic acetate and phosphate species, which affects film hydration (Bodmeier et al., 1996).

Increased in the agitation rate of the release medium (50 rpm to 150 rpm) had no impact on drug release (**Fig. 22**); consequently, it could be expected that the release will be independent of the hydrodynamic conditions of the gastrointestinal tract.

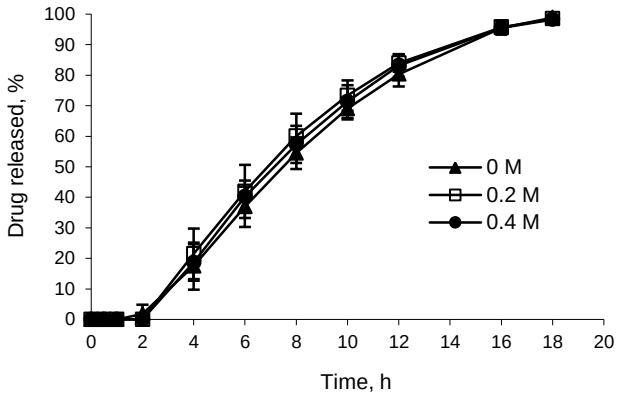

Fig. 20 Effect of the ionic strength of the release medium on diprophylline release from coated tablets in 0.1 N HCl (drug 50% w/w, Avicel® 50% w/w, Kollicoat® SR:Eudragit® RL 70:30, cl 10% w/w).

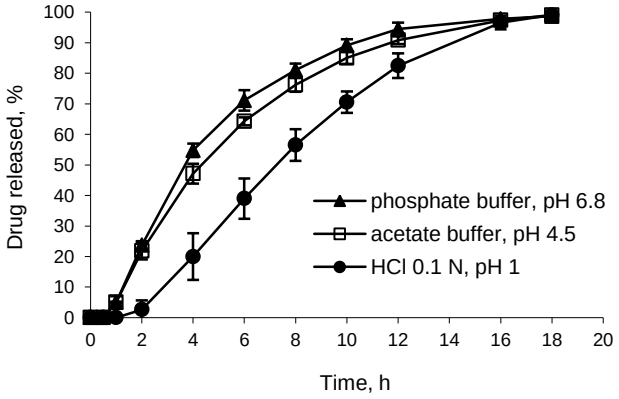

Fig. 21 Effect of the pH of the release medium on diprophylline release from coated tablets (drug 50% w/w, Avicel® 50% w/w, Kollicoat® SR:Eudragit® RL 70:30, cl 10% w/w).

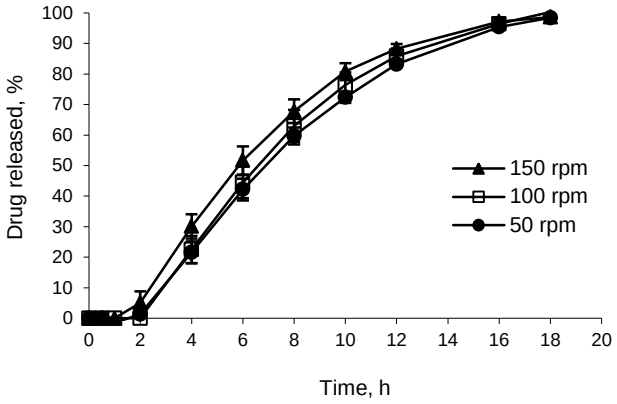

Fig. 22 Effect of the agitation rate of the release medium on diprophylline release from coated tablets in 0.1 N HCl (drug 50% w/w, Avicel® 50% w/w, Kollicoat® SR:Eudragit® RL 70:30, cl 8% w/w).

Diprophylline release was decreased and the lag time was increased with increased coating level (6% to 10% w/w) (**Fig. 23**). Nevertheless, an increase on coating level had no effect on the coat strength, and the tablets deformed under the probe without rupturing (**Fig. 24**). At any coating level, the coating tolerated pressures higher than 40 N, which is 20 times stronger than the gastric destructive force (1.9 N under fed conditions and 1.5 N under fasting conditions; Kamba et al., 2000). *In vitro* result implied the robustness of the film coat and the capability to survive through the GI tract.

Drug solubility is another factor that affects the release rate (Gao et al., 1996). To study effect of drug solubility, drugs with different solubility (metoprolol, diprophylline, and theophylline) were used as model drugs. Release of metoprolol (solubility 1000 mg/mL) was slower than diprophylline (solubility 212 mg/mL) and was similar to theophylline (solubility 8 mg/mL), despite the high solubility of metoprolol (**Fig. 25**). This may be explained by the difference in molecular size among these drugs; metoprolol is the largest ((684, 254, and 180) g/mol, respectively), which makes the diffusion through the coat more difficult.

To investigate effect of excipient on the drug release, the water-soluble filler (lactose) was replaced the water-swellable filler (MCC). The drug release decreased with increased water-soluble filler (0%, 50% and 100% w/w) (**Fig. 26**). This might be due to the swelling capacity of MCC, which increased pore size of the coat and facilitated the diffusion process. After 2 h of

incubation of the tablets in the release medium, the increased tablet weight was 58%, 46%, and 23% and increased surface area was 37%, 27%, and 3%, respectively.

Additionally, because diffusion process through membrane is concentration dependent, diprophylline release was increased as the drug content increased (50%, 65%, and 80% w/w) (**Fig. 27**).

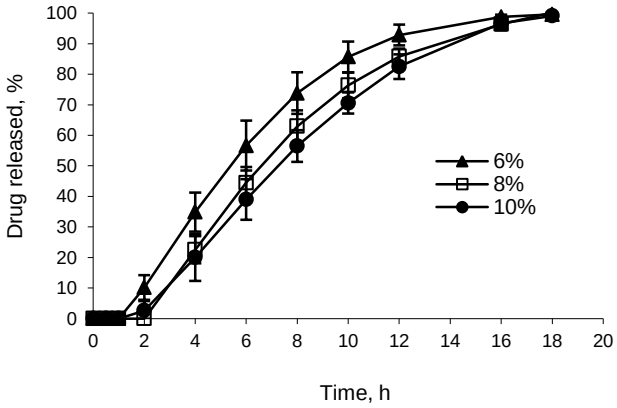

Fig. 23 Effect of the coating level on diprophylline release from coated tablets in 0.1 N HCl (drug 50% w/w, Avicel® 50% w/w, Kollicoat® SR:Eudragit® RL 70:30).

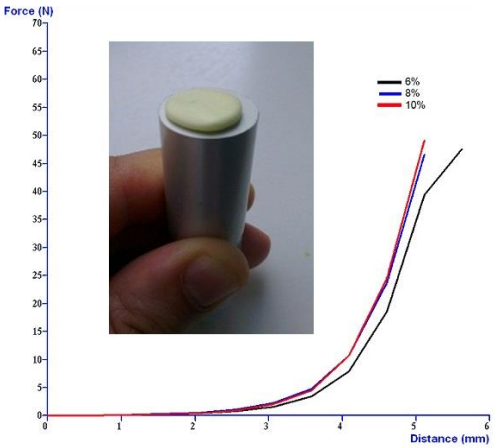

Fig. 24 Effect of the coating level on film's strength after 18 h in 0.1 N HCl (drug 50% w/w, Avicel® 50% w/w, Kollicoat® SR:Eudragit® RL 70:30).

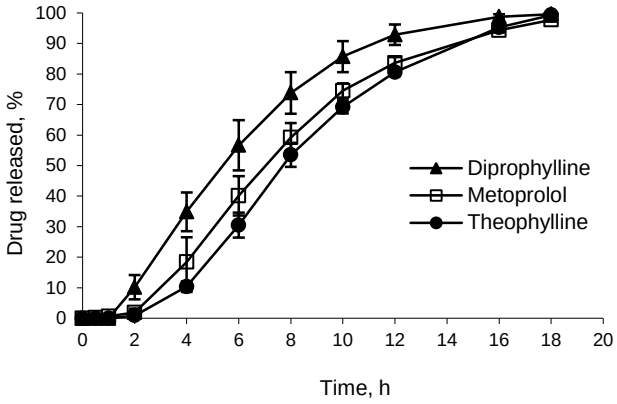

Fig. 25 Effect of the drug solubility on the release from coated tablets in 0.1 N HCl (drug 50% w/w, Avicel® 50% w/w, Kollicoat® SR:Eudragit® RL 70:30, cl 6% w/w).

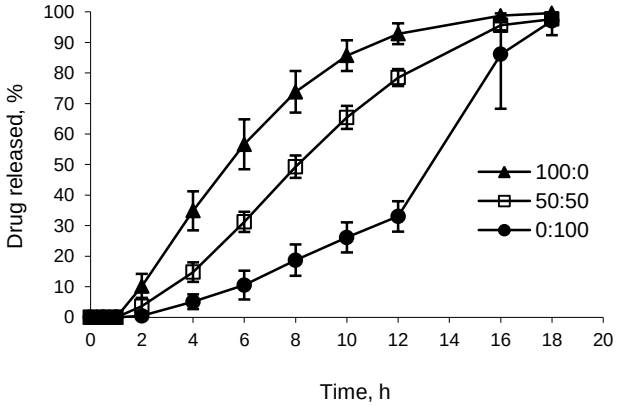

Fig. 26 Effect of the excipients (Avicel®:FlowLac®) on diprophylline release from coated tablets in 0.1 N HCl (drug 50% w/w, excipient 50% w/w, Kollicoat® SR:Eudragit® RL 70:30, cl 6% w/w).

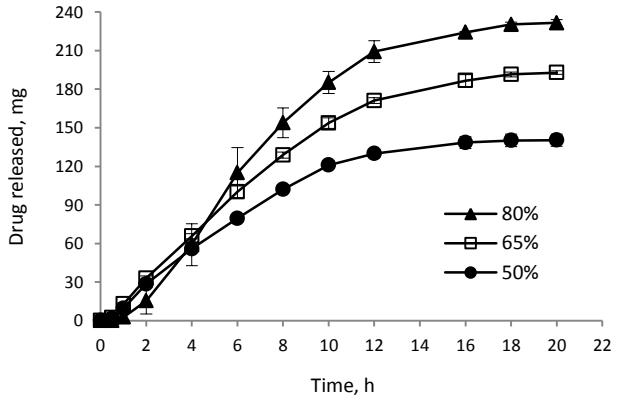

Fig. 27 Effect of the drug content on diprophylline release from coated tablets in 0.1 N HCl (Kollicoat® SR:Eudragit® RL 70:30, cl 10% w/w).

To study stability of the tablets, accelerated stability testing was performed for four weeks. Diprophylline release was decreased when the tablets stayed longer in the stability chamber (0, 1, 2, and 4) week(s) and the amount of undetected drug (depending on theoretical amount of diprophylline in each tablet, 125 mg) was 0, 9.6, 28.4, and 41.8%, respectively (**Fig. 28**). However, metoprolol release was unchanged when stored under same conditions for 7 days (**Fig. 29**). To investigate whether chemical interaction was reason for this, FTIR and DSC analysis were performed. No changes in the IR spectra were noticed (**Fig. 30**) and DSC analysis showed all the endothermic peaks at different time interval under accelerated storage conditions centered at 166 °C and remain unchanged (**Fig. 31**). These results confirmed that decreased drug release was not because of chemical interaction.

At low pH values, where the cellulose carboxyl groups are predominantly in their nonionized form, an increase in added ionic strength causes an increase in the amount of drug adsorbed by MCC (Franz and Peck, 1982). When lower HCl concentration (0.05 N) was used as a dissolution medium, 98.5% diprophylline was obtained from physical adsorption study. This result infers that physical interaction (adsorbing drug by MCC) was the reason for the decreased drug release. Drugs containing amine functionalities like ampicillin, amoxicillin and phenothiazine derivatives are prone to adsorption onto MCC through interaction with carboxyl groups (El-Samaligy et al., 1986; Okada et al., 1987).

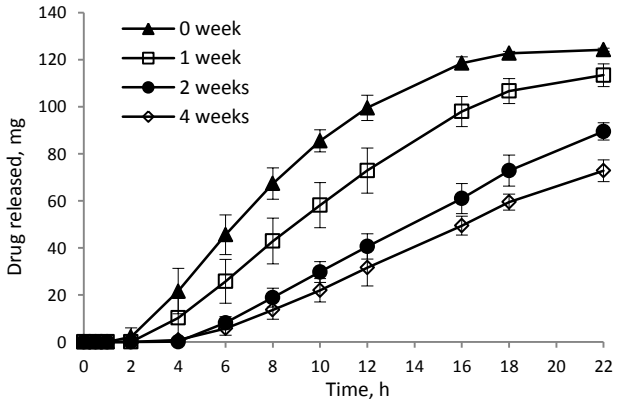

Fig. 28 Effect of the storage conditions on the diprophylline release from coated tablets in 0.1 N HCl (drug 50% w/w, Avicel® 50% w/w, Kollicoat® SR:Eudragit® RL 70:30, cl 10% w/w).

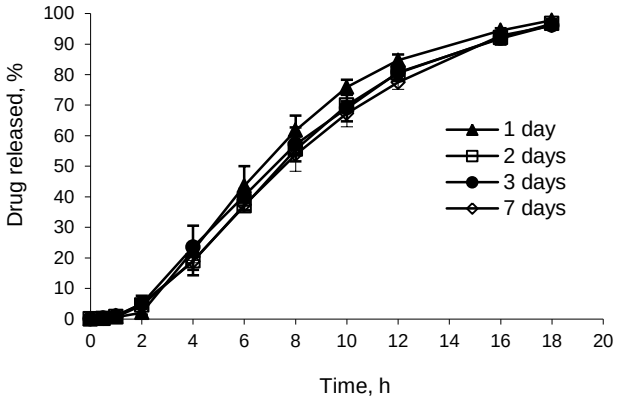

Fig. 29 Effect of the curing duration on metoprolol release from coated tablets in 0.1 N HCl (drug 50% w/w, Avicel® 50% w/w, Kollicoat® SR:Eudragit® RL 70:30, cl 6% w/w).

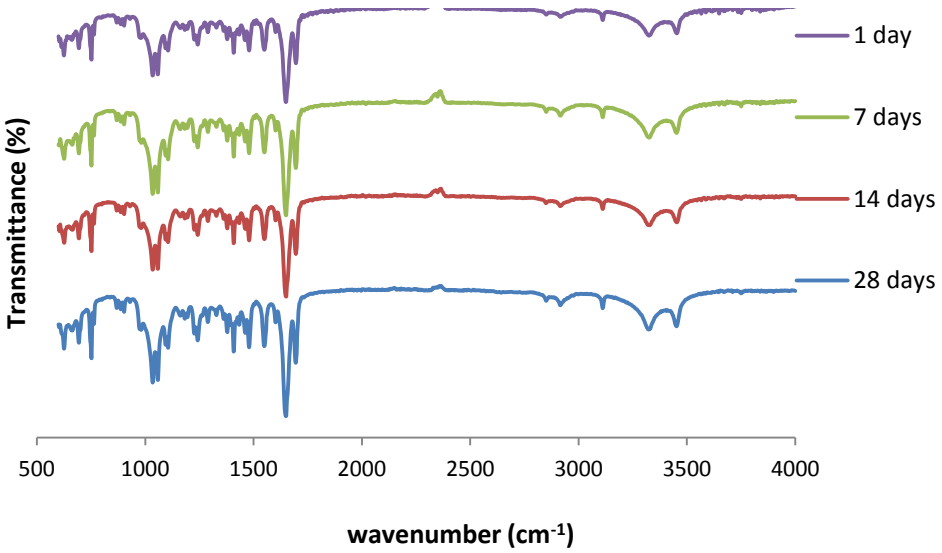

Fig. 30 IR spectra of ground tablets at different time interval (drug 50%, Avicel® PH 101 50%, 40 °C / 75% RH).

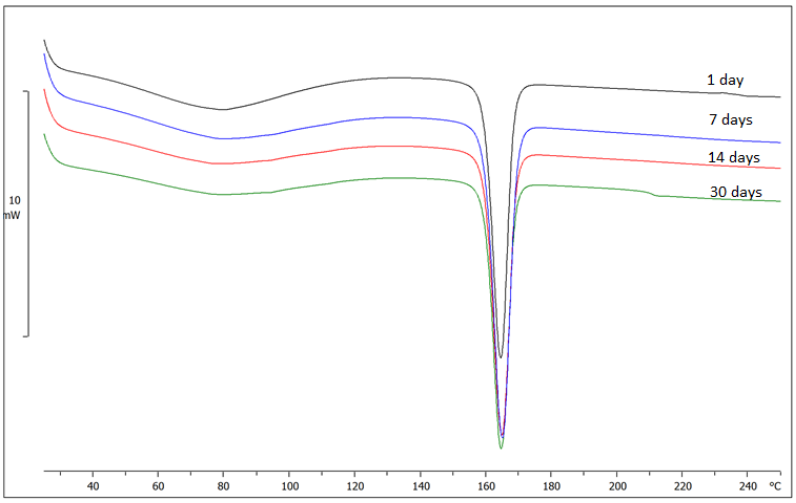

Fig. 31 DSC thermograms of tablets at different time interval (drug 50%, Avicel® PH 101 50%, 40 °C / 75% RH).

Conclusions

Controlled-release single-unit tablet were prepared by using Kollicoat® SR 30 D and Eudragit® RL 30 D blends as coating materials. Curing at 40 °C/ 75% RH was required for complete polymer coalescence. Drug releases was influenced by polymer blend ratio, buffer species, drug solubility, drug content, type of the excipient, and type of drug (MCC adsorbed diprophylline). However, ionic strength, agitation rate, and coating level showed no effect on drug release. Kollicoat® SR 30 D and Eudragit® RL 30 D is an interesting polymer blend. The film's flexibility and permeability of this blend make it suitable for controlled-release single-unit reservoir tablets.

3.3. Cellulose acetate butyrate as controlled-release polymer: Osmotic tablets

Background

The osmotic pump tablet is one of the most important dosage forms for orally controlled drug delivery (Liu and Wang, 2008). Although different types of oral osmotic systems were reported in the literature (Santus and Baker, 1995), in 1970s Theeuwes developed the simplest form of the osmotic device called elementary osmotic pump tablet (Theeuwes, 1975). This system utilizes osmotic pressure as driving the force for controlled delivery of drugs. In its simplest design, it consists of an osmotic core (containing the drug with or without an osmagent) coated with a semipermeable membrane having drilled orifice for drug delivery. Once this system encounters the GI fluids, the osmotically driven water enters the system through the semipermeable membrane, dissolves the soluble agents, and exits through the delivery orifice.

Cellulose acetate (CA) was one of the first materials used for manufacturing semipermeable membrane in elementary osmotic pumps developed by ALZA Corporation. In addition to CA, cellulose acetate butyrate CAB 171-15PG was used as semi-permeable film-forming materials (Shanbhag et al., 2007). Both CA and CAB 171-15PG are insoluble in water; hence, they were applied from organic solutions like acetone. The biggest disadvantages of this process are explosion and flammability hazards, as well as environmental considerations, and the high viscosity of polymer solutions.

CAB-553-0.4 exhibited good solubility in organic solvents, while being more hydrophobic than CA (Eastman, 2005). Hence, a permeable polymer like Eudragit® RL PO (Evonik, 2012), could increase the hydrophilicity of cellulose acetate butyrate polymer.

In this part, other polymers were identified for preparation of osmotic tablets, to overcome the limitation of CA (solubility in highly flammable organic solvent). Strong and alcohol-soluble polymers like CAB-553-0.4 or high molecular weight ethylcellulose (EC std. 100 premium) in a blend with Eudragit® RL PO as permeable polymer was used as a coating material.

Results and discussion

Cellulose acetate is one of the most suitable membranes for osmotic drug-delivery systems due to its mechanical strength and semipermeable property. Osmotic tablets are coated using film coating spray equipment mainly with organic solvents such as acetone and methyl acetate. These solvents are flammable and are used only with good ventilation. In this study, osmotic tablets were prepared using other polymers like CAB:Eudragit® RL PO or ethylcellulose: Eudragit® RL PO that are soluble in a safer organic solvent like ethanol.

Effect of polymer blends ratios 40:60, 50:50, and 60:40 of CAB:Eudragit® RL PO on caffeine release in 0.1 N HCl is shown in (**Fig. 32**). With increased Eudragit® RL PO content (40, 50 and 60% w/w), lag times (which represents the time required for film hydration and starting drug release) were shorter, and caffeine release was faster. This is due to high-permeability property of Eudragit® RL, which might increase water penetration through the coat. **Fig. 33** shows the effect of CAB:Eudragit® RL PO ratio on the film medium uptake and dry mass loss. Film's medium uptake was increased with increased Eudragit® RL ratio correspondingly and with increased medium uptake, dry mass loss was increased due to increased plasticizer dissolution.

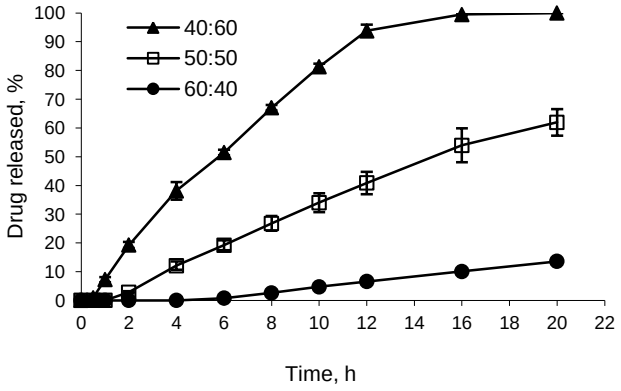

Fig. 32 Effect of CAB:Eudragit® RL PO ratio on the caffeine release in phosphate buffer pH 6.8 (cl 10% w/w).

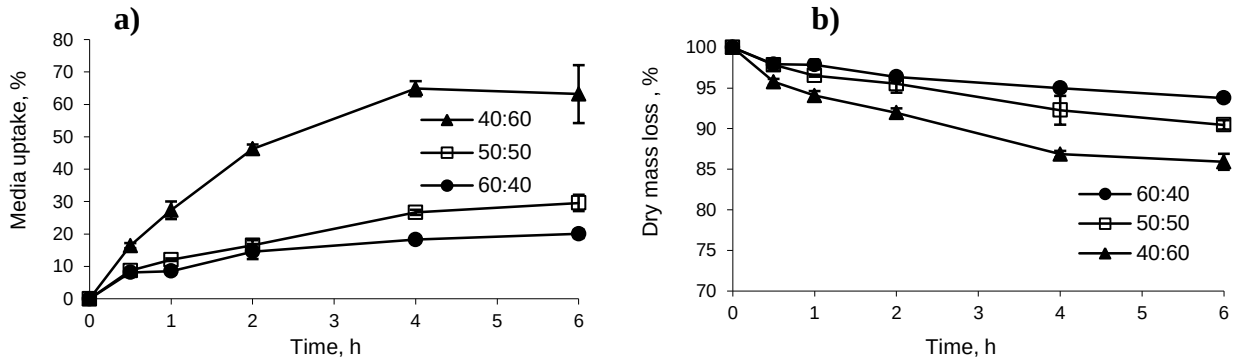

Fig. 33 Effect of CAB:Eudragit® RL PO ratio on film **a)** media uptake in 0.1 N HCl, and **b)** dry mass loss (TEC 20% w/w).

Although ethylcellulose is not water soluble, it shows some physical interaction with water, therefore, defining ethylcellulose as a relatively hydrophobic polymer (Agrawal et al., 2003). To investigate the suitability of polymers as a coating material for osmotic tablets, high molecular weight ethylcellulose (EC 100 cp) was compared to cellulose acetate butyrate (**Fig. 34**). The lag time was longer and caffeine release rate was slower when ethylcellulose replaced cellulose acetate butyrate (Fig. 34a), due to hydrophilicity difference between these polymers. The media uptake study (Fig. 34b) shows that cellulose acetate butyrate film is more hydrophilic than ethylcellulose film (Eudragit® RL ratio was constant 60% w/w) as the media uptake was 65% and 20% w/w during 4 h incubation in 0.1N HCl, respectively.

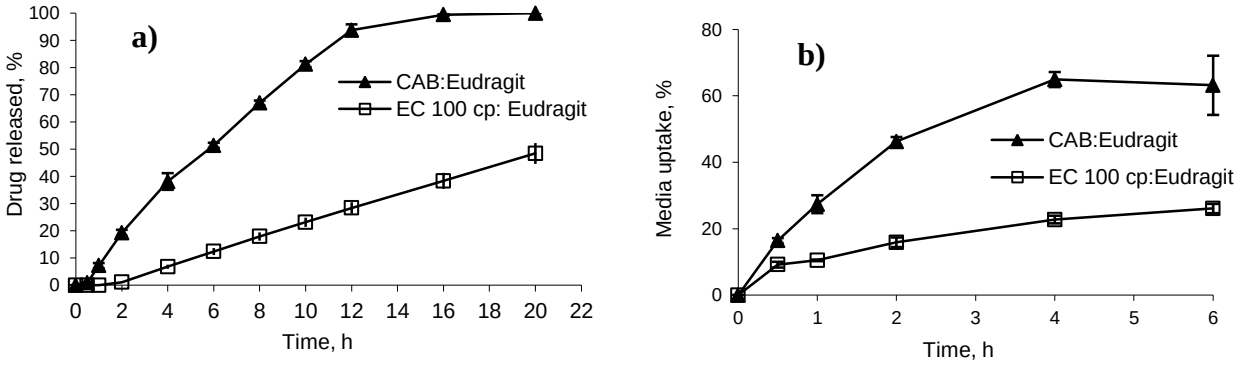

Fig. 34 Effect of type of polymer blends (40:60) on **a)** caffeine release in phosphate buffer pH 6.8 (cl 10% w/w) and **b)** film medium uptake in 0.1 N HCl.

Mechanical properties of the films were measured keeping Eudragit® RL PO ratio constant (60% w/w). In the wet state, the film tensile strength was 16.9 N/cm^2 and 3.6 N/cm^2, and elongation percent was 86.4% and 15.7% for CAB:Eudragit® RL and ethylcellulose:Eudragit® RL, respectively. Cellulose acetate butyrate is stronger and more flexible than high molecular weight ethylcellulose (EC std. 100) in dry and wet states (**Table 3**).

Table 3 Effect of type of polymer blends on the film tensile strength and elongation at break, (film thickness 0.24 ± 0.03 mm*, 20% TEC

Polymer blend (40:60)	State	Tensile strength* N/cm^2	Elongation* %
CAB:Eudragit® RL	Dry	29.77	42.99
	Wet	16.92	86.44
EC:Eudragit® RL	Dry	7.28	17.35
	Wet	3.62	15.71

* S.D. was less than 5%

To study the mechanism of drug release, the release was conducted in the medium of different osmotic pressure (sucrose was added into the dissolution medium). The lag time was longer and caffeine release was decreased with increased sucrose concentration (**Fig. 35**). This finding confirms that osmotic pumping is the mechanism, which governs the drug release.

The kinetics of osmotic drug release are directly related to the solubility of the drug within the core and osmotic pressure of the core (McClelland et al., 1991). **Fig. 36** shows effect of drug solubility on the release profile and rate from the osmotic tablets. With increased drug solubility {carbamazepine 0.13 mg/mL (Wyttenbach et al., 2007), theophylline 13.9 mg/mL (Lentz et al., 2002), caffeine 21.45 mg/mL (Wyttenbach et al., 2007) and propranolol HCl 130 mg/mL (Takka et al., 2001)} the drug release was faster (Fig. 36a). Because the release rate inside the osmotic tablet depends on the solubility of the solutes. The release rate of caffeine and theophylline was approximately constant (Fig. 36b), and both fitted well into zero-order kinetics (R^2 = 0.982 and 0.988, respectively). Zentner et al previously published similar results; Drugs with a solubility of ≤ 50 mg/mL would be released with ≥ 95% zero-order kinetics (Zentner et al., 1991).

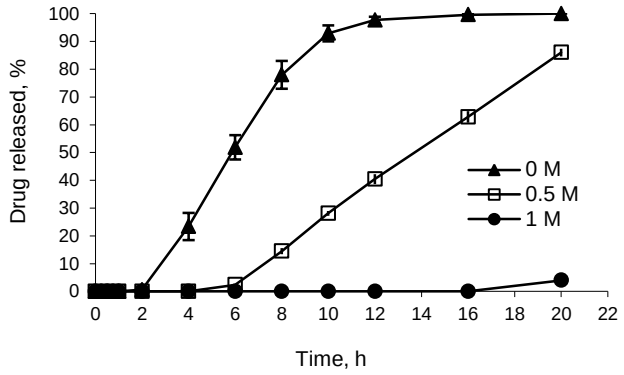

Fig. 35 Effect of sucrose concentrations on the caffeine release in distilled water (CAB:Eudragit® RL 40:60, cl 10% w/w).

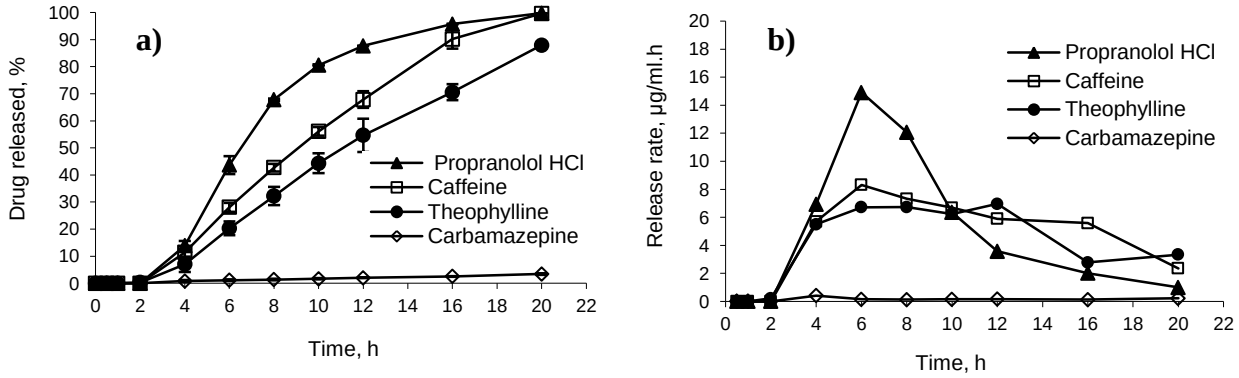

Fig. 36 Effect of drug solubility on **a)** release profile and **b)** release rate, in phosphate buffer pH 6.8 (CAB:Eudragit® RL 40:60, cl 30%w/w).

In order to study the effect of pH on drug release, releases of the tablets were conducted in different pH media; the lag time (2 h) and drug release rates (5.8%/h) in 0.1 N HCl and phosphate buffer pH 6.8 was similar. In acetate buffer pH 4.5, the lag time was shorter (0.5 h) and caffeine release was faster (10.7%/h), as shown in (**Fig. 37**). This is due to exchange of chloride counter ion of the cationic quaternary ammonium group of Eudragit® RL to anionic acetate group, which affects film hydration (Bodmeier et al., 1996).

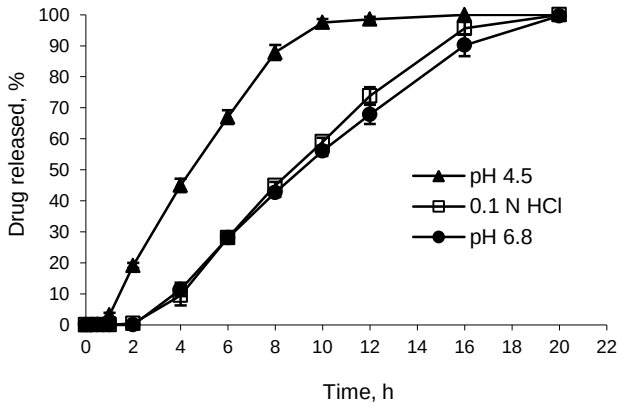

Fig. 37 Effect of pH of the release medium on caffeine release (CAB:Eudragit® RL 40:60, cl 30% w/w).

Plasticizer is used to improve the membrane physical properties (Bindschaedler et al., 1987). Liu et al. found that hydrophilic plasticizer (PEG-200) increases the drug release (Liu et al., 1999). At higher plasticizer content (10% and 20%) w/w, caffeine release was faster, and the tablet rupture force was lower (30 N and 13 N, respectively) (**Fig. 38**). This is probably because of leaching out of the plasticizer, which leaves pores and makes the film weaker.

The drug release kinetics from osmotic tablets were modulated by varying the membrane thickness (Liu et al., 2000; Ramakrishna and Mishra, 2002) or composition (Liu and Wang, 2008). **Fig. 39** illustrates the effect of increasing coating level (10%, 20%, and 30% w/w) of CAB:Eudragit® RL (40:60) on caffeine release and rupture force. As coating level increased, the lag times were increased, and the drug releases were decreased (t_{80} was 10, 12, and 14) h, respectively (Fig. 39a). This is due to increased film thickness, which requires longer time for hydration. Moreover, the increased coating level increased the tablets coat rupture force (4 N, 10.5 N, and 13.3 N, respectively) (Fig. 39b). Kamba et al. confirmed that the mechanical destructive force in the human's stomach under fed conditions is 1.9 N, and 1.5 N under fasting condition (Kamba et al., 2000). The rupture force of the osmotic tablet was higher than the gastric destructive force (2, 5, and 7 times, respectively). *In vitro* test showed that the osmotic tablet was mechanically strong enough to withstand the gastric destructive force.

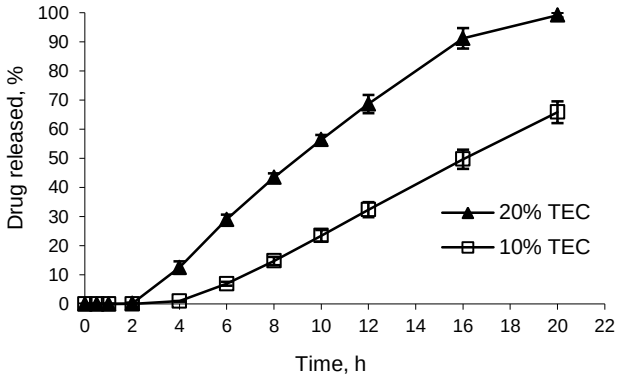

Fig. 38 Effect of plasticizer content on caffeine release in phosphate buffer pH 6.8 (CAB:Eudragit® RL 40:60, cl 30% w/w).

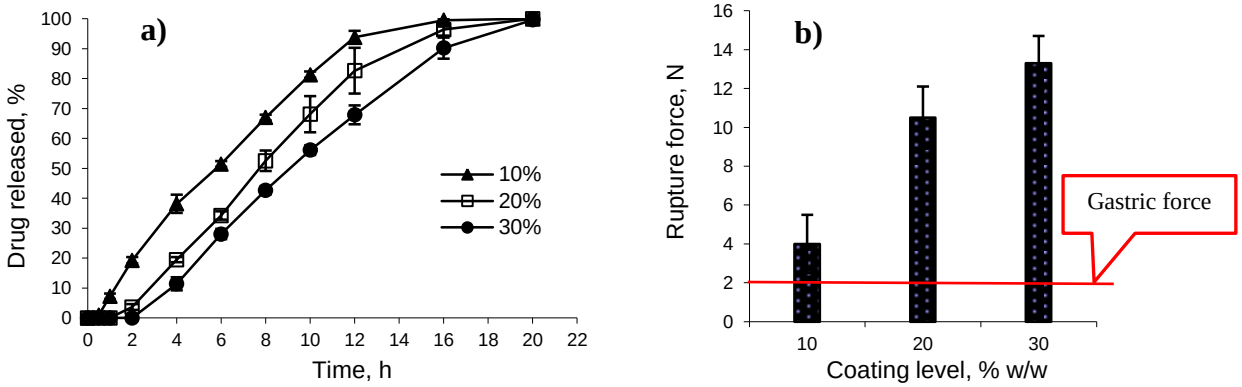

Fig. 39 Effect of coating level on **a)** caffeine release in phosphate buffer pH 6.8 and **b)** mechanical rupture force (CAB:Eudragit® RL 40:60).

The release studies from osmotic tablets were carried at various agitation rates (50 rpm to 150 rpm). Similar to previous reports (Makhija and Vavia, 2003), the release profile of caffeine was independent of the agitation rate of the release media (**Fig. 40**), and hence it can be expected that the release will be independent on the hydrodynamic conditions of the GI tract.

In addition, increased core drug content from 30% to 70% had no influence on the caffeine release (**Fig. 41**). 50 mg caffeine was released within 13 h for each drug content (Fig. 41a). Therefore, at a higher drug content, a longer time was needed for complete drug release (Fig. 41b).

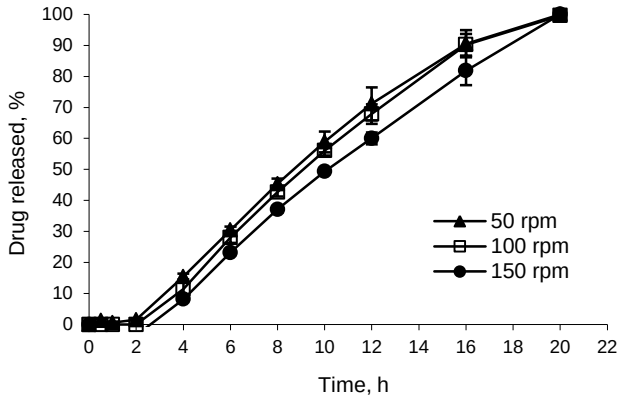

Fig. 40 Effect of agitation rate on caffeine release in phosphate buffer pH 6.8 (CAB:Eudragit® RL 40:60, cl 30% w/w).

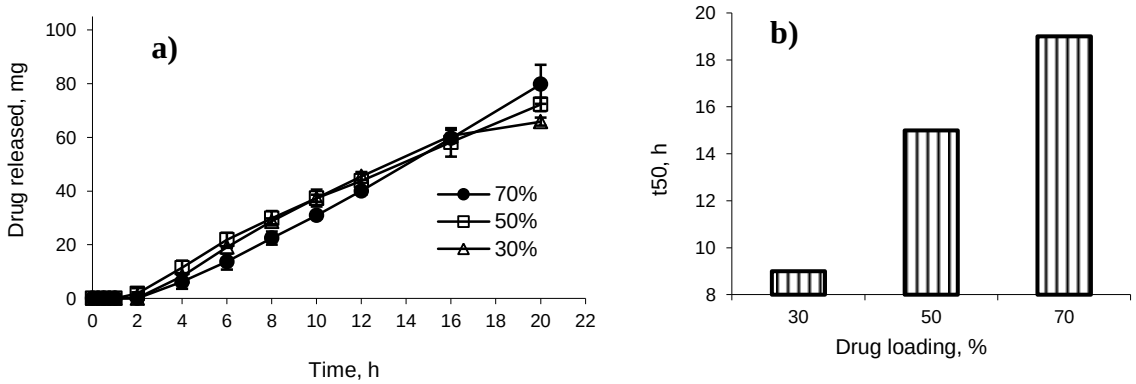

Fig. 41 Effect of drug content on **a)** release rate in phosphate buffer pH 6.8 and **b)** time for 50% caffeine release (CAB:Eudragit® RL 40:60, cl 30% w/w).

In order to investigate the effect of the delivery orifice, the release profile from drilled and un-drilled osmotic tablet were compared (**Fig. 42**). No significant change in drug release profile was observed ($f_2 > 50$) (Fig. 42a). Swelling of the un-drilled tablets was noticed and visual inspection showed a small crack at the edge of the tablets (Fig. 42b). This is due to increased hydrostatic pressure inside the tablet, which caused the drug release from un-drilled tablets. The drilled tablet did not show any swelling and crack.

The tablets were submitted to accelerated stability test. Samples were maintained for 3 months in an accelerated stability chamber at 40 ± 2 °C and 75 ± 5% relative humidity. The result (**Fig. 43**) showed no change in the drug release. These results infer stability of the CAB:Eudragit® RL PO blends as coating materials.

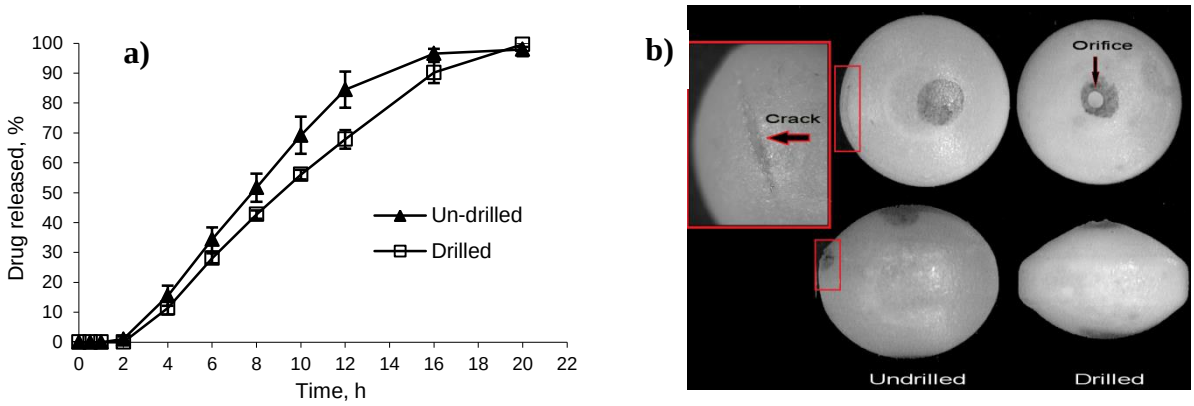

Fig. 42 Effect of delivery orifice on **a)** caffeine release and **b)** coat crack in phosphate buffer pH 6.8 (CAB:Eudragit® RL 40:60, cl 30% w/w).

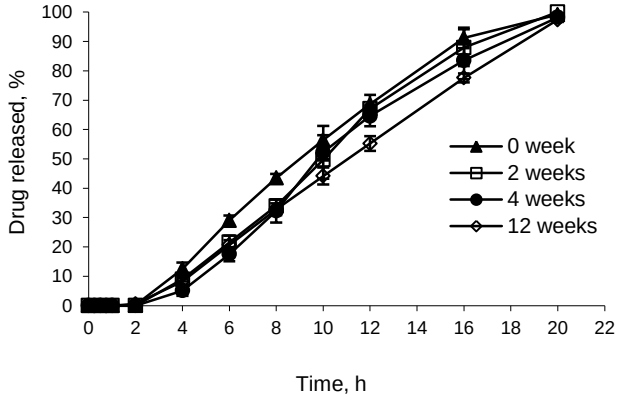

Fig. 43 Effect of the storage conditions on the caffeine release in phosphate buffer pH 6.8 (CAB:Eudragit® RL 40:60, cl 30% w/w).

Conclusions

Cellulose acetate butyrate:Eudragit® RL PO blend is an interesting combination that characterized by its strength and permeability, and these makes it suitable for osmotic tablet preparation. CAB-553-0.4 is stronger, more flexible, and more permeable than high molecular weight ethylcellulose (EC std. 100). Drug release from the osmotic tablet system was determined to be robust to varying conditions like core drug load, coating level (rate was constant), agitation rate, and storage conditions. *In vitro* study showed that the elementary osmotic tablets were strong enough and may withstand the gastric destructive force.

3.4. Cellulose acetate butyrate as controlled-release polymer: Multiparticulates

Background

Multi-unit pellet systems have gained much attention in the last two decades, due to their flexibility during formulation development and numerous advantages over single-unit dosage forms. When taken orally, multiparticulates disperse in the GI tract, maximizing absorption, minimizing side effects, reduce the inter- and intra-patient variability (Ghebre-Sellassie, 1994) and avoid the risk of local irritation (Bechgaard and Gyda, 1978). Furthermore, the all-or-nothing effect can be circumvented, and the variability of the gastric emptying time is less (Digenis, 1990; Karrout et al., 2009).

Drug release from pharmaceutical dosage forms could be controlled by polymeric film coating. Several types of polymers like methacrylic acid copolymer, polyvinyl acetate, and ethylcellulose were applied as coating films to pellets from organic solutions or aqueous dispersions (Bodmeier et al., 1996; Dashevsky et al., 2010; Heinicke and Schwartz, 2007)

The objective of this work was to use cellulose acetate butyrate (CAB-553-0.4) as a novel film-forming polymer for preparing controlled-release pellet dosage form and to characterize factors, which may affect the drug release.

Results and discussion

There are many reasons for applying film coatings to pellets, like modifying drug release, taste masking, improving stability, elegancy, and improving mechanical integrity. The vast majority of the polymers used in film coating are either cellulose derivatives, such as the cellulose ethers, or acrylic polymers and copolymers (Cole et al., 1995). Cellulose acetate butyrate-553-0.4 is a member of series Eastman cellulose acetate butyrate, which characterized by high-tensile strength, and alcohol solubility.

The diprophylline release from cellulose acetate butyrate coated pellets in pH 6.8 phosphate buffer decreased and lag time increased with increased coating level (5%, 10% and 15%, w/w). The short lag time was probably caused by the time required for the dissolution medium to diffuse through the coating and for the drug concentration gradient across film coating to be

established. The drug release time (t_{50}) of coated pellets with MCC and NP starter core was 6 h, 12 h and 18 h and 4 h, 6 h and 8 h, respectively (**Fig. 44**). The combined osmotic activity of the sucrose core and the highly soluble drug apparently caused a higher water uptake compared to insoluble MCC starter cores. The resulting stronger hydrostatic pressure led to more and larger cracks in the cellulose acetate butyrate coating, thus increasing the drug release from NP pellets. Drug release seems to be predominantly controlled by the polymeric membrane barrier and the starter core.

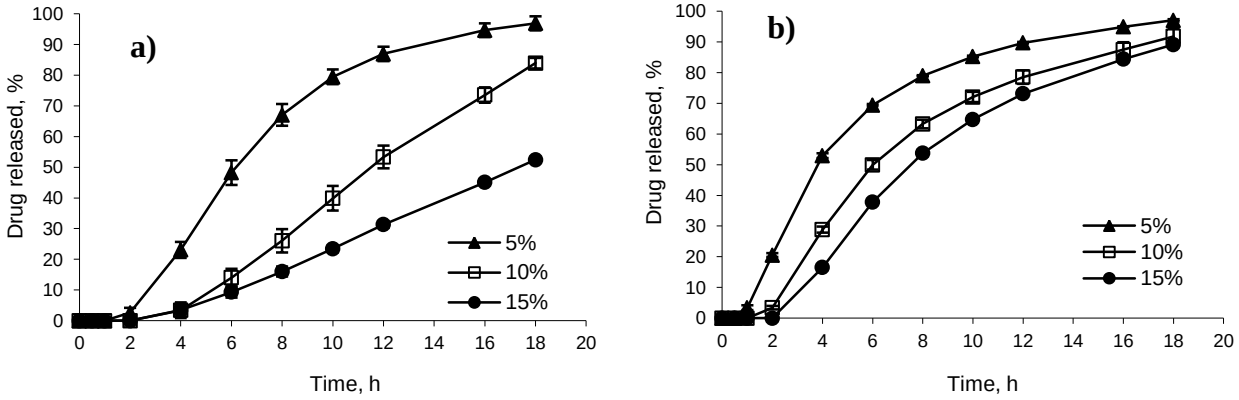

Fig. 44 Effect of coating level on diprophylline release in PBS from coated pellets: **a)** starter core-MCC 780 µm and **b)** starter core-NP 710-850 µm.

It is desirable to obtain pH-independent drug release with extended release dosage forms, The release of diprophylline from cellulose acetate butyrate coated pellets was independent of pH of the release medium (**Fig. 45**). Cellulose acetate butyrate is thus not sensitive to the pH of the release medium.

For the majority of coated dosage forms, an increase in drug solubility is reflected by a faster release and shorter lag times (Ragnarsson et al., 1992; Kim, 1999). Effect of drug solubility on the release from cellulose acetate butyrate coated pellets is shown in **Fig. 46**, the release of diprophylline was faster than caffeine, and carbamazepine release was negligible. This was usually attributed to steeper diffusion gradients and increased osmotic pressure, which resulted in higher tensile stress on the coating and finally higher permeability, e.g. by film thinning and potential formation of micro-cracks in the coating (Ragnarsson et al., 1992; Schultz and Kleinebudde, 1997; Heinicke and Schwartz, 2007).

Pore-formers are often added to the coating formulations to adjust the drug release of extended-release coatings. During the dissolution, these pore-formers leach out of the coat, making the membrane more permeable and increasing the drug release. HPC was used as a pore-former to enhance the release of water-insoluble carbamazepine. Carbamazepine release was increased with increased HPC content (20%, 30%, and 40%, w/w) (**Fig. 47**).

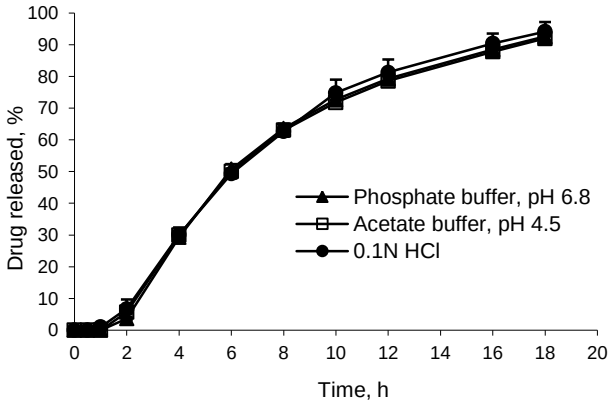

Fig. 45 Effect of pH of the release medium on diprophylline release from coated pellets (cl 10% w/w, starter core NP 710-850 µm).

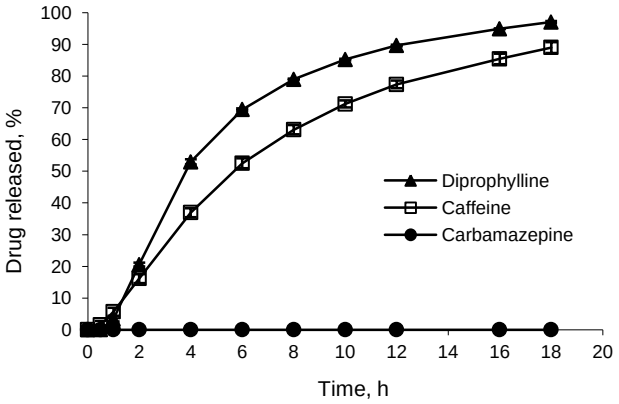

Fig. 46 Effect of the drug solubility on the release in PBS (cl 5% w/w, starter core NP 710-850 µm).

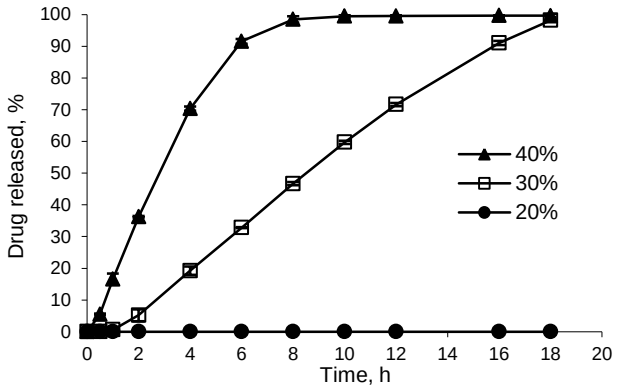

Fig. 47 Effect of the pore-former (HPC) on carbamazepine release in PBS (cl 5% w/w, starter core NP 710-850 µm).

A faster release at higher drug loadings of highly soluble propranolol hydrochloride was reported (Rekhi et al., 1995). Similarly, with increased drug loading (15% - 45%, w/w), diprophylline release was increased (**Fig. 48**). Probably, this was due to the more pronounced swelling, which resulted in higher tensile stress acting on the coating (stated above) or the increases in drug loading inevitably lead to higher amounts of binder inside the pellets, which caused more swelling (Katrin, 2011).

The diprophylline release from compressed pellets (50% w/w pellets and 50% MCC) coated with cellulose acetate butyrate was started immediately (no lag time), and the drug release was faster than from the original pellets irrespective to the type of starter cores (**Fig. 49**). The drug release from uncompressed and pellets compressed at 10 kN was 3.5%/h and 5.1%/h, and 5.4%/h and 5.7%/h when MCC and NP were used as a starter core. Despite increasing the release rate (due to damage to the coated pellets during compression), the pellets did not lose the extended release properties (t_{80} was 14 h and 10 h, respectively). This could be regarded as an advantage of cellulose acetate butyrate over ethylcellulose, which is widely used for controlled-release dosage forms (Tarvainen et al., 2003) but easily ruptured under compression, leading to the loss of the extended release properties (Dashevsky et al., 2004a). Moreover, increased compression force from 10 kN to 20 kN had no impact on drug release regardless of the type of starter core.

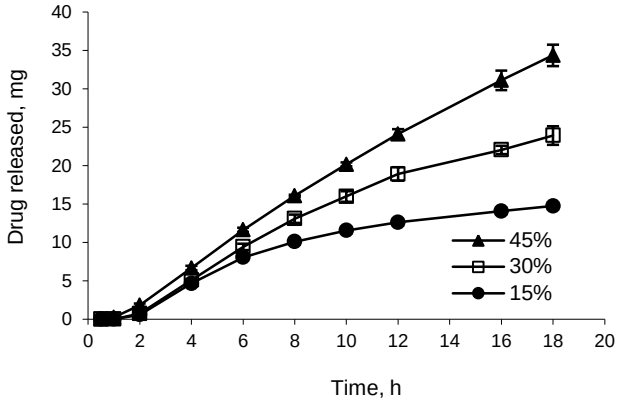

Fig. 48 Effect of the drug loading on diprophylline release in PBS from coated pellets (cl 10% w/w, starter core NP 710-850 µm).

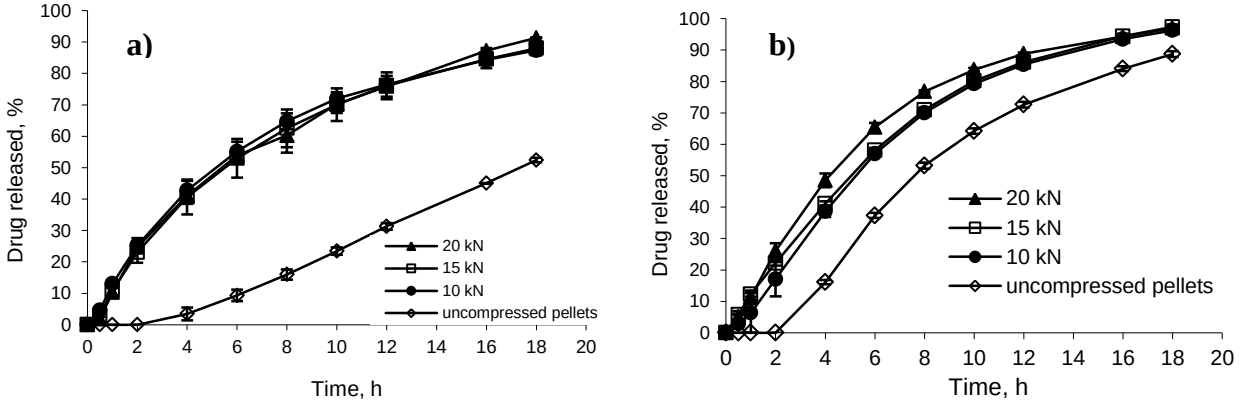

Fig. 49 Effect of the compression force on the diprophylline release from tableted pellets in PBS (cl 15% w/w, pellet content 50% w/w, Avicel® PH 200 50% w/w, starter core **a)** MCC 780 µm and **b)** NP 710-850 µm).

On the other hand, increased pellets content (50% - 70%, w/w) of the tableted pellets had no influence on the drug release irrespective to type and size of starter core (the drug release was faster from pellets made of smaller starter core, due to increased surface area, i.e. thinner the film coat) (**Fig. 50**); however, the tablets strength decreased.

One drawback of aqueous coatings is the further gradual coalescence of the polymer particles during storage, which leads to denser films and potentially decreasing release rates over time (Wu and McGinity, 2000). In contrast, organically coated drug-delivery systems are mostly considered storage stable (Kranz and Gutsche, 2009). Effect of storage conditions on

diprophylline release from cellulose acetate butyrate coated pellets is illustrated in **Fig. 51**. Drug release was unchanged for 12 weeks under stress condition (40 °C/ 75% RH).

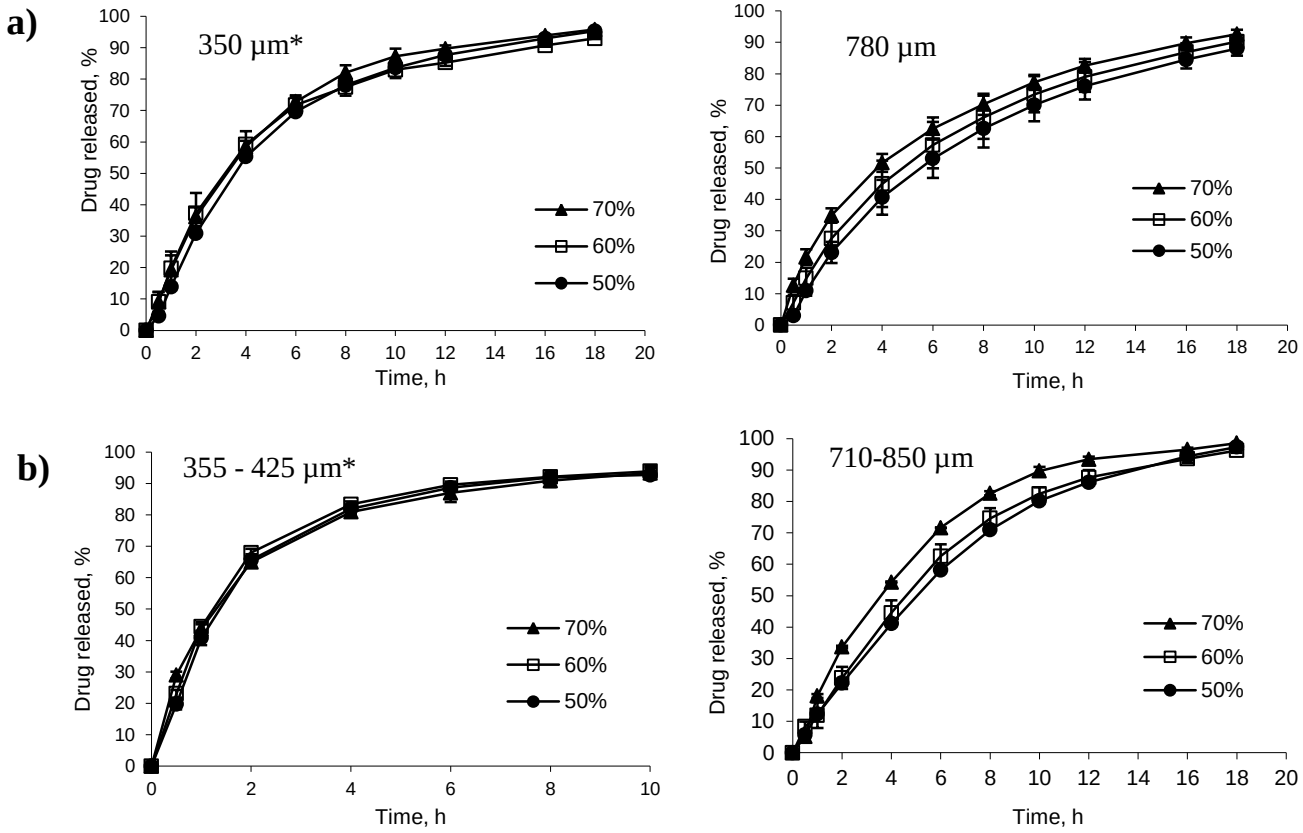

Fig. 50 Effect of the pellet's content and size of the starter core on the diprophylline release from tableted pellets in PBS (cl 15% w/w, compression force 15 kN, starter core **a)** MCC and **b)** NP).
*compression force 10 kN

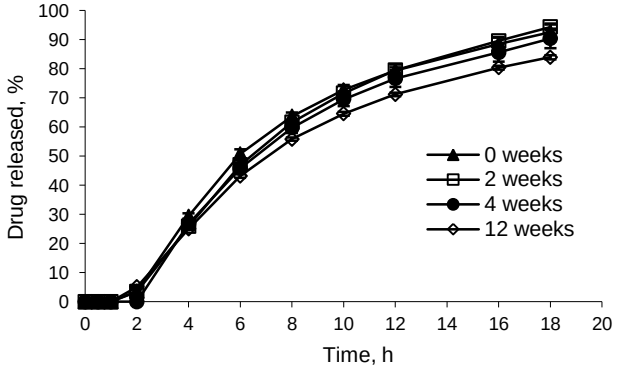

Fig. 51 Effect of the storage conditions on diprophylline release in PBS from coated pellets (cl 10% w/w, starter core NP 710-850 µm).

Conclusions

Cellulose acetate butyrate coated pellets showed stable release profile and no pH effect. The drug release could be easily modified by adjusting coating level, addition of water-soluble pore-former and selecting a different type of starter core. Pellets could be tableted, and the film coat was strong enough to keep the extended release properties. Cellulose acetate butyrate (CAB-553-0.4) could be a promising polymer for film coating of pellet dosage forms.

3.5. Increase tablettability of pellets through Eudragit® RL top coating

Background

Pellets can be administered orally either filled into hard capsules or compressed into rapidly disintegrating tablets. The major challenge during compression of coated pellets is the stress, which can rupture the coating and hence change the release characteristics of the formulations (Altaf et al., 1998). Ideally, the compacted pellets should not fuse into a non-disintegrating matrix during compaction and should disintegrate rapidly into individual pellets in GI fluids. Dashevsky et al. reported a slower drug release from tableted pellets due to retardation of tablet disintegration (Dashevsky et al., 2004a).

Several types of polymers like methacrylic acid copolymer, polyvinyl acetate, and ethylcellulose were applied as organic solutions or aqueous dispersions to coat pellets (Bodmeier et al., 1996; Dashevsky et al., 2010; Heinicke and Schwartz, 2007). Due to their flexibility, acrylic polymers are more suitable for compression of coated pellets (Bodmeier and Paeratakul, 1994a) rather than ethylcellulose. Pellets coated with acrylic polymers were compressed without damage to the coating (Lehmann et al., 1993). However, the drug release from compressed pellets coated with the aqueous ethylcellulose dispersion was much faster when compared to the release of the uncompressed pellets (Bansal et al., 1993). Standard tableting excipients (microcrystalline cellulose, lactose, or sorbitol) were layered on ethylcellulose-coated pellets to form a cushion layer in order to protect the integrity of the brittle ethylcellulose coating during compression (Hosseini et al., 2013).

One of the important parameters, which characterizes whether the tablet is sufficiently strong is the tensile strength. This is the maximum tensile stress that can be tolerated in the tablet before it breaks. Various inert excipients have to be used to assist the compaction process and to prevent the rupture and damage of the coated pellets. Theoretically, 29% of excipients are needed to fill the void space between densely packed spheres. The excipients should result in hard and rapidly disintegrating tablets at low compression forces and should not affect the drug release (Bodmeier, 1997). The hardness of compacts decreased with increasing amounts of pellets (Beckert, 1995) and the maximum content of pellets that give tablets, which are strong enough, was found to be 40% w/w (Lundqvist and Podczeck, 1997).

The objective of this study was to prepare a hard tablet with high pellet content (70% w/w coated pellets and 30% w/w microcrystalline cellulose) at low-compression force (5 kN). For this purpose, Eudragit® RL was used as a top-coating polymer due to its permeability and flexibility.

Results and discussion

During tableting of coated pellets, the major challenge is the risk of losing the extended release properties of the original pellets due to fractures in the functional polymer coating (Dashevsky et al., 2004a). As pellets' content increased; the amount of drug releases also increased, indicating higher proportion of damaged pellets and high friability of the tablets (Beckert, 1995). Accordingly, Eudragit® RL (5% w/w) was used as a top-coating polymer to prepare tablets with sufficient strength out of 70% w/w loaded pellets at low compression force (5 kN).

Effect of increased compression force (5 kN - 15 kN) on the release from tableted-pellets, which were coated with cellulose acetate butyrate and ethylcellulose organic solutions, and tablet's tensile strength is shown in **Fig. 52**. The diprophylline release from tableted pellets increased as the compression force increased (Fig. 52a and b), which indicated more damage to the coated pellets with increasing compression force. In addition, tablet strength increased with increased compression force (Fig. 52c); however, tablets made of cellulose acetate butyrate-coated pellets were two times stronger than tablets made of ethylcellulose-coated pellets at any compression force, despite the lower coating level of the former (15% and 20% w/w, respectively). This is probably due to the differences in the mechanical properties between these polymers (former is stronger and more flexible than later) (section 3.3).

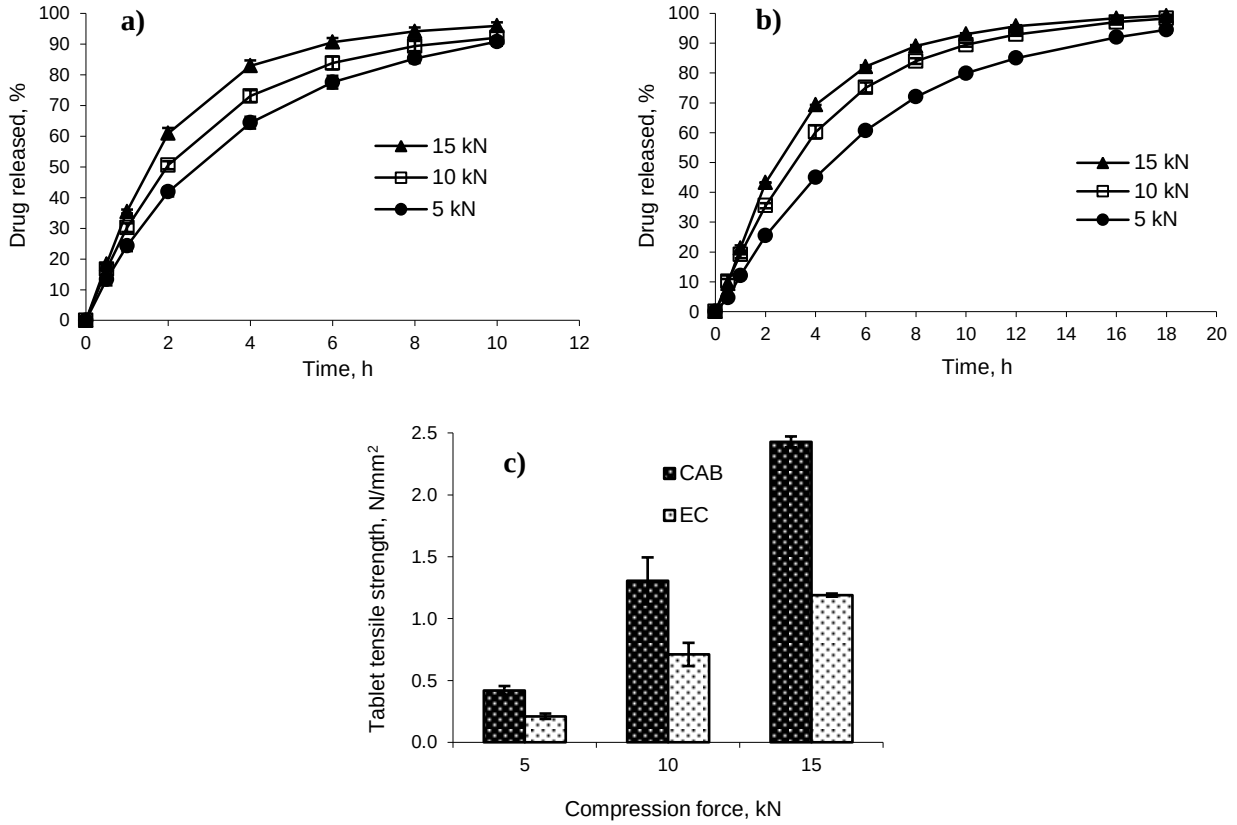

Fig. 52 Effect of compression force on diprophylline release in PBS from tableted pellets **a)** CAB coated pellets and **b)** EC-coated pellets, and **c)** tablet tensile strength (pellets content 70% w/w).

To study the effect of Eudragit® RL top-coat on the release from tableted pellets and tablet's strength, three extended-release polymers (Kollicoat® SR 30 D, cellulose acetate butyrate, and ethylcellulose), and two delay-release polymers (Eudragit® L, and HPMCP) were used as coating materials.

Irrespective to the type of extended release polymers, the release from Eudragit® RL top-coated pellets was similar to the release from Eudragit® RL top-uncoated pellets (**Fig. 53**). Diprophylline release from coated pellets with extended-release polymer was in order of Kollicoat® SR> cellulose acetate butyrate > ethylcellulose coated pellet, due to the permeability difference between these polymers. In case of Kollicoat® SR, the water-soluble ingredients (2.7% polyvinylpyrrolidon and 0.3% SLS) dissolve and then leach out the coat causing the fastest release among these polymers, while cellulose acetate butyrate is more hydrophilic than ethylcellulose (section 3.3). The release rates from tableted pellets (70% w/w at 5 kN) compared to un-tableted pellets were unchanged or slightly increased; moreover, the extended release

properties of the formulations were maintained (**Fig. 53**). For enteric-coated pellets, approximately 50% diprophylline was release from tableted Eudragit® L and HPMCP coated pellets within 2 h in 0.1 N HCl due to the brittleness of the polymers and the coating rupture during the compression. However, the drug release was decreased when Eudragit® RL top-coat was applied to pellets prior to compression (20% and 30% respectively) (**Fig. 54**). This is probably due to the total increased coating level of the pellets and the flexibility of Eudragit® RL top-coat (with 20% TEC) which helps to accommodate the pressure and decrease the coat rupture during compression.

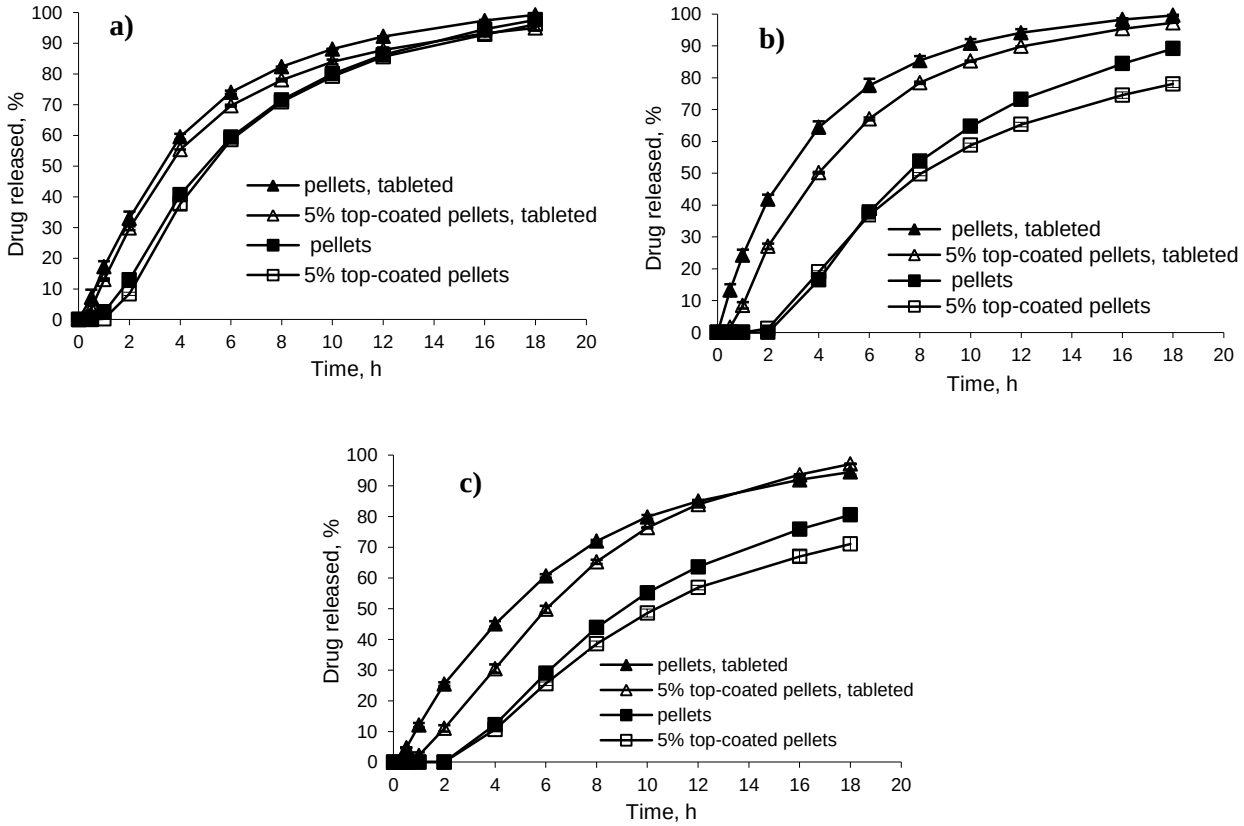

Fig. 53 Effect of Eudragit® RL top-coat on the diprophylline release from tableted and un-tableted pellets in PBS: **a)** Kollicoat® SR cl 20%, **b)** cellulose acetate butyrate cl 15% and **c)** ethylcellulose cl 20% (pellets content 70% w/w, compression force 5 kN).

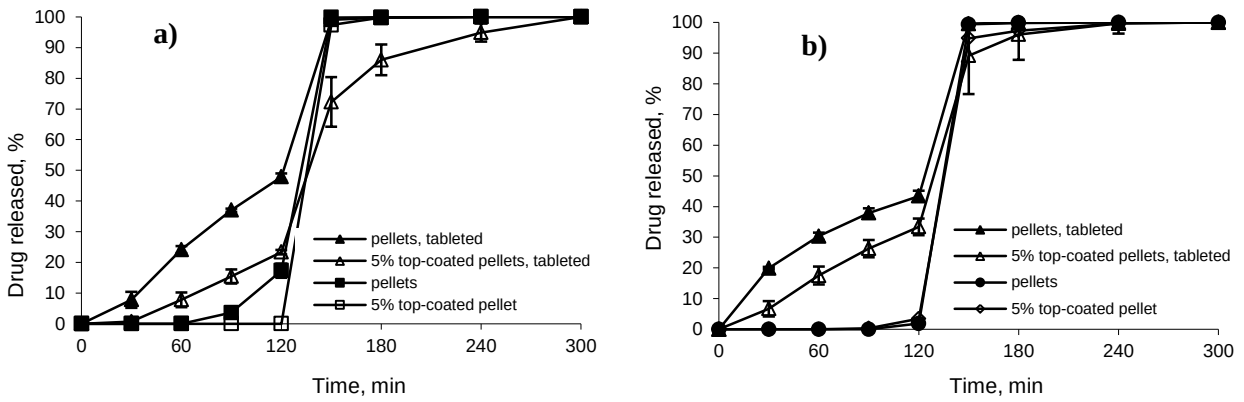

Fig. 54 Effect of Eudragit® RL top-coat on the diprophylline release from tableted and un-tableted pellets in 0.1 N HCl (2 h) followed by PBS: **a)** Eudragit® L cl 20% and **b)** HPMCP cl 20% (pellets content 70% w/w, compression force 5 kN).

Fig. 55 shows the effect of Eudragit® RL top-coat on tablets' strength. The tablets' hardness of ethylcellulose, HPMCP, cellulose acetate butyrate, Eudragit® L, and Kollicoat® SR coated pellets which were top-coated with Eudragit® RL was 74, 70, 70, 89, and 91 N, and when compared to tablets made with Eudragit® RL top-uncoated pellets, the tablets' strength was increased (390, 235, 136, 77, and 8%, respectively). These results confirm the effectiveness of Eudragit® RL as a top-coating polymer to increase tablets' strength and to increase pellets compactibility. Eudragit® RL top-coating had the least effect on Kollicoat® SR coated pellets, no further study was done for this type of pellets.

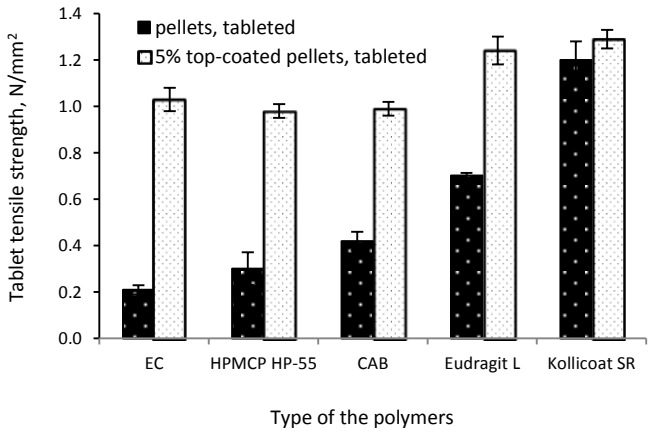

Fig. 55 Effect of Eudragit® RL top-coat (5% w/w) on tablets tensile strength (pellets content 70% w/w, compression force 5 kN).

A plasticizer incorporated into a polymeric material, increases the intermolecular separation of the polymer molecules, and improves polymer's toughness and flexibility, so that lower thermal processing temperatures can be employed (Zhu et al., 2002). **Fig. 56** shows effect of plasticizer (TEC) content (0%, 10%, and 20%) in the Eudragit® RL top-coat on diprophylline release from tableted cellulose acetate butyrate-coated pellets and tablets' strength. The diprophylline release was unchanged irrespective to the plasticizer content (Fig. 56a); however, the tablet's strength increased (29, 88, and 136%, respectively) (Fig. 56b), due to increased polymer flexibility.

Despite the mechanism of film formation from organic solutions of polymers differs from polymeric aqueous dispersions (Nimkulrat et al., 2004). The drug release from tableted pellets, which were top-coated with Eudragit® RL organic solution and aqueous dispersion was unchanged (**Fig. 57**) and tablets' tensile strength was similar (0.94 N/ mm^2 and 0.99 N/mm^2).

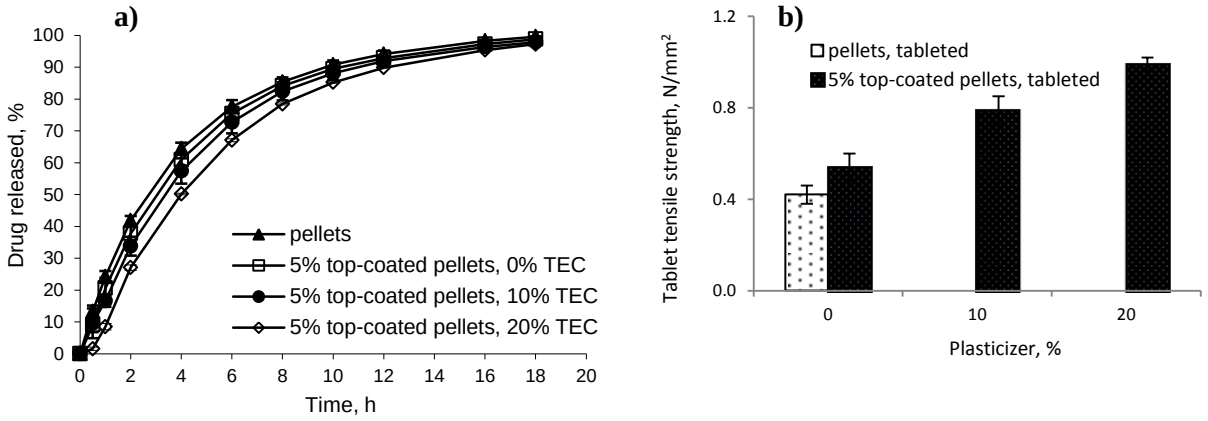

Fig. 56 Effect of plasticizer in the Eudragit® RL top-coat on **a)** diprophylline release from tableted pellets in PBS and **b)** tablet's tensile strength (cellulose acetate butyrate cl 15%, pellets content 70% w/w, compression force 5 kN).

The dissolution profiles should remain consistent not only following changes to a process, but also throughout the shelf life of the dosage form. The current ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines recommend accelerated stability testing at 40 °C / 75% RH (ICH, 2003). For cellulose acetate butyrate- and ethylcellulose- coated pellets (**Fig. 58** and **Fig. 59**), the drug release was unchanged for 12 weeks under the tested conditions. These findings confirmed stability of the cellulose acetate butyrate- and ethylcellulose-coated polymers, and that Eudragit® RL top-coat did not influence their stability. Similarly, Tyagi and Kori reported no remarkable changes in the

drug release from ethylcellulose loaded microspheres formulation at different storage conditions (Tyagi and Kori, 2014).

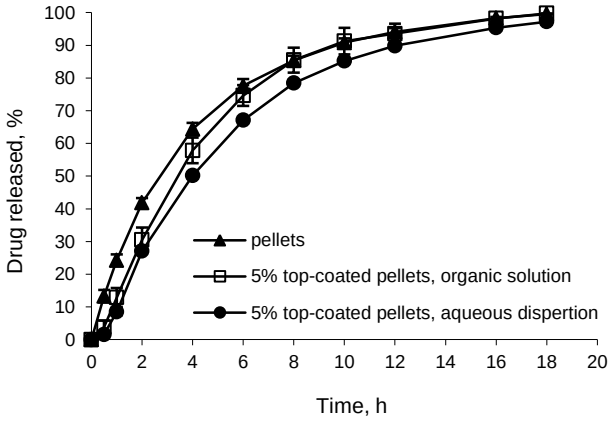

Fig. 57 Effect of the top-coat vehicle on diprophylline release from tableted pellets in PBS (cellulose acetate butyrate cl 15%, pellets content 70% w/w, compression force 5 kN).

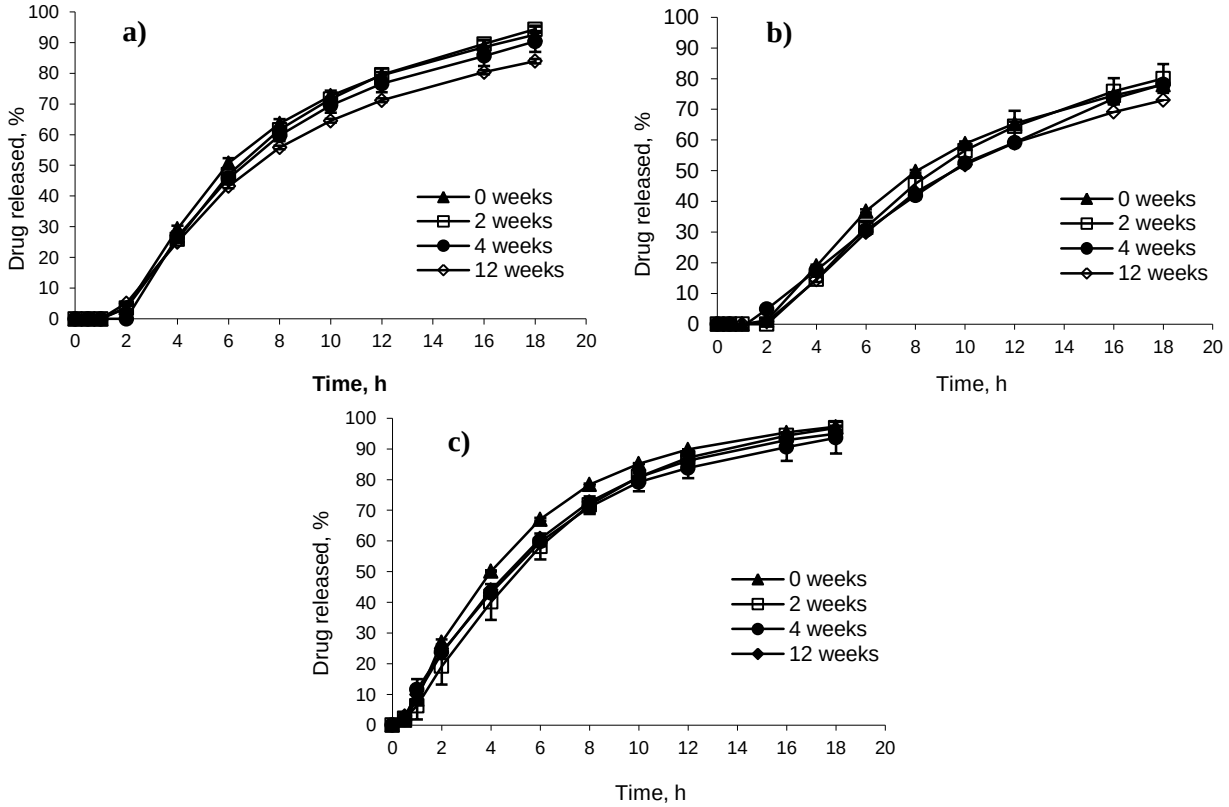

Fig. 58 Effect of the storage conditions on the diprophylline release in PBS from cellulose acetate butyrate coated pellets: **a)** without top-coat, **b)** Eudragit® RL top-coated pellets, and **c)** tableted Eudragit® RL top-coated pellets 5 kN (cellulose acetate butyrate cl 15%, pellets content 70% w/w).

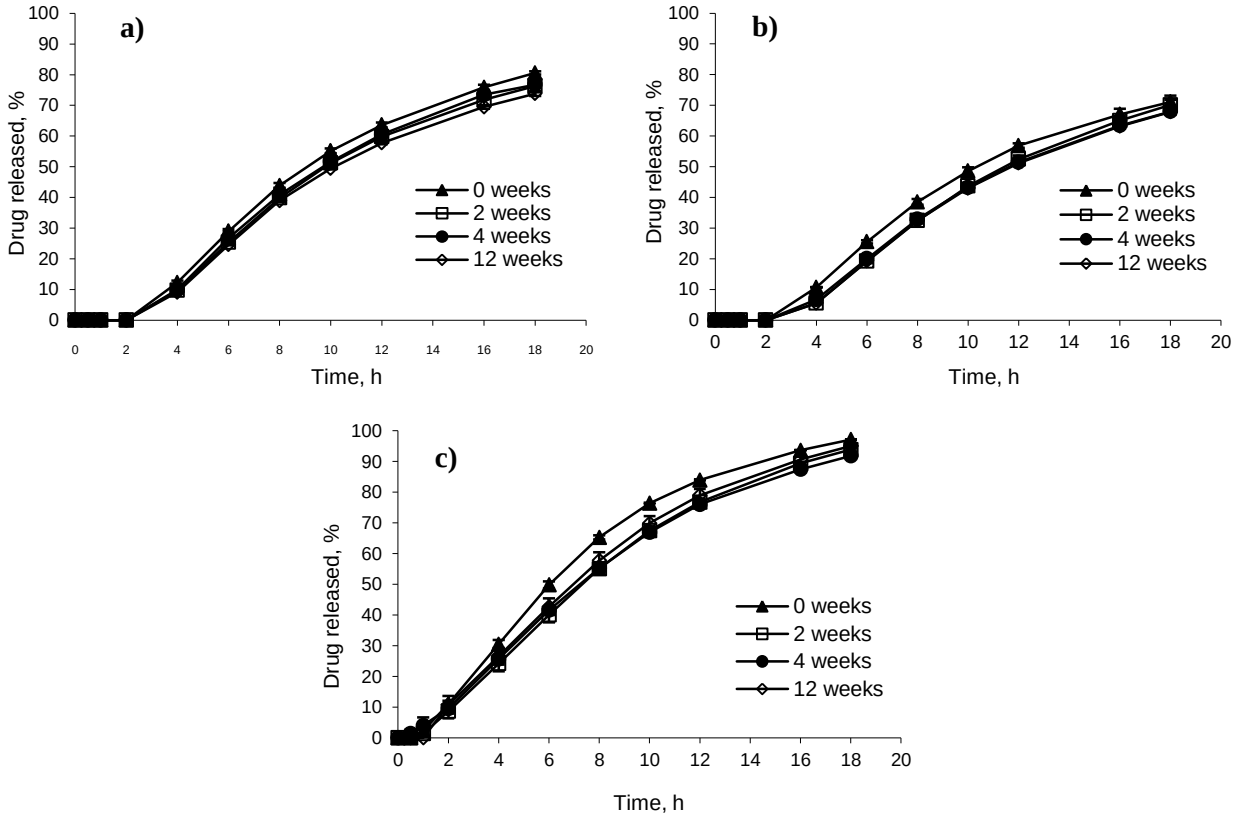

Fig. 59 Effect of the storage conditions on the diprophylline release in PBS from ethylcellulose coated pellets: **a)** without top-coat, **b)** Eudragit® RL top-coated pellets, and **c)** tableted Eudragit® RL top-coated pellets 5 kN (ethylcellulose cl 20%, pellets content 70% w/w).

On the other hand, **Fig. 60** and **Fig. 61** illustrate effect of storage conditions on the drug release from enteric-coated pellets (Eudragit® L and HPMCP). In 0.1 N HCl medium, the drug release from Eudragit® L was higher than from HPMCP coated pellets (Fig. 60a and Fig. 61a). Unlike to extended release polymers, drug releases from Eudragit® L and HPMCP coated pellets increased with time when Eudragit® RL was used as a top-coat (un-tableted and tableted; Fig. 60bc and Fig. 161bc). **Fig. 62** explains that presence of 10% w/w plasticizer increased drug release by 20% within 2 h in 0.1 N HCl. From this result, it was inferred that increased drug release from enteric-coated pellets was probably due to presence of plasticizer in the Eudragit® RL top-coat film (20% w/w); however, these results need further investigation.

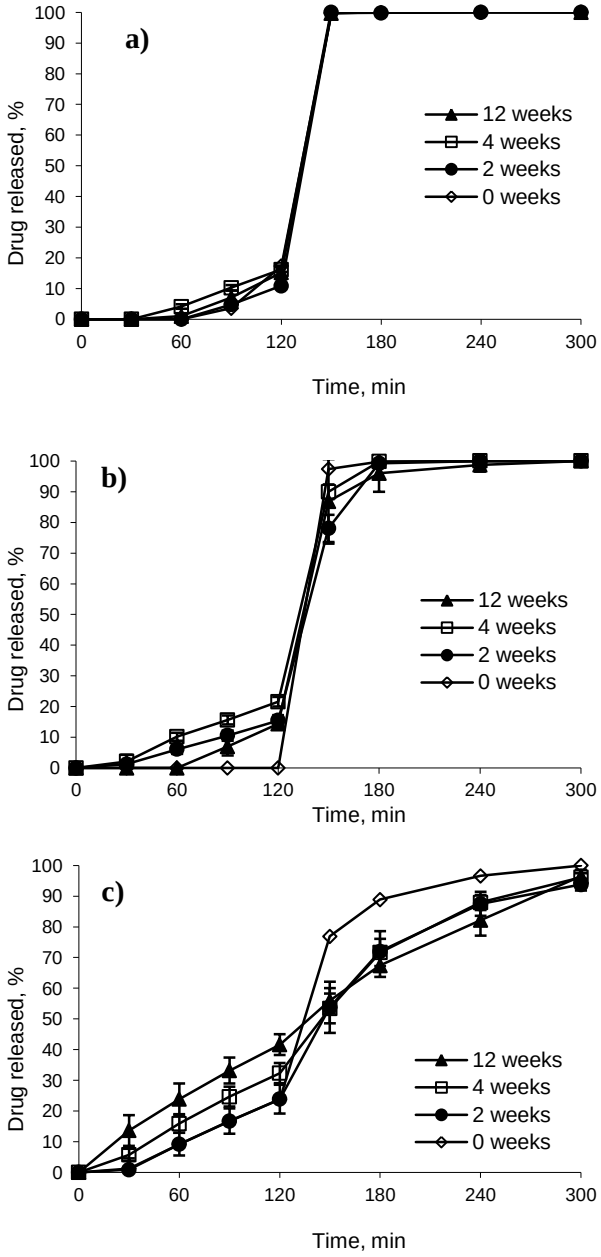

Fig. 60 Effect of the storage conditions on the diprophylline release in 0.1 N HCl (2 h) followed by PBS from Eudragit® L coated pellets: **a)** without top-coat, **b)** Eudragit® RL top-coated pellets, and **c)** tableted Eudragit® RL top-coated pellets 5 kN (Eudragit L cl 20%, pellets content 70% w/w).

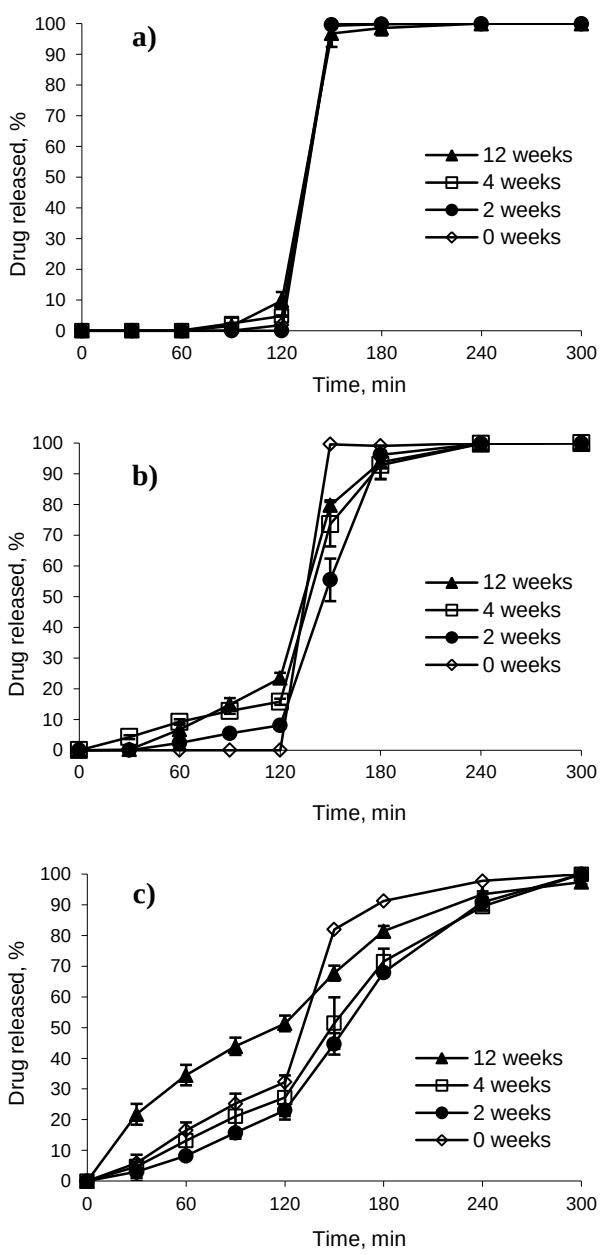

Fig. 61 Effect of the storage conditions on the diprophylline release in 0.1 N HCl (2 h) followed by PBS from HPMCP coated pellets: **a)** without top-coat, **b)** Eudragit® RL top-coated pellets, and **c)** tableted Eudragit® RL top-coated pellets 5 kN (HPMCP cl 20%, pellets content 70% w/w).

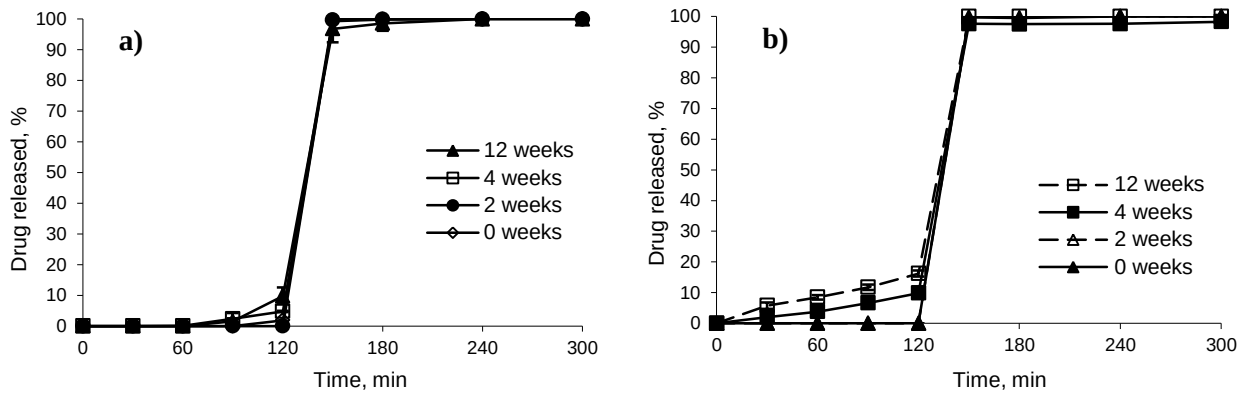

Fig. 62 Effect of plasticizer content on the diprophylline release in 0.1 N HCl (2 h) followed by PBS: **a)** 0% w/w TEC and **b)** 10% w/w TEC (HPMCP cl 20% w/w).

Conclusions

Hard tablets were prepared with high pellets content (70% w/w) at low compression force (5 kN) and extended release properties were maintained through the thin layer of Eudragit® RL top-coat (5% w/w). Plasticizer content of the Eudragit® RL top-coat was a key factor which affected tablets' tensile strength. Polymer coating type did not show any effect. Stability study showed that Eudragit® RL top-coating could be useful for extended release polymers like cellulose acetate butyrate and ethylcellulose rather than enteric polymers like Eudragit® L and HPMCP.

3.6. Cellulose acetate butyrate as controlled-release polymer: Matrix tablets

Background

A significant proportion of carriers in oral drug-delivery systems is polymeric materials fabricated in matrix-type systems. A matrix device is a simple design consisting of a drug dispersed and/or dissolved homogenously throughout a polymeric matrix (Colombo et al., 2000).

The controlled-release excipients for matrix preparation can be divided into water-soluble and water-insoluble carriers. Tablets prepared with the former dissolve or erode with time, depending on their molecular weight and solution viscosity (Viridén et al., 2009), whereas tablets made with the latter stay intact during drug release and are excreted as an empty scaffold (Barra et al., 2000). Examples of soluble carriers are hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose, carbopols polyvinyl alcohol and poly(ethylene oxide) (Rao et al., 1988; Bravo et al., 2004; Tapia-Albarran and Villafuerte-Robles, 2004; Morita et al., 2000; Apicella et al., 1993). Meanwhile, Kollidon® SR, Eudragit® RS and ethylcellulose can be regarded as a typical example of insoluble carriers. (Kranz et al., 2005; Caraballo et al., 1996; Neau et al., 1999).

Cellulose acetate butyrate was investigated cellulose acetate butyrate as a novel coating material for osmotic pump tablet and pellet dosage form (Section 3.3 and 3.4). The objective of this study was to use cellulose acetate butyrate as a carrier for preparation of matrix tablets. Effect of granulation fluid, polymer content, drug content, compression force, granule's size, drug solubility and surface area/volume ratio, which may affect the drug release were investigated. Additionally, tablet robustness toward agitation rate, pH, and ionic strength of the dissolution medium were studied.

Results and discussion

Matrix drug-delivery systems can be advantageous over coated systems exhibiting homogeneous character, an ease of manufacture, and absence of problems, which might arise during the coating procedure. In this study, CAB-553-0.4 was used a novel polymer for preparation of extended release matrix tablets.

Effect of granulation fluid ratio (water:isopropanol) on the caffeine release is seen in **Fig. 63**. Isopropanol (100%) was used as a least as possible because an excess amount of it resulted in a sticky wet mass and difficult to be sieved. With increased isopropanol/water ratios (0%, 50%, and 100%) w/w, stronger granules were achieved (inspected manually) and the caffeine release was slower. Moreover, granulation prior to tablet compression has significantly decreased the drug release compared to directly compressed tablets.

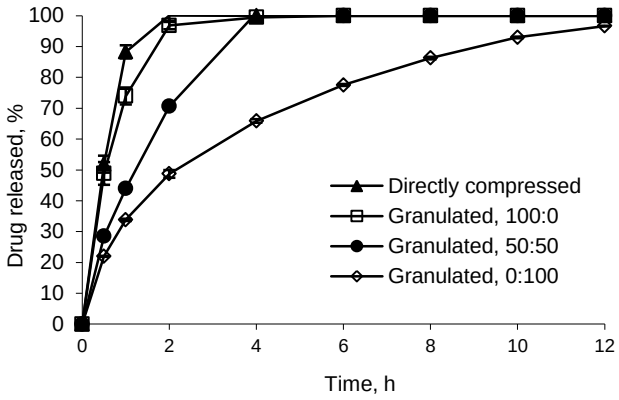

Fig. 63 Effect of the granulation fluid (water:isopropanol) on the caffeine release in PBS (cellulose acetate butyrate 30%, lactose 20% and caffeine 50% w/w).

X-ray diffraction studies were undertaken to investigate the effect of the granulation process on the crystal structure of caffeine. The XRD patterns for cellulose acetate butyrate, caffeine, CAB:caffeine physical mixtures and tablets (after grinding) are shown in **Fig. 64**. From the characteristic peaks (11.72˚, 20.42˚, 23.92˚, 26.30˚, 26.88˚, 28.26˚, and 36.30˚) of caffeine powder, can be inferred to traits of a crystalline structure. While for cellulose acetate butyrate polymer, there was no peak observed, as it has no crystalline structure. The crystalline structure of caffeine preserved in the physical mixture and tablets (CAB:caffeine, 30:70) and no new peaks appearing on the patterns of caffeine. This result confirms that the release retardation was

not because of the change in the crystalline structure. Probably, it was due to solubilizing effect of isopropanol, which dissolved or softened cellulose acetate butyrate and resulted in partially coated drug.

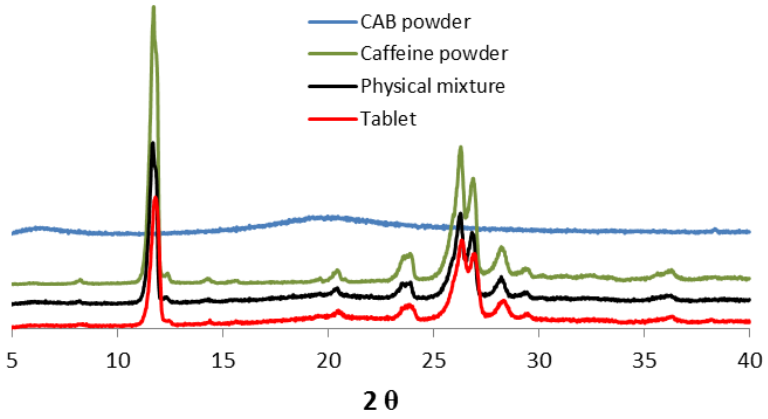

Fig. 64 PXRD patterns of CAB, caffeine, physical mixture, and tablet (CAB:caffeine, 30:70).

Increased cellulose acetate butyrate content (30%, 40%, and 50%, w/w) at constant caffeine content (50%, w/w), had no influence on the drug release (**Fig. 65**). On the other hand, with increased caffeine content from 50% to 80% w/w (lactose content 0%), the release was unchanged (f_2 > 50), however, further increase caffeine content to 90% w/w resulted in a significant increase in the release (f_2 = 45.8) (**Fig. 66**). The most extensively used model to determine drug release mechanism is the Korsmeyer-Peppas mathematical model (Tapia-Albarran and Villafuerte-Robles, 2004). Korsmeyer derived a simple relationship, which described drug release from a polymeric system (Korsmeyer et al., 1983):

$$M_t / M_\infty = Kt^n$$

M_t is the amount of drug releases at time t; M_∞ is the amount of drug releases after infinite time; K is a release rate constant incorporating structural and geometric characteristics of the dosage form, n is the diffusional exponent indicative of the mechanism of drug release. Peppas used this n value in order to characterize the release profile (Peppas, 1985).

At 80% w/w caffeine content, the best linearity was found in Korsmeyer equation plot (R^2 = 0.999). The n value, which was equal to 0.45, indicates that the Fickian diffusion is the overall solute diffusion mechanism.

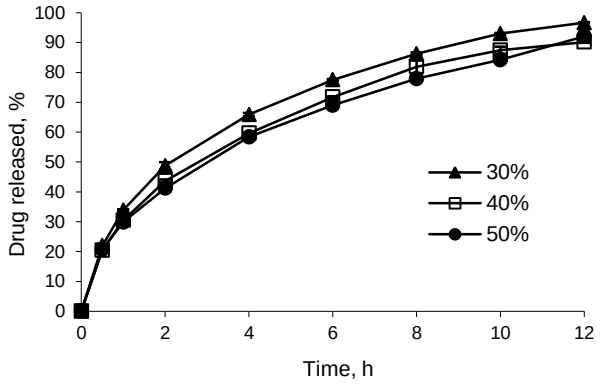

Fig. 65 Effect of cellulose acetate butyrate content on the caffeine release in PBS (caffeine 50% w/w).

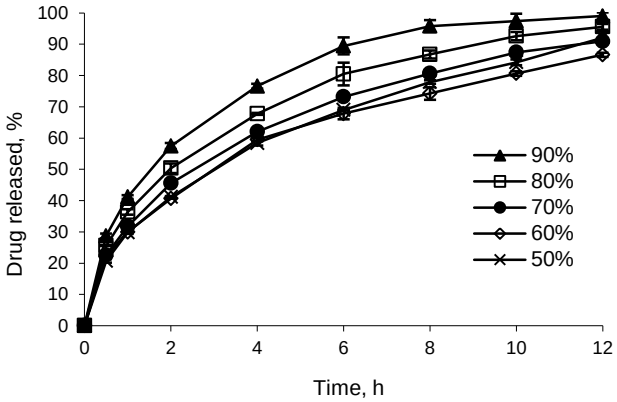

Fig. 66 Effect of drug content on the caffeine release in PBS (lactose 0%).

The importance and influence of compression force on drug release are well-reported (Dabbagh et al., 1996). The effect of the tablet compression forces on the drug release rate was studied by applying 10 kN, 15 kN, and 20 kN force, the drug release was unchanged with increased tablet compression force (**Fig. 67**).

Wikberg and Alderborn studied the relationship between granule/pellet size and compression behavior (Wikberg and Alderborn, 1990). At 70% w/w caffeine loaded tablets, increasing granular size (0.15 mm - 1.40 mm) did not affect the drug release (**Fig. 68**). To study the effect of surface area / volume ratio, different weights (150 mg, 120 mg, and 90 mg) of the blends were compressed at the same punch diameter (8 mm) and the same compression force (15 kN) (**Fig. 69**). Increased surface area/volume ratio (1.4, 1.6, and 2, mm^2/mm^3) had no impact on the drug release ($f_2 \geq 50$) and on the tablets' strength (Fig. 70a and 70b, respectively).

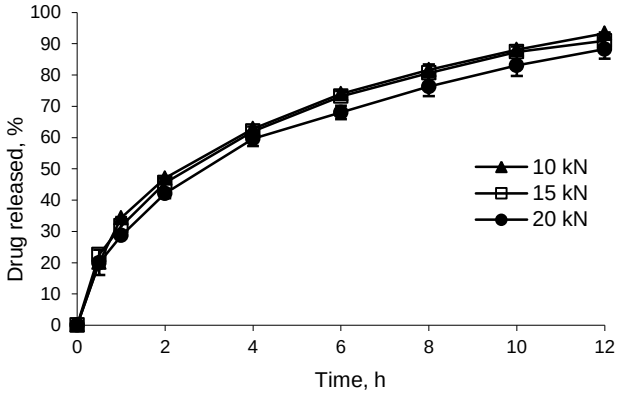

Fig. 67 Effect of tablet compression force on the caffeine release in PBS (cellulose acetate butyrate 30%, caffeine 70% w/w).

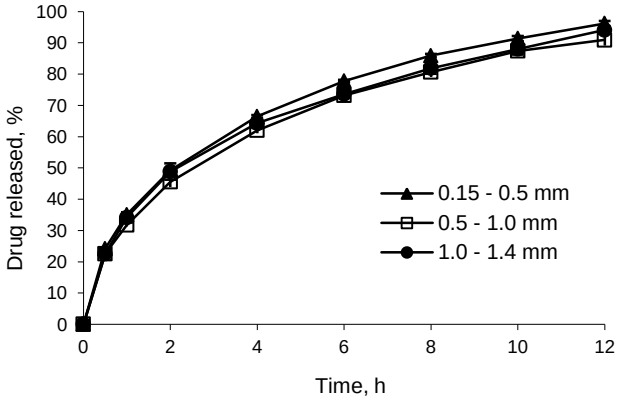

Fig. 68 Effect of granular sizes on the caffeine release in PBS (cellulose acetate butyrate 30%, caffeine 70% w/w).

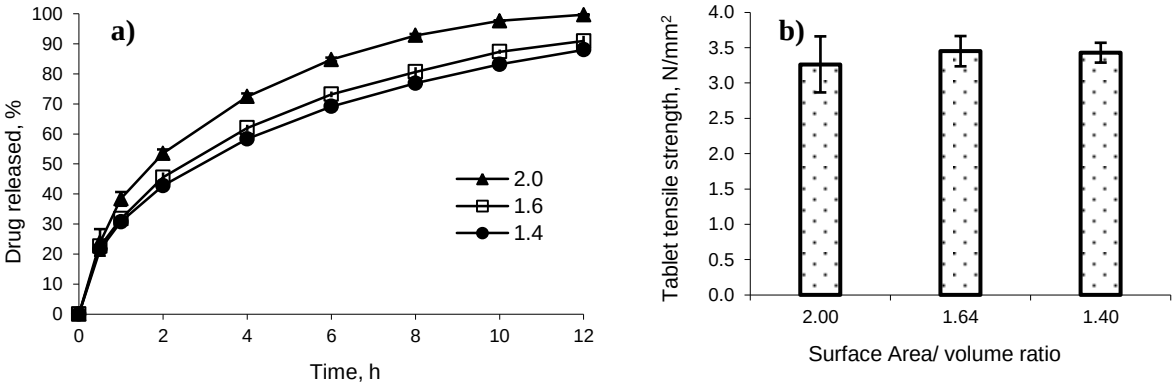

Fig. 69 Effect of the surface area / volume ratio (mm^2/mm^3) on **a)** the caffeine release in PBS and **b)** tablet tensile strength (cellulose acetate butyrate 30%, caffeine 70% w/w).

Effect of different intrinsic solubility on drug release from cellulose acetate butyrate matrix is illustrated in **Fig. 70**. To keep carbamazepine in sink condition during release study, tablets were prepared at lower weight (80 mg) and smaller size (7 mm). The higher the drug solubility (diprophylline > caffeine > carbamazepine), the faster was the release. A drug with high solubility displays a faster release, while drugs with poor aqueous solubility often demonstrate an incomplete release because of the impact of solubility on dissolution rate from a formulation (Wen and Park, 2010).

Two major variables of the gastrointestinal fluids are ionic strength and pH, which can affect the rate at which a drug is released from extended-release matrices (Johnson et al., 1993; Hodsdon et al., 1995). Johnson et al. reported that the ionic strength of GI fluids in the human under both fasted and fed states and various physiological pH conditions covers a range of 0 M – 0.4 M (Johnson et al., 1993). The effect of ionic strength (different amount of NaCl was added into the release medium) and pH of the dissolution medium on the caffeine release from the cellulose acetate butyrate matrix tablet are seen in **Fig. 71** and **Fig. 72**, respectively. Caffeine release was unchanged with increased ionic strength and pH of the release medium.

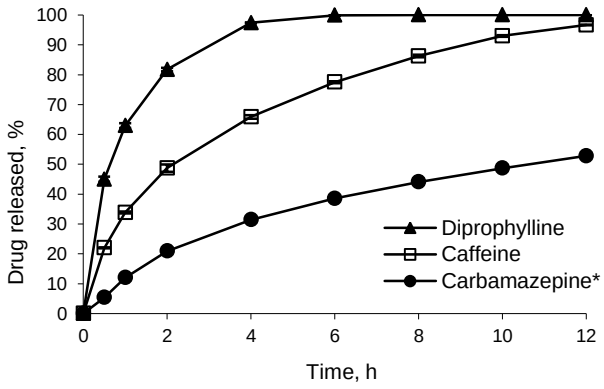

Fig. 70 Effect of drug solubility on the drug release in PBS (cellulose acetate butyrate 30%, drug 70% w/w, 15 kN).

* tablet diameter was 7 mm and weight 80 mg

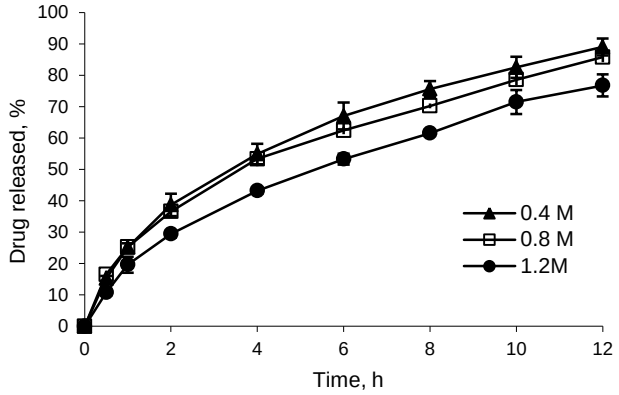

Fig. 71 Effect of the ionic strength of the release medium on the caffeine release in PBS (cellulose acetate butyrate 30%, caffeine 70% w/w).

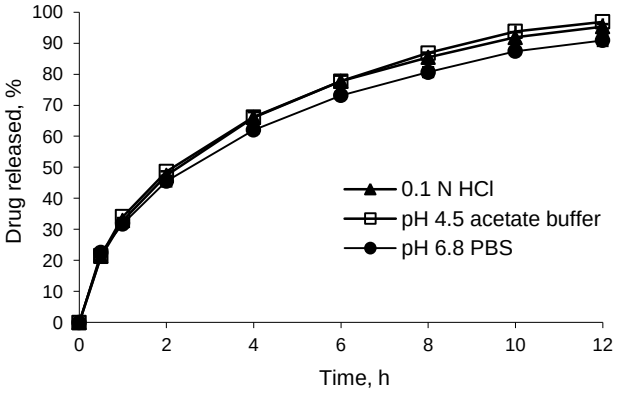

Fig. 72 Effect of the pH of the release medium on the caffeine release (cellulose acetate butyrate 30%, caffeine 70% w/w).

To study the impact of hydrodynamic force on *in vitro* drug release, the tablets were tested for dissolution at different agitation rates. Caffeine release was unaffected by increased agitation rate from 50 rpm to 150 rpm (**Fig. 73**). Accelerated stability testing was performed to find out how the drug release from the tablets could be changed with time under the influence of temperature and humidity. The obtained results (**Fig. 74**) showed no change in the drug release. These results confirm the stability of the cellulose acetate butyrate matrix tablet.

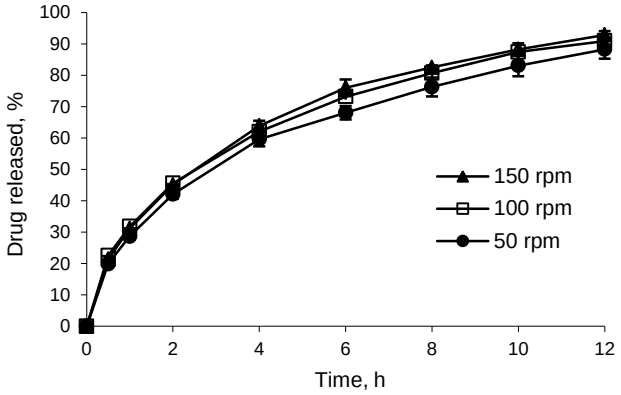

Fig. 73 Effect of agitation rate on the caffeine release in PBS (cellulose acetate butyrate 30%, caffeine 70% w/w).

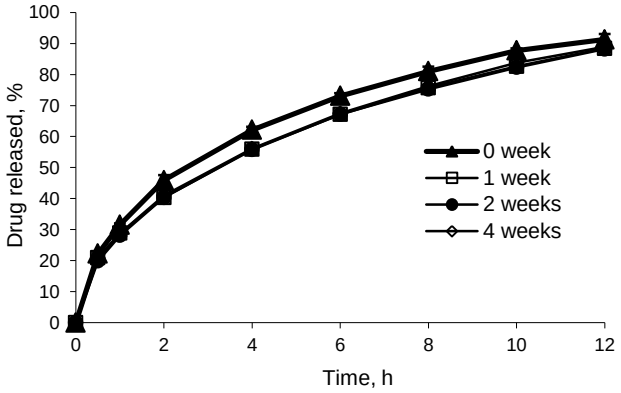

Fig. 74 Effect of the storage conditions on the caffeine release in PBS (cellulose acetate butyrate 30%, caffeine 70% w/w).

Conclusions

Controlled-release matrix tablets were prepared with cellulose acetate butyrate as a carrier. The tablets were characterized by its robustness to increased compression force, drug loading, granular size, surface area/volume ratio, ionic strength, pH and agitation. The granulating solvent (isopropanol) was the main factor that affected drug release. Good stability was another feature of cellulose acetate butyrate matrix tablet. In summary, cellulose acetate butyrate (CAB-553-0.4) could be used as a carrier for preparation of a controlled-release matrix dosage form.

3.7. Preparation and characterization of high ibuprofen loaded matrix tablets

Background

A simple approach to manufacture controlled-release dosage forms is to compress drug, retardant carrier and additives into matrix tablets, in which the drug is dispersed and/or dissolved homogenously through a polymeric carrier (Colombo et al., 2000). In general, materials used as a carrier for matrix device include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, poly (ethylene oxide), xanthan gum, sodium alginate (Hasan et al., 2003; Remington, 2002; Aulton, 2002). Polyvinyl acetate, acrylate polymers and their copolymers, and ethylcellulose can be regarded as a typical example of insoluble carriers. (Kranz et al., 2005; Caraballo et al., 1996; Neau et al., 1999).

Non-steroidal anti-inflammatory drugs (NSAIDs) are highly effective in the treatment of rheumatoid and osteoarthritis but their long-term use can cause gastrointestinal (GI) toxicity like stomach and duodenum ulceration and bleeding (Dhikav et al., 2002; Laine et al., 2003). Ibuprofen, a member of this group (NSAIDs), has a short plasma half-life (1-3 h) and GI toxicity profile, which makes it an ideal candidate for preparing controlled release drug products. Various polymers like hydroxypropylmethylcellulose, Eudragit® RS, ethylcellulose have been used as matrix carrier for preparation of ibuprofen controlled release tablets (Khan and Jiabi, 2000; Vueba et al., 2005; Tabandeh and Mortazavi, 2014; Patel et al., 2011).

High drug loading formulations have recently been drawing increased attention due to patient preferences for smaller dosage size as well as a growing interest in fixed dose combination products. Maximization of drug loading can effectively decrease dosage form sizes as well as reduce manufacturing batch sizes to provide cost savings (Cai et al., 2013).

The objective of this work was to prepare and characterize high ibuprofen loaded (95% w/w) controlled release matrix tablets. Polymers with different physicochemical properties (permeability) like Eudragit® RL PO, Eudragit® RS PO, and ethylcellulose were used as carriers.

Results and discussion

Ibuprofen is a member of the propionic acid subgroup of the large family of NSAIDs, and is widely used, all over the world. GI disturbance and ulceration is major adverse effects of ibuprofen. The objective of this work is preparation on high dose ibuprofen extended-release tablets.

Effect of different polymers on ibuprofen release from matrix tablets is shown in (**Fig. 75**). Surprisingly, 100% ibuprofen was released from ibuprofen tablets (only drug without polymer) within 14 h, and presence of 5% w/w ethylcellulose or Eudragit® RS had not significant effect on the drug release ($f_2 > 50$). However, ibuprofen release decreased significantly ($f_2 = 31$) when 5% w/w Eudragit® RL was used (Fig. 75a). Probably this was due to the physicochemical nature of Eudragit® RL, which made hardest tablet (30, 34, 38 and 47 N, respectively) (Fig. 75b). Unlike ethylcellulose and Eudragit® RS tablets which completely disintegrated, flexible porous masses (20% of the tablet initial tablets weight, after drying) were left at the bottom of the dissolution vessels with Eudragit® RL tablets at the end of the release study (**Fig. 76**).

In contrast to Wu and McGinity, who reported changes in the IR spectra due to interaction of ibuprofen with the Eudragit® RS 30 D polymer through the carboxyl acid groups (Wu and McGinity, 2001). No changes in the IR spectra of ibuprofen were found from ibuprofen:Eudragit® RL (95:5) tablet (**Fig. 77**), and the spectrum was unaffected with increased Eudragit® RL content to 50% w/w before and after the release study (residue).

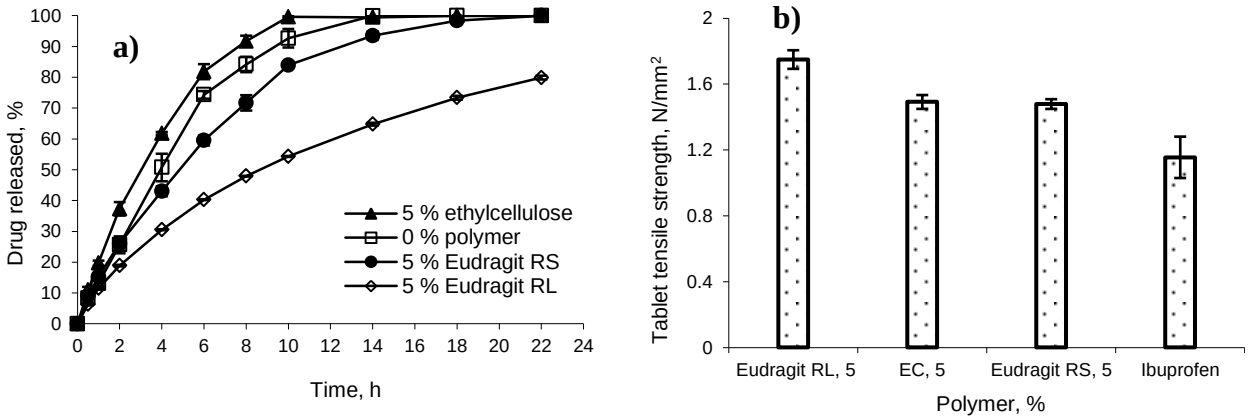

Fig. 75 Effect of polymer type on: **a)** ibuprofen release from matrix tablets in PBS and **b)** tablets' tensile strength (ethanol:water 20:80).

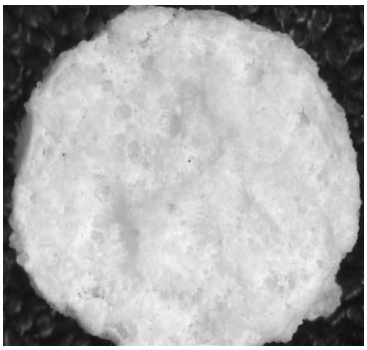

Fig. 76 Tablet residue after release study in PBS (ibuprofen:Eudragit® RL 95:5).

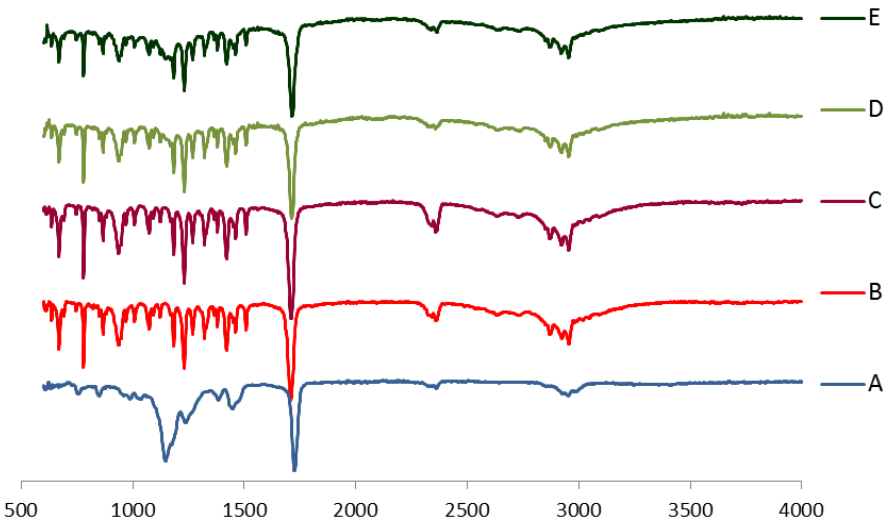

Fig. 77 IR spectra of ibuprofen:Eudragit® RL tablets **A**) 0:100, **B**) 100:0, and **C**) 95:5, **D**) 50:50 before the release and **E**) 50:50 after the release (residue).

Effect of granulation fluid (ethanol:water) on ibuprofen release from ibuprofen:Eudragit® RL is illustrated in **Fig. 78**; The ibuprofen release was unchanged as ethanol content increased and stronger granules were obtained (inspected manually); however, use of more than 20% w/w ethanol caused stickiness and manual sieving was difficult.

For ethylcellulose and Eudragit® RS matrix tablets, an increase of ethanol content in the granulation fluid from 20% to 30% w/w decreased the ibuprofen release significantly (f_2 < 50) (**Fig. 79**), and increased tablets' strength (34 N to 44 N) and (38 N to 50 N), respectively. Further increase ethanol content to 40% did not influence ibuprofen release and tablets' strength. From these results, it is inferred that granulation fluid is an important factor that affects ibuprofen release irrespective of the polymer used. Similar release profiles of ibuprofen were obtained from tablet containing highly permeable polymers like Eudragit® RL and low permeable

polymer like ethylcellulose and Eudragit® RS when different ratio of ethanol:water (20:80 and 30:70) were used as granulation fluid (**Fig. 80**).

The mechanism of ibuprofen release from Eudragit® RL PO matrix tablet appeared to be simple diffusion controlled and the data could be adequately described by the Higuchi square root of time (R^2 = 0.998); similarly, Shaikh et al. reported Higuchi release profile for ibuprofen from matrix tablets containing ethylcellulose (Shaikh et al., 1987).

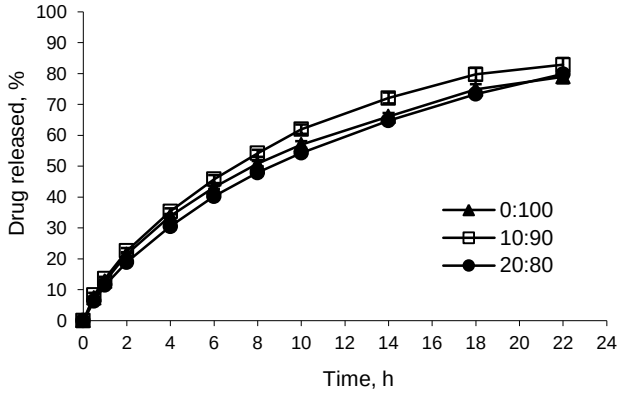

Fig. 78 Effect of granulation fluid (ethanol:water) on ibuprofen release from Eudragit® RL matrix tablet in PBS (ibuprofen:Eudragit® RL 95: 5).

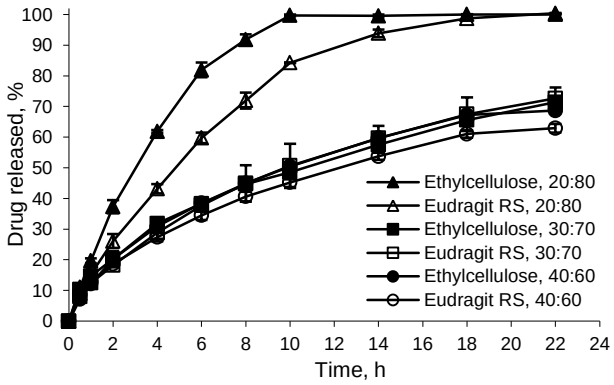

Fig. 79 Effect of granulation fluid (ethanol:water) on ibuprofen release from ethylcellulose and Eudragit® RS matrix tablet in PBS (ibuprofen:polymer 95:5).

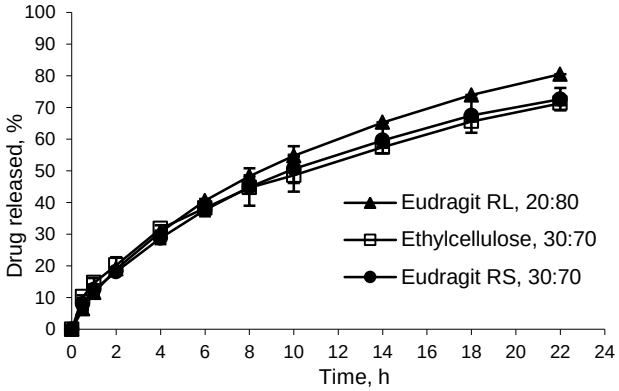

Fig. 80 Effect of granulation fluid (ethanol:water) on ibuprofen release from matrix tablet in PBS (ibuprofen:polymer 95:5).

Effect of ibuprofen:Eudragit® RL ratio on the drug release and tablets' strength is shown in **Fig. 81**. The ibuprofen release decreased and tablets hardness increased (51, 54, and 65 N), with increased ibuprofen content (50%, 65%, and 80%, respectively); while at 95% ibuprofen content, drug release increased significantly ($f_2 < 50$) and tablets' hardness decreased (46 N). Percolation threshold of Eudragit® RL content is probably the key parameter. At 95% drug content; the polymer is below percolation threshold, hence the drug release was faster.

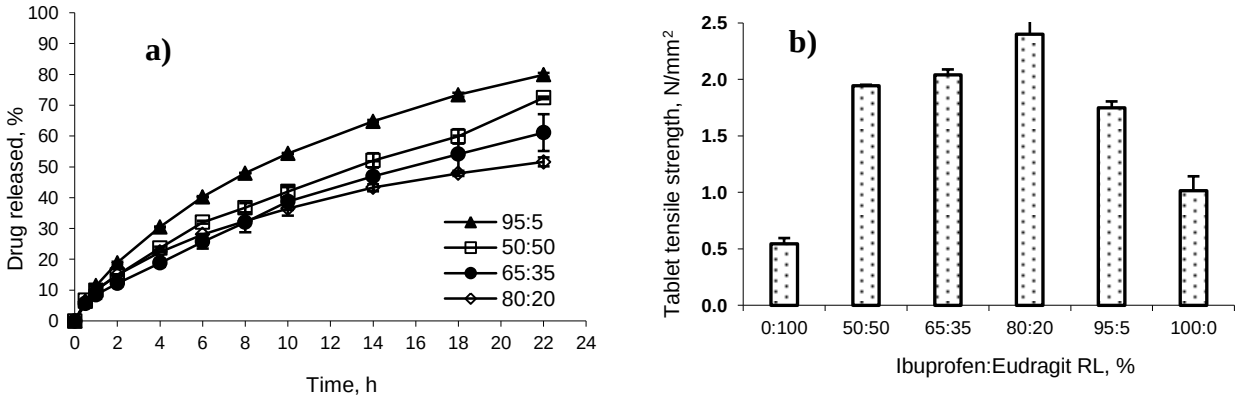

Fig. 81 Effect of ibuprofen:Eudragit® RL ratio **a)** on the drug release in PBS and **b)** tablet tensile strength (ethanol:water 20:80, 15 kN).

In order to investigate the robustness of tablets, effect of granule size, compression force, agitation rate of the release medium, and surface area/volume ratio were studied. Increasing the granules' size from 0.1 mm to 1.45 mm had no influence on ibuprofen release (**Fig. 82**). Similarly, ibuprofen release was unchanged with increased compression force (5 kN, 10 kN, and

15 kN) (**Fig. 83**), and with increased agitation rate (50, 100, and 150 rpm) of the release medium (**Fig. 84**). Different weights of granules (90 mg, 120 mg, and 150 mg) were compressed at the same compression force (15 kN) using the same punch size (8 mm) to achieve different surface area/volume ratio (182, 146, and 126 mm^2/mm^3). Ibuprofen release increased significantly (f_2 < 50) as surface area/volume ratio increased to 182 mm^2/mm^3 (**Fig. 85**).

The accelerated stability testing was performed to find out how the drug release from the manufactured tablets could be changed with time under the influence of temperature and humidity. The obtained results (**Fig. 86**) showed no change in the drug release. These results affirm stability of the high loaded ibuprofen matrix tablets.

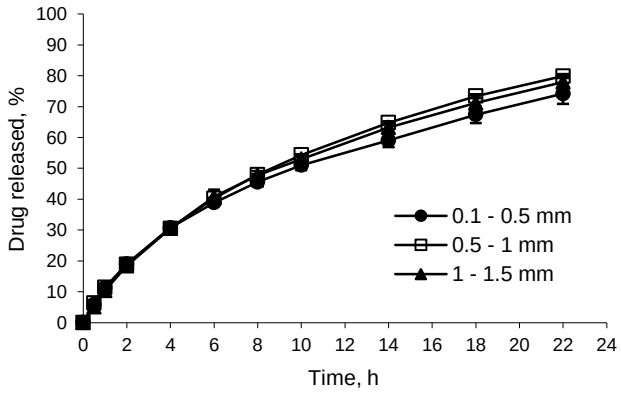

Fig. 82 Effect of granules size on ibuprofen release in PBS (ibuprofen:Eudragit® RL 95:5).

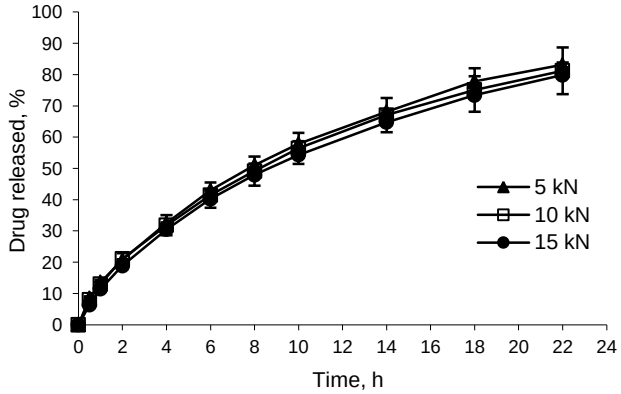

Fig. 83 Effect of compression force on ibuprofen release in PBS (ibuprofen:Eudragit® RL 95:5).

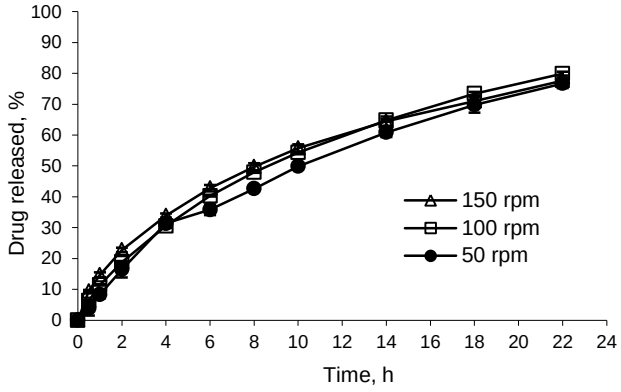

Fig. 84 Effect of agitation rate of the release medium on ibuprofen release in PBS (ibuprofen:Eudragit® RL 95:5).

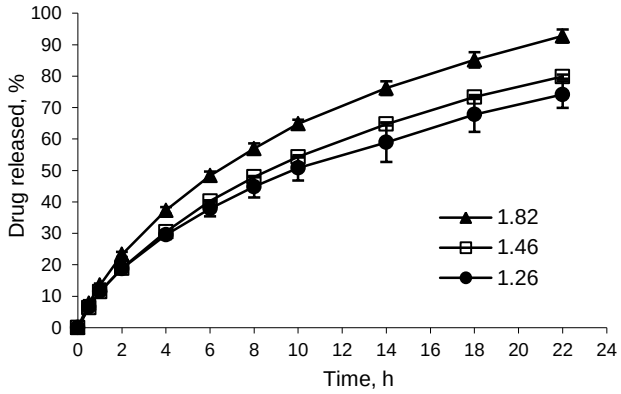

Fig. 85 Effect of surface area /volume ratio (mm^2/mm^3) on the ibuprofen release in PBS (ibuprofen:Eudragit® RL 95:5).

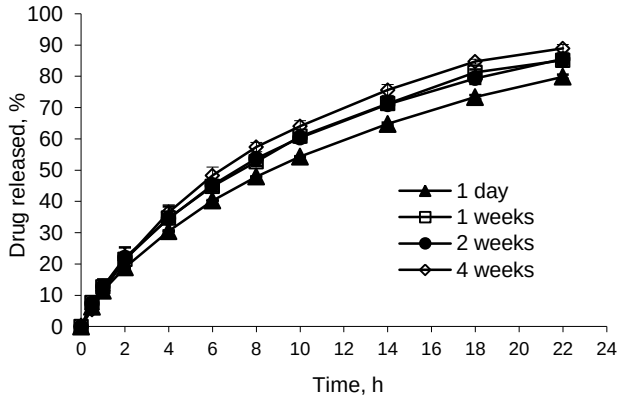

Fig. 86 Effect of the storage conditions on the ibuprofen release in PBS (ibuprofen:Eudragit® RL 95:5).

Conclusions

Controlled release high dose ibuprofen matrix tablets (95% drug content) were prepared with different polymers including Eudragit® RL, Eudragit® RS and ethylcellulose. There was a direct relation between tablets' strength and ibuprofen release. Similar release profiles were obtained by varying granulation fluids' ratio with different polymers. Ibuprofen release was independent of granule size, compression force, and agitation rate, however, the release increased as surface area/volume ratio was increased. The drug release did not change after one month of storage at accelerated stability conditions.

3.8. Preparation and characterization of an oral controlled-release tablet of a water-insoluble drug, with Eudragit® RL PO as a water-insoluble permeable carrier: Role of curing conditions

Background

Polymers have played an important role in the advancement of drug delivery technology by providing controlled release of therapeutic agents in constant doses over long periods of both hydrophilic and hydrophobic drugs (Liechty et al., 2010). Several polymers like hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, carbopols, polyvinyl alcohol, and acrylic resins were used for the purpose of controlled-release formulations of different drugs (Ranga Rao et al., 1988; Mäki et al., 2006; Bravo et al., 2004; Morita et al., 2000; McGinity et al., 1983).

When polymeric films are subjected to storage at temperatures above their glass transition temperatures (T_g), polymer particles undergo further coalescence and inter-diffusion of polymer chains occurs. This process is often referred to as further gradual coalescence or curing (Harris et al., 1986). During the curing stage, the microstructure of the polymer film has altered, resulting in changes in the water diffusivity and the mechanical properties of the film (Bodmeier and Paeratakul, 1994b). The effect of curing time on the release of theophylline from pellets coated with Eudragit® RS 30D or RL 30D was reported (Maejima and McGinity, 2001). However, the effects of heat-treating have only been studied for a few matrices (Omelczuk and McGinity, 1993; Billa et al., 1998;. Azarmi et al., 2005).

The aim of this study was a) using Eudragit® RL PO as a carrier for preparation of controlled release matrix tablet, and b) to investigate effect of curing conditions on polymer coalescence in compressed form rather than aqueous dispersion. Carbamazepine was used as a model drug.

Results and discussion

With increased ethanol content (0 – 20% w/w) in the granulation fluid, stronger granules were achieved (inspected manually) and the drug release decreased (**Fig. 87**). Ethanol acts as a co-solvent, which increases solubility of carbamazepine and probably the drug was partially coated by the softened Eudragit. Using ethanol above 20% w/w in granulation fluid made a sticky wet mass and was difficult to be sieved.

To investigate effect of curing, tablets were subjected to different temperature for 24 h (**Fig. 88**). Drug release slowly decreased as temperature increased. At temperature of 70 °C, the drug releases rate was significantly decreased and they fitted well into zero order kinetic (R^2 = 0.997 and 0.994) for both directly compressed and granulated compressed tablets. Probably this is due to softening of the polymer above its T_g, of ~ 63 °C, polymer chain movement and redistribution of the polymer in the tablet matrix (Azarmi et al., 2005).

Because temperature of 70 °C is too high and may cause drug degradation, curing of the tablets were performed at a lower temperature with high relative humidity. Surana concluded that increases in the environmental relative humidity (RH), caused a progressive decrease in T_g as a result of the plasticizing effect of water (Surana et al., 2003). Effect of the relative humidity on the drug release is shown in **Fig. 89**. The drug release from tablets, which were cured at 40 °C with 75% RH was similar to the release from tablets that cured at 70 °C for both directly compressed and granulated compressed tablets.

Moreover, maximum tablets' moisture-uptake was 2.9 ± 0.03% w/w within 24 h curing; with longer curing, tablets' moisture uptake and drug release was unchanged (**Fig. 90**).

The most commonly used model to determine drug release mechanism is Korsmeyer-Peppas mathematical model (Tapia-Albarran and Villafuerte-Robles, 2004).

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

M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the dosage form, n is the diffusional exponent indicative of the mechanism of drug release. The n value for granulated compressed tablets was 1.17 (> 0.89); so, the release mechanism of this matrix tablet

is super case II transport, and in this transport the release mechanism is unknown or more than one release phenomena is present in the preparation (Korsmeyer et al., 1983).

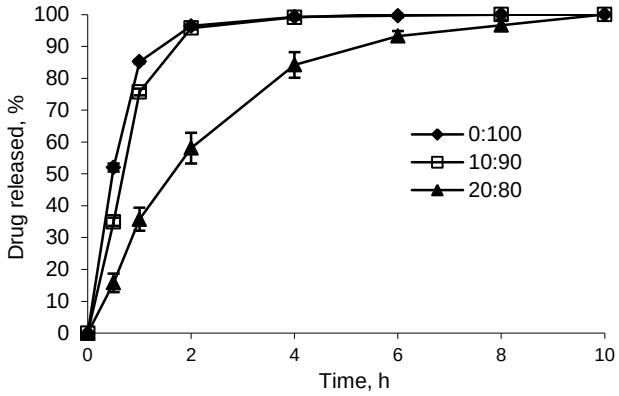

Fig. 87 Effect of granulation fluid (ethanol:water) on the carbamazepine release in PBS from granulated compressed tablet.

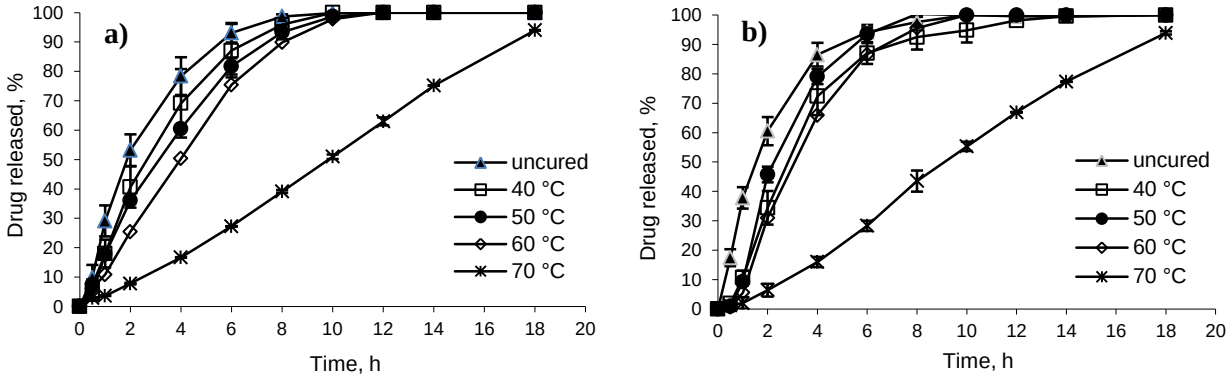

Fig. 88 Effect of curing temperature on the carbamazepine release in PBS from **a)** directly compressed tablets and **b)** granulated compressed tablet.

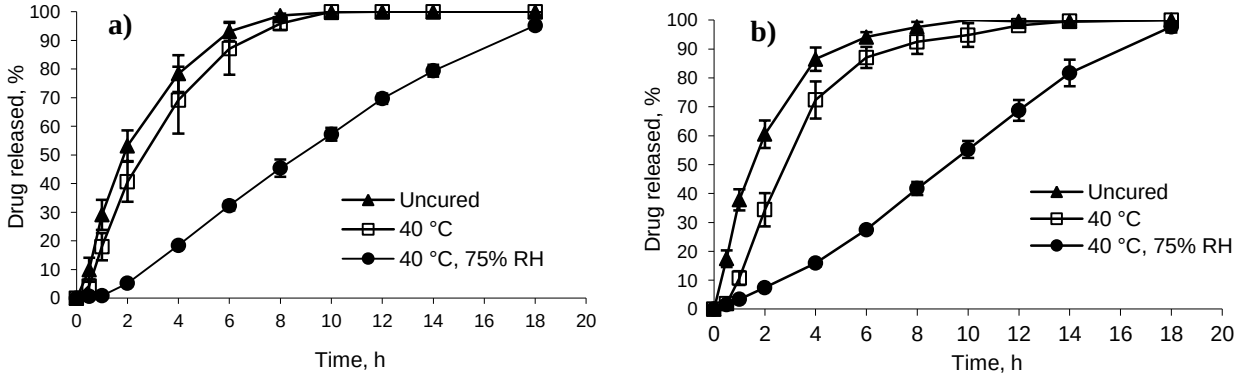

Fig. 89 Effect of relative humidity (RH) on the carbamazepine release in PBS form **a)** directly compressed tablets and **b)** granulated compressed tablet.

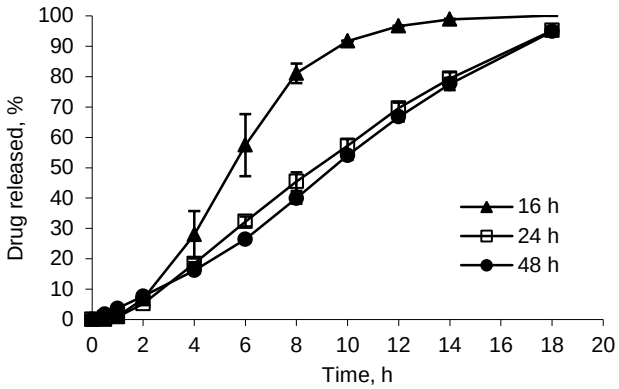

Fig. 90 Effect of curing duration on the carbamazepine release in PBS (directly compressed 40 °C /75% RH).

X-ray diffraction studies were undertaken to investigate the effect of curing upon the tablet and confirming whether the drug retardation was because of polymer coalescence or changing crystal structure of carbamazepine. The XRD patterns for pure carbamazepine, pure Eudragit® RL PO, carbamazepine:Eudragit® RL PO granulated compressed tablets uncured and cured **Fig. 91**. From peaks of the carbamazepine exhibited at a diffraction angle of 2θ (12.40˚, 15.10˚, 15.92˚, 19.88˚, 24.96˚, 27.30˚ and 32.06˚) can be inferred to a high crystalline structure. While for Eudragit® RL PO the peak cannot be recognized because it has not crystalline structure. In the cases of granulated compressed tablets uncured and cured, the characteristic peaks and the crystalline structure of carbamazepine persisted. Moreover, there were no new characteristic peaks appearing on the patterns of the drug.

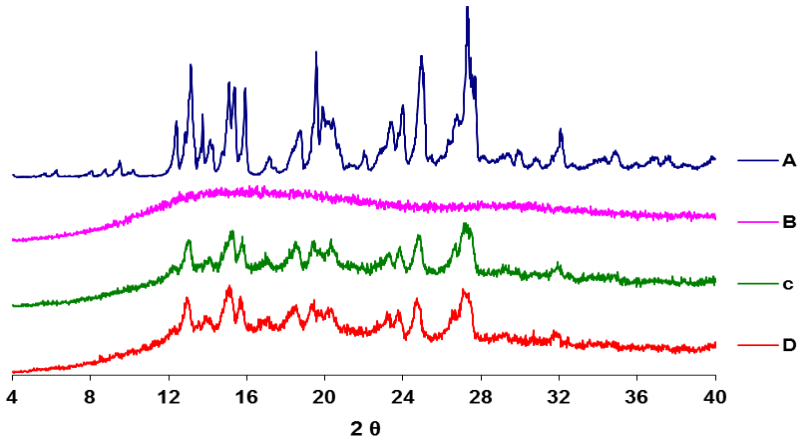

Fig. 91 PXRD patterns of: **A.** carbamazepine, **B.** Eudragit® RL PO, **C.** carbamazepine:Eudragit® RL PO granulated tablet uncured, **D.** carbamazepine:Eudragit® RL PO granulated tablet cured (40 °C/ 75% RH).

The importance and influence of compression force on drug release is well reported (Dabbagh et al., 1996). Tablets' strength was increased (0.9, 1.2 and 1.4, N/mm^2), and the drug release was decreased with increased the compression force (10 kN, 15 kN, and 20 kN) (**Fig. 92**). The decrease in the release rate may be due to a decrease in porosity owing to the formation of continuous matrix at higher applied forces (Desai et al., 1966).

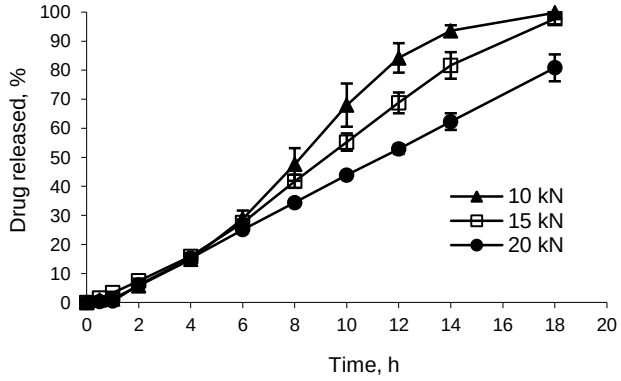

Fig. 92 Effect of compression force on the carbamazepine release in PBS (drug content 30% w/w, granulated compressed).

The relationship between granule/pellet size and compression behavior have been studied (Wikberg and Alderborn, 1990). **Fig. 93**. Shows effect of granules size on the drug release; drug release was decreased with increased granules size, this is due to a higher degree of consolidation of the compacts formed from larger granules as a result of plastic deformation and fragmentation than those from smaller granules (Eichie and Kudehinbu, 2009). Nevertheless, with increased the compression force to 20 kN and curing duration to 48 h, drug release from tablets made with small granules (0.43 mm - 0.71 mm) was unchanged (f_2 >50) (**Fig. 94**).

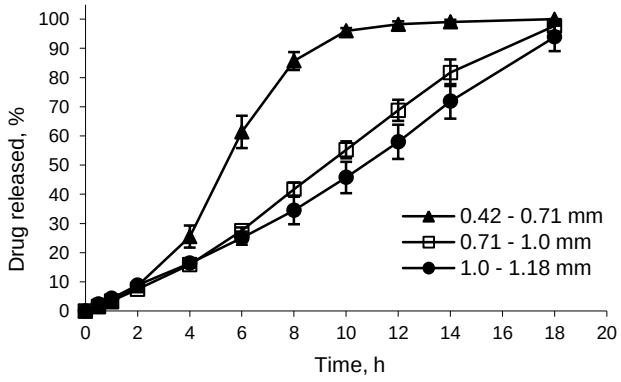

Fig. 93 Effect of granule's size on the carbamazepine releases in PBS.

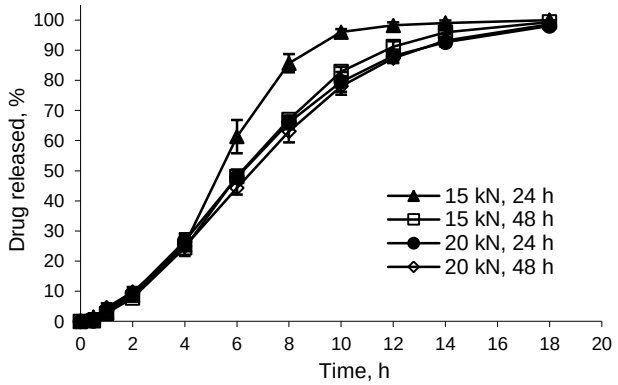

Fig. 94 Effect of curing duration and compression force on the carbamazepine release in PBS (0.43 mm - 0.71 mm, 40 °C/ 75% RH).

In order to investigate effect of surface area/volume ratio on the drug release, same weight (120 ± 5 mg) was tableted with different punch size (7 mm, 8 mm, and 9 mm) at the same compression force (15 kN). As seen in **Fig. 95**, the drug release was increased as the surface area/volume ratio (1.27, 1.40, and 1.54 mm^2/mm^3) increased. Moreover, the drug release proportionally increased with agitation rate (75 rpm to 150 rpm), because of increasing erosion, which is one of the mechanisms controlling drug release from the matrix (**Fig. 96**).

Maximization of drug loading can effectively decrease dosage form sizes as well as reduce manufacturing batch sizes to provide cost savings (Cai et al., 2013). The drug release was unchanged with increased drug content from 30% to 50% w/w (**Fig. 97**), On the other hand, effect of Eudragit® RL:Eudragit® RS ratio on the carbamazepine release is illustrated in **Fig. 98**. Carbamazepine release increased with increased Eudragit® RL ratio. The percentage of functional monomers for Eudragit® RL is approximately 10%, and for Eudragit® RS approximately 5%. Therefore Eudragit® RL has a greater permeability for dissolved drugs.

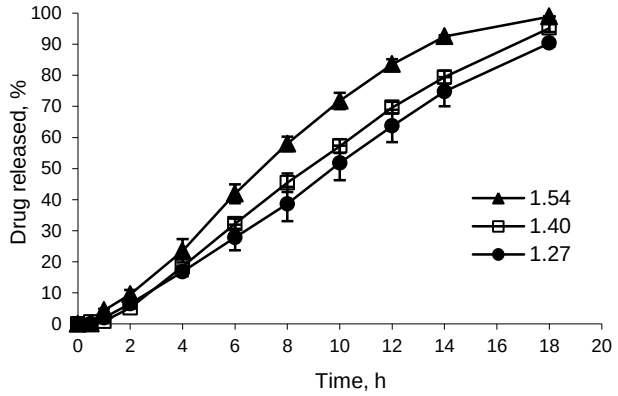

Fig. 95 Effect of surface area/volume ratio (mm^2 /mm^3) on the carbamazepine release in PBS (directly compressed).

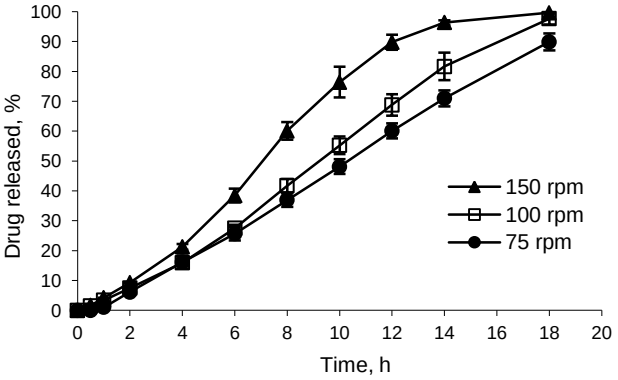

Fig. 96 Effect of speed of agitation rate on the carbamazepine release in PBS from granulated compressed tablets.

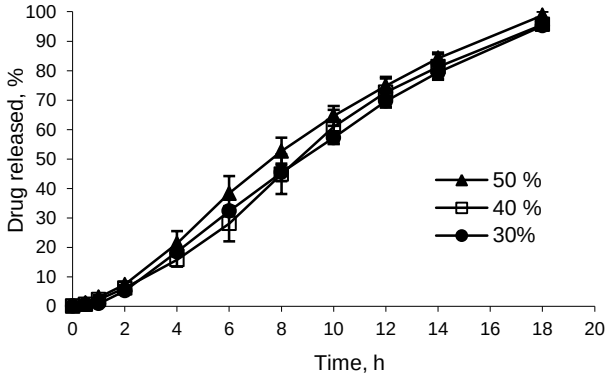

Fig. 97 Effect of drug content on the carbamazepine release in PBS (directly compressed).

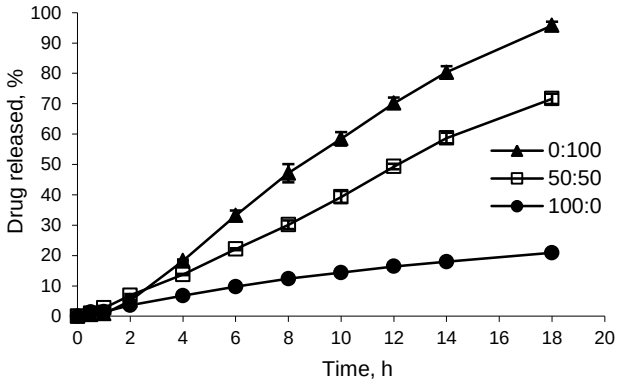

Fig. 98 Effect of Eudragit® RS:Eudragit® RL ratio on the carbamazepine release in PBS (directly compressed).

Conclusions

Controlled-release tablets can be prepared by using Eudragit® RL PO as a hydrophilic carrier for water-insoluble drugs like carbamazepine. The results showed that curing temperature and humidity have a great impact on drug release. At curing temperature equal or more than T_g of the polymer, polymer particles coalesced and carbamazepine released at zero-order kinetic. PXRD showed no change of carbamazepine crystalline structure. The prepared matrix tablet was robust against drug content and up to 50% w/w carbamazepine had not effect on the release. Drug release proportionally changed with surface area/volume ratio, polymer permeability, and agitation rate.

SUMMARY

4. SUMMARY

Use of unconventional polymer blends of Kollicoat® SR 30 D and Eudragit® RL 30 D:

Among the dissolution test conditions, hydrodynamic properties (agitation rate) and mechanical destructive force are important factors, which affect the dissolution behavior of the dosage form. In hydrogel-type tablets, *in vivo* drug release was much faster than that expected from *in vitro* dissolution tests due to the peristalsis of the gastrointestinal tract. Moreover, because single-unit reservoir tablets required a strong/flexible and permeable polymer, there are few publications in this respect, due to lack of polymer with these properties.

The main objective of this part was to use polymer blends of Kollicoat® SR 30 D and Eudragit® RL 30 D as coating materials to increase the mechanical robustness of HPMC matrix tablets and to prepare single-unit reservoir tablets. The effect of polymer blend ratio, curing conditions, coating level, drug content, drug solubility, ionic strength, pH, agitation rate, type of excipient and storage conditions on drug release were evaluated.

For coated HPMC matrix tablets, HPMC and film coat can control the drug release, which could easily be adjusted by varying the polymer blend ratio, which also affected the mechanical properties of the films. Flexibility increases as Kollicoat® SR 30 D increases and Young's modulus increases as Eudragit® RL 30 D increases. At 8% w/w coating level, a force of 3.2 N was required to rupture the swollen tablet after 16 h in the release medium. The coated tablets were robust; coating level (6% to 10%, w/w) and agitation rate (50 rpm to 150 rpm) had no influence on the drug release. A water-insoluble model drug was not released; however, release of water-soluble drugs increased as the drug content increased and decreased as HPMC content increased. Curing at 40 °C/ 75% RH was required for polymer coalescence as it made the film more flexible.

However, for single-unit reservoir tablets, drug release significantly decreased when tablets were cured at 40 °C/ 75% RH for 24 h. Drug release was accelerated by increased Eudragit® RL content, buffer species (phosphate ≥ acetate > chloride ion), drug solubility (diprophylline > metoprolol ≥ theophylline), type of the excipient (MCC > lactose) and increased drug content (50% to 80%, w/w). Ionic strength (0 M to 0.4 M), increased agitation rate of the dissolution medium (50 rpm to 150 rpm), and coating level (6% to 10%, w/w) showed no effect on drug release. *In vitro* release studies showed that the reservoir tablets were strong enough to withstand gastric destructive force.

Use of cellulose acetate butyrate (CAB-553-0.4) as a novel polymer in controlled-release drug delivery:

Advances in polymer science have led to the development of several novel drug-delivery systems. Cellulose acetate is an example that is used for preparation of osmotic tablet; however, toxic solvents and flammability hazard are the greatest disadvantages of the process. Hence, alternative polymers with sufficient strength, permeability, and solubility in a safer organic solvent (like alcohol) are desirable. The objective was to use CAB-553-0.4 (alcohol soluble) as a novel polymer. It was used as a coating material for preparation of osmotic tablets and multiparticulate pellets and as a carrier for high-dose matrix tablets.

For osmotic tablets, factors like polymer blend ratio, drug solubility, plasticizer, coating level, delivery orifice, medium molar concentration, pH, agitation rate, and storage conditions were investigated. With increasing Eudragit® RL PO/CAB ratios, higher medium uptake of the film was observed due to higher permeability of Eudragit® RL polymer, resulting in shorter lag times and faster drug release from the osmotic tablets. Replacing ethylcellulose with cellulose acetate butyrate as a coating material led to shorter lag times and faster drug release due to increased film permeability, moreover, films' strength and flexibility increased. Drug release was osmotically controlled, and it was dependent on drug solubility (the higher the solubility, the faster was the release), buffer species (acetate > phosphate = chloride ion), and plasticizer content (increased plasticizer 10% to 20% w/w, drug release was faster, and rupture force was lower). The caffeine release rate was constant at 10% to 30% w/w coating level, 50 rpm to 150 rpm agitation rate, and 30% to 70% w/w core drug content. *In vitro* study showed that at a 20% w/w coating level, the tablet coat could tolerate forces of more than five times of the gastric destructive force. Drug release was unchanged when the tablets were kept under accelerated storage conditions for one month.

For multiparticulate pellets, other factors like pore-former, type and size of the starter core and compression force were studied (in addition to above factors). The diprophylline release from cellulose acetate butyrate coated pellets decreased, and lag time increased with increased coating level. The release from pellets with sugar nonpareil starter core was faster than with MCC cores, due to higher osmotic activity. The release of diprophylline was faster than caffeine and no release from carbamazepine pellets was seen. For water-insoluble drugs, release could be modified by addition of a pore-former. With increasing drug content (15%, 30% and 45%, w/w), diprophylline release was faster (1.0, 1.6 and 2.7 mg/h). Tableted pellets showed extended

release with no effect of increased compression force from 10 kN to 20 kN and pellet content from 50% to 70%, w/w. Drug release from cellulose acetate butyrate coated pellets was stable during storage under stress condition (40 °C/ 75% RH).

The cellulose acetate butyrate matrix tablets were characterized with respect to the effect of granulation fluids, granule size, compression force, and SA/V ratio. An increased isopropanol content (0%, 50%, and 100% w/w) in the granulating fluid, resulted in decreased caffeine release. Nevertheless, no changes in the X-ray characteristic peaks and the crystalline structure of caffeine were noticed before and after granulation and compression. The mechanism of caffeine release was Fickian diffusion. Polymer content, drug content (up to 80% w/w), compression force (10 kN to 20 kN), granular size (0.15 mm to 1.4 mm) and surface area / volume ratio had no effect on drug release. However, drugs with higher solubility showed an increased release (diprophylline > caffeine > carbamazepine). The release of caffeine from the tablets was robust concerning the effect of the dissolution medium: increased ionic strength (0.4 M to 1.2 M), agitation rate (50 rpm to 150 rpm), and pH did not influence the release. Under accelerated stability conditions, the drug release was unchanged.

Increase tablettability of pellets through Eudragit® RL top coating

The major challenge during compression of coated pellets is the stress, which can rupture the coating and hence change the release characteristics of the formulations, in addition, the hardness of compacts decreased with increasing amounts of pellets.

In order to increase the tensile strength of tableted pellets (pellets' content 70% w/w), pellets were top-coated with Eudragit® RL polymer. Effect of Eudragit® RL topcoat, vehicle type (aqueous or organic), and plasticizer content on drug release was investigated. The diprophylline release (from tableted cellulose acetate butyrate- and ethylcellulose-coated pellets) and tablets' tensile strength increased as the compression force increased; however, tablets made of cellulose acetate butyrate-coated pellets were two times stronger than tablets made of ethylcellulose-coated pellets. Drug release from Eudragit® RL top-coated pellets was in the order of Kollicoat® SR> cellulose acetate butyrate > ethylcellulose and similar to the release from Eudragit® RL top-uncoated pellets (tableted and un-tableted); however, at 5 kN compression force, Eudragit® RL top-coating increased tablets' strength (8%, 135%, and 390%, respectively). For tableted enteric-coated (Eudragit® L and HPMCP) pellets, tablet's strength increased (77% and 225%,

respectively) and within 2 h in 0.1 N HCl, diprophylline release decreased (20% and 30%) when pellets were top-coated with Eudragit® RL. The plasticizer content (0, 10, and 20%) of Eudragit® RL top-coat did not influence the drug release; though, it increased tablet's strength (29%, 88%, and 136%, respectively). Use of organic solution of Eudragit® RL instead of aqueous dispersion did not affect drug release and tablet's strength. Cellulose acetate butyrate- and ethylcellulose-coated pellets were stable with or without Eudragit® RL top-coating, while the drug release increased with time from Eudragit® L- and HPMCP-coated pellets when top-coated with Eudragit® RL under accelerated stability conditions for twelve weeks.

Eudragit® matrix system:

The preparation of a controlled-release high-dose matrix tablets has always been a challenge due to the relatively large amount of excipients generally needed to provide a specific delivery profile resulting in too large dosage forms.

High dose ibuprofen loaded controlled-release matrix tablets were prepared and characterized; Eudragit® RL PO, Eudragit® RS PO, and ethylcellulose were used as carrier. In addition, the role of curing conditions for Eudragit® RL PO matrix tablets was evaluated.

Ibuprofen release from ibuprofen:Eudragit® RS or ibuprofen:ethylcellulose (95:5) matrix tablet was similar to the release from 100% ibuprofen tablet (no polymer). However, ibuprofen release significantly decreased from ibuprofen:Eudragit® RL at the same ratio (95:5), and tablet strength increased. Nevertheless, there was no drug-polymer interaction detected by IR. Increasing the ethanol content in the granulation fluid up to 20% w/w did not influence ibuprofen release from Eudragit® RL matrix tablet. For Eudragit® RS and ethylcellulose matrix tablet, increased ethanol content up to 30% w/w decreased ibuprofen release significantly, and increased tablet strength. Same release profile and release rate of ibuprofen were obtained from different polymers (Eudragit® RL, and ethylcellulose or Eudragit® RS) when different ethanol:water ratio was used (20:80 and 30:70, respectively) as granulation fluid. An increase of ibuprofen content (50%, 65%, and 80%) in the Eudragit® RL matrix decreased drug release rate and increased tablet strength; however, at 95% ibuprofen content, the drug release was faster and tablet' strength was lower. An increase of compression force (5 kN to 15 kN), granule size (0.106 mm to 1.45 mm) and agitation rate (50 rpm to 150 rpm) had no impact on ibuprofen release. Increased surface

area/volume ratio to 1.82 mm^2/mm^3 increased the ibuprofen release significantly. Furthermore, storage under accelerated stability conditions had no influence on ibuprofen release.

Increase ethanol content in the granulation fluid retards carbamazepine release from Eudragit® RL PO matrix tablets. Curing temperature had a crucial role in drug release retardation; at 70 °C/24 h, drug release followed zero-order kinetic because of polymer coalescence. Drug release profile from tablets cured at 70 °C was similar to release profiles of tablets cured at 40 °C/75% relative humidity. X-ray study showed no change in the crystalline structure of carbamazepine. As curing duration increased, moisture uptake increased and drug release was retarded more; beyond 24 h, curing had no further effect. Increased compression force increased tablet strength and decreased drug release rate. The larger the granules size, the slower was the drug release; increased compression force and curing duration for tablets prepared from small granules had no impact on drug release. Drug release proportionally changed with surface area/volume ratio, polymer permeability, and agitation rate. However, drug release was unchanged with increased drug content up to 50% w/w.

ZUSAMMENFASSUN

5. ZUSAMMENFASSUNG

Einsatz von unkonventionellen Polymermischungen aus Kollicoat® SR 30 D und Eudragit® RL 30 D:

Bei Freisetzungstests sind die hydrodynamischen Eigenschaften (Rührgeschwindigkeit) und die mechanischen Zerstörungskräfte wichtige Faktoren, die das Freisetzungsverhalten einer Arzneiform beeinflussen. Wegen der Peristaltik des Gastrointestinaltraktes haben Hydrogel-Tabletten *in vivo* eine viel schnellere Wirkstofffreisetzung, als aufgrund der *In-vitro*-Freisetzungstests erwartet würde. Monolithische Reservoir-Tabletten erfordern Polymere mit Eigenschaften wie Stärke/Flexibilität und Permeabilität. Da Polymere dieser Art fehlen, gibt es nur wenige Publikationen zu diesem Thema.

Das Hauptziel dieses Teils der Arbeit war es, unkonventionelle Polymermischungen aus Kollicoat® SR 30 D und Eudragit® RL 30 D als Überzugsmaterialien zu verwenden um die mechanische Robustheit von HPMC-Matrixtabletten zu erhöhen und monolithische Reservoir-Tabletten herzustellen. Die Einflüsse des Polymermischverhältnisses, der Temperungsbedingungen, der Überzugsmenge, des Wirkstoffgehalts, der Wirkstofflöslichkeit, der Ionenstärke, des pH-Wertes, der Rührgeschwindigkeit, der Art der Hilfsstoffe und der Lagerbedingungen auf die Wirkstofffreisetzung wurden ausgewertet.

Für überzogene HPMC-Matrixtabletten kann die Freisetzung sowohl durch HPMC als auch durch den Filmüberzug kontrolliert werden. Die Freisetzung konnte leicht durch Variation des Polymermischverhältnisses eingestellt werden, was auch die mechanischen Eigenschaften der Filme beeinflusste. Die Flexibilität erhöht sich bei einem höheren Kollicoat® SR 30 D-Anteil und der Young-Modulus nimmt zu bei einem höheren Anteil von Eudragit® RL 30 D. Bei 8% m/m Überzugsmenge war eine Kraft von 3,2 N erforderlich, um die gequollene Tablette nach 16 h im Freisetzungsmedium zum Zerbersten zu bringen. Die überzogenen Tabletten waren robust; weder der Beschichtungsgrad (6% bis 10%, m/m) noch die Rührintensität (50 rpm bis-150 rpm) hatten Einfluss auf die Wirkstofffreisetzung. Der wasserunlösliche Modellarzneistoff wurde nicht freigesetzt. Die Freisetzung der wasserlöslichen Arzneistoffe wurde durch einen höheren Wirkstoffgehalt erhöht und durch einen höheren HPMC-Gehalt verlangsamt. Tempern bei 40 °C/ 75% RH war für die Polymer-Koaleszenz erforderlich, da es den Film flexibler macht.

Die Wirkstofffreisetzung monolithischer Reservoir-Tabletten war signifikant verringert durch Tempern bei 40°C/ 75% RH über 24 h. Gesteigert wurde die Wirkstofffreisetzung jedoch durch einen höheren Eudragit® RL-Anteil, die Pufferspezies (Phosphat ≥ Acetat ≥ Chlorid), die Wirkstofflöslichkeit (Diprophyllin > Metoprolol ≥ Theophyllin), die Art des Hilfsstoffs (MCC > Laktose) und durch einen höheren Wirkstoffgehalt (50% bis 80%, m/m). Im Gegensatz dazu hatten die Ionenstärke (0 M bis 0,4 M), eine erhöhte Rührgeschwindigkeit im Freisetzungsmedium (50 rpm bis 150 rpm) und die Überzugsmenge (6% bis 10%, m/m) keine Auswirkung auf die Wirkstofffreisetzung. *In-vitro*-Studien zeigten, dass die monolithischen Reservoir-Tabletten stark genug waren, um den zerkleinernden Kräften im Magen zu widerstehen.

Verwendung von Celluloseacetatbutyrat CAB-553-0.4 als neuartiges Polymer für die kontrollierte Wirkstofffreisetzung:

Fortschritte in den Polymerwissenschaften haben zur Entwicklung mehrerer neuartiger Wirkstoff-Darreichungssysteme geführt. Ein Beispiel ist Celluloseacetat, welches für die Herstellung osmotischer Tabletten verwendet wird. Doch toxische Lösungsmittel und deren hohe Entzündlichkeit sind die größten Nachteile dieses Prozesses. Daher sind Polymere mit ausreichender Stärke und Permeabilität, die sich in einem sichereren organischen Lösungsmittel (wie Ethanol) lösen lassen, als Alternative wünschenswert. Das Ziel war CAB-553-0.4 (löslich in Ethanol) als neuartiges Polymer zu verwenden. Es wurde als Überzugsmaterial zur Herstellung von osmotischen Tabletten, multipartikulären Pellets und als Matrixträgerstoff verwendet.

Für die osmotischen Tabletten wurden Faktoren wie das Polymer-Mischverhältnis, die Arzneistofflöslichkeit, Weichmacher, die Überzugsmenge, die Freisetzungs-Öffnung, die Molarität des Freisetzungsmediums, der pH-Wert, die Rührgeschwindigkeit und die Lagerbedingungen untersucht. Mit zunehmendem Eudragit® RL PO/CAB-Verhältnis konnte, aufgrund der höheren Permeabilität des Polymers Eudragit® RL, eine stärkere Aufnahme von Medium in den Film beobachtet werden, was zu kürzeren Latenzzeiten und schnellerer Wirkstofffreisetzung aus den osmotischen Tabletten führte. Das Ersetzen von Ethylcellulose durch Celluloseacetatbutyrat als Überzugsmaterial führte zu kürzeren Latenzzeiten und schnellerer Wirkstofffreisetzung aufgrund der erhöhten Durchlässigkeit des Films. Darüber

hinaus waren Filmstärke und -flexibilität erhöht. Die Wirkstofffreisetzung war osmotisch kontrolliert, und hing ab von der Arzneistofflöslichkeit (je höher die Löslichkeit, desto schneller die Freisetzung), Pufferspezies (Acetat > Phosphat = Chloridionen) und vom Weichmachergehalt (bei höherer Weichmacherkonzentration (10% bis 20%) war die Freisetzung schneller und die Reißfestigkeit geringer). Die Koffein-Freisetzungsrate war konstant für 10% bis 30% m/m Überzugsmenge, Blattrührerdrehzahlen von 50 rpm bis 150 rpm und 30% bis 70%, m/m Wirkstoffgehalt des Kerns. Eine *In-vitro*-Studie zeigte, dass der Filmüberzug der Tablette bei 20% m/m Überzugsmenge einer Kraft standhalten konnte, die mehr als fünfmal größer war als die zerkleinernden Kräfte im Magen. Die Wirkstofffreisetzung war unverändert nach einem Monat Lagerung unter den Bedingungen des beschleunigten Stabilitätstests.
Für multipartikuläre Pellets wurden weitere Faktoren (zusätzlich zu den oben genannten Faktoren) wie Porenbildner, Art und Größe des Starterkerns und Presskraft untersucht. Die Diprophyllin-Freisetzung aus Pellets mit einem Celluloseacetatbutyrat-Überzug nahm ab und die Latenzzeit verlängerte sich mit zunehmender Überzugsmenge. Die Freisetzung aus Pellets mit Zucker-Starterkernen war, durch die höhere osmotische Aktivität, schneller als bei solchen mit MCC-Kernen. Die Diprophyllin-Freisetzung war schneller als die Koffein-Freisetzung und Carbamazepin wurde gar nicht freigesetzt. Die Freisetzung von wasserunlöslichen Arzneistoffen konnte durch die Zugabe eines Porenbildners beeinflusst werden. Mit zunehmendem Wirkstoffgehalt (15%, 30% und 45% m/m) wurde die Diprophyllin-Freisetzung beschleunigt (1,0, 1,6 und 2,7 mg/h). Tablettierte Pellets wiesen ein retardiertes Freisetzungsprofil auf, welches nicht beeinflusst wurde durch erhöhte Presskraft (10 kN bis 20 kN) und Pellet-Anteil (50% bis 70%, m/m). Die Wirkstofffreisetzung aus Pellets mit Celluloseacetatbutyrat-Überzug blieb während der Lagerung unter Stressbedingungen (40 °C/75% RH) stabil.

Die CAB-Matrixtabletten wurden bezüglich des Einflusses der Granulierflüssigkeit, der Korngröße, der Presskraft und des Oberflächen/Volumen-Verhältnisses untersucht. Eine Erhöhung des Isopropanolgehaltes (0%, 50%, und 100%, m/m) der Granulierflüssigkeit führte zu einer verringerten Koffein-Freisetzung. Dennoch wurden keine Änderungen der charakteristischen röntgendiffraktriometrischen Peaks und der kristallinen Struktur von Koffein vor und nach der Granulierung und Verpressung beobachtet. Der Freisetzungs-Mechanismus von Koffein folgte dem Gesetz der Fick'schen Diffusion. Polymeranteil, Wirkstoffgehalt (bis zu 80% m/m), Presskraft (10 kN bis 20 kN), Korngröße (0,15 mm bis 1,4 mm) und

Oberfläche/Volumen-Verhältnis hatten keinen Einfluss auf die Wirkstofffreisetzung. Aber Wirkstoffe mit höher intrinsischer Löslichkeit zeigten eine schnellere Freisetzung (Diprophyllin > Koffein > Carbamazepin). Die Freisetzung von Koffein aus den Tabletten war robust hinsichtlich des Einflusses des Lösungsmediums: erhöhte Ionenstärke (0,4 M bis 1,2 M), Rotationsgeschwindigkeit der Blattrührer (50 rpm bis 150 rpm) und pH-Wert wirkten sich nicht auf die Freisetzung aus. Nach Lagerung unter Bedingungen des beschleunigten Stabilitätstests war die Wirkstofffreisetzung unverändert.

Verbesserte Tablettierbarkeit von Pellets durch zusätzlichen Eudragit® RL-Überzug

Die größte Herausforderung beim Verpressen von überzogenen Pellets ist die Belastung durch den Pressdruck, welcher zum Reißen des Überzugs und dadurch zu veränderten Freisetzungscharakteristiken der Formulierung führen kann. Des Weiteren reduzierte ein erhöhter Pelletanteil die Bruchfestigkeit der Tabletten.

Um die Bruchfestigkeit der aus den Pellets hergestellten Tabletten (Pelletanteil 70% m/m) zu erhöhen, wurden die Pellets zusätzlich mit dem Polymer Eudragit® RL beschichtet. Die Auswirkungen des zusätzlichen Eudragit® RL-Überzugs, des Überzugsmediums (wässrig oder organisch) und des Weichmachergehalts auf die Wirkstofffreisetzung wurden untersucht. Die Diprophyllin-Freisetzung (aus verpressten Pellets beschichtet mit Celluloseacetatbutyrat oder Ethylcellulose) und die Bruchfestigkeit der Tabletten nahm mit steigender Presskraft zu. Jedoch waren Tabletten aus Pellets beschichtet mit Celluloseacetatbutyrat zweimal härter als Tabletten aus Pellets mit einem Ethylcellulose-Überzug. Die Freisetzungsgeschwindigkeit aus Pellets mit zusätzlichem Eudragit® RL-Überzug folgte der Rangordnung Kollicoat® SR > Celluloseacetatbutyrat > Ethylcellulose und war ähnlich der Freisetzung der Pellets ohne zusätzliche Eudragit® RL-Beschichtung (verpresst und unverpresst). Jedoch erhöhte der Eudragit® RL-Überzug bei 5 kN Presskraft die Bruchfestigkeit der Tabletten (8%, 135% und 390%). Für verpresste Pellets mit magensaftresistentem Filmüberzug (Eudragit® L und HPMCP) erhöhte sich die Bruchfestigkeit der Tabletten (77% und 225%) durch den zusätzlichen Eudragit® RL-Überzug und die Diprophyllin-Freisetzung innerhalb von 2 h in 0,1 N HCl war verringert (20% und 30%). Der Weichmachergehalt (0%, 10%, und 20%) des Eudragit® RL-Überzugs beeinflusste die Wirkstofffreisetzung nicht, aber die Bruchfestigkeit der Tablette wurde erhöht (29%, 88% und 136%). Die Verwendung einer organischen Lösung von Eudragit®

RL anstelle der wässrigen Dispersion hatte keinen Einfluss auf Wirkstofffreisetzung und Bruchfestigkeit der Tabletten. Pellets mit Celluloseacetatbutyrat- und Ethylcellulose-Beschichtung waren mit oder ohne zusätzlichen Eudragit® RL-Überzug stabil. Hingegen nahm die Wirkstofffreisetzung von Pellets mit Eudragit® L- und HPMCP-Beschichtung, die einen zusätzlichen Eudragit® RL-Überzug hatten, während des beschleunigten Stabilitätstests über 12 Wochen mit der Zeit zu.

Eudragit® Matrix-System:

Die Herstellung von hochdosierten Matrixtabletten mit kontrollierter Wirkstofffreisetzung war schon immer eine Herausforderung, da die große Menge an Hilfsstoffen, die im Allgemeinen benötigt wird um ein spezifisches Freisetzungsprofil zu erreichen, zu übergroßen Arzneiformen führt.

Matrixtabletten mit hoher Ibuprofen-Beladung und kontrollierter Freisetzung wurden hergestellt und charakterisiert; Eudragit® RL PO, Eudragit® RS PO und Ethylcellulose wurden als Trägerstoffe verwendet. Zusätzlich wurde bei Eudragit® RL PO-Matrixtabletten der Einfluss der Temperungsbedingungen untersucht.

Die Ibuprofen-Freisetzung aus Matrixtabletten mit Ibuprofen:Eudragit® RS oder Ibuprofen: Ethylcellulose (95:5) war ähnlich wie die aus reinen Ibuprofen-Tabletten (ohne Polymer). Jedoch war die Ibuprofen Freisetzung signifikant verlangsamt in Ibuprofen:Eudragit® RL-Matrixtabletten des gleichen Mischverhältnisses (95:5) und die Tablettenhärte war erhöht. Dennoch konnte keine Polymer-Arzneistoff-Interaktion im IR-Spektrum beobachtet werden. Erhöhen des Ethanolgehaltes in der Granulierflüssigkeit bis zu 20% beeinflusste die Ibuprofen-Freisetzung aus Eudragit® RL-Matrixtabletten nicht. Für Eudragit® RS- und Ethylcellulose-Matrixtabletten verringerte die Erhöhung des Ethanolgehalts bis zu 30% die Ibuprofen-Freisetzung signifikant und erhöhte die Bruchfestigkeit. Gleiche Freisetzungsprofile und gleiche Freisetzungsraten von Ibuprofen wurden mit verschiedenen Polymeren (Eudragit® RL, Ethylcellulose oder Eudragit® RS) erreicht, wenn verschiedene Ethanol:Wasser-Verhältnisse in der Granulierflüssigkeit verwendet wurden (20:80 und 30:70). Eine Erhöhung des Ibuprofen-Gehaltes (50%, 65%, und 80%) in der Eudragit® RL-Matrix verringerte die Freisetzungsrate und erhöhte die Bruchfestigkeit der Tablette. Bei 95% Ibuprofen-Anteil wurde der Wirkstoff jedoch

schneller freigesetzt und die Bruchfestigkeit der Tabletten war niedriger. Erhöhen der Presskraft (5 kN bis 15 kN), die Korngröße (0,106 mm bis 1,45 mm) und die Rotationsgeschwindigkeit der Blattrührer (50 rpm bis 150 rpm) hatten keine Auswirkungen auf die Ibuprofen-Freisetzung. Hingegen wurde die Ibuprofen-Freisetzung durch eine Erhöhung des Oberfläche/Volumen-Verhältnis auf 1,82 mm^2/mm^3 deutlich schneller. Außerdem hatte die Lagerung beim beschleunigten Stabilitätstest keine Auswirkungen auf die Ibuprofen-Freisetzung.

Ein höherer Ethanolgehalt im der Granulierflüssigkeit verlangsamte die Carbamazepin-Freisetzung aus Eudragit® RL PO-Matrixtabletten. Die Temperatur beim Tempern spielte eine entscheidende Rolle für die Retardierung der Wirkstofffreisetzung; bei Temperungsbedingungen von 70 °C/24 h folgte die Freisetzung einer Kinetik nullter Ordnung aufgrund der Polymer-Koaleszenz. Das Arzneistofffreisetzungsprofil der Tabletten, die bei 70 °C getempert wurden, war ähnlich derer, die bei 40 °C/ 75% relativer Luftfeuchtigkeit getempert wurden. Röntgendiffraktometrische Untersuchungen zeigten keine Veränderung der Kristallstruktur von Carbamazepin. Bei längerem Tempern nahm die Feuchtigkeitsaufnahme zu und die Wirkstofffreisetzung war verlangsamt. Tempern von mehr als 24 h hatte keinen zusätzlichen Effekt. Außerdem führte eine höhere Presskraft zu erhöhter Tablettenbruchfestigkeit und verlangsamter Freisetzungsgeschwindigkeit. Je größer die Korngröße war, desto langsamer war die Wirkstofffreisetzung. Erhöhte Presskraft und längere Temperungszeit hatten für Tabletten aus kleinen Granulatkörnern keine Auswirkungen auf die Wirkstofffreisetzung. Die Arzneistofffreisetzung war proportional zum Oberfläche/Volumen-Verhältnis, zur Polymerpermeabilität und zur Rührgeschwindigkeit. Jedoch blieb die Arzneistofffreisetzung unverändert beim Erhöhen des Arzneistoffgehaltes bis zu 50% m/m.

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PUBLICATIONS AND PRESENTATIONS

7. PUBLICATIONS AND PRESENTATIONS

Research articles

1. **R. Ali**, A. Dashevsky, R. Bodmeier. Kollicoat® SR 30 D and Eudragit® RL 30 D as unconventional polymer blends; increase mechanical robustness of HPMC matrix tablet (manuscript in preparation)
2. **R. Ali**, R. Bodmeier. Kollicoat® SR 30 D and Eudragit® RL 30 D as unconventional polymer blends: preparation and characterization of monolithic reservoir tablet (manuscript in preparation)
3. **R. Ali,** M. Walther, R. Bodmeier. Cellulose acetate butyrate as a novel oral controlled-release polymer; osmotic pump tablet (manuscript in preparation)
4. **R. Ali,** R. Bodmeier. Cellulose acetate butyrate as a novel oral controlled-release polymer; Multiparticulates dosage form (manuscript in preparation)
5. **R. Ali,** R. Bodmeier. Increase pellets' tablettability through Eudragit® RL top coating (manuscript in preparation)
6. **R. Ali,** R. Bodmeier. Cellulose acetate butyrate as a novel oral controlled-release polymer; matrix tablet dosage form (manuscript in preparation)
7. **R. Ali,** M. Walther, R. Bodmeier. Preparation and characterization of high ibuprofen loaded matrix tablet (manuscript in preparation)
8. **R. Ali,** R. Bodmeier. Preparation and characterization of an oral controlled-release tablet of water-insoluble drug, using Eudragit® RL PO as a hydrophilic carrier; role of curing conditions (manuscript in preparation)

Poster presentations

1. **R. Ali**, A. Dashevsky, R. Bodmeier. Coating of HPMC Matrix Tablet in Order to Increase Mechanical Robustness. AAPS Annual Meeting and Exposition, San Antonio, USA, # T2090, 2013
2. **R. Ali**. R. Bodmeier. Characterization of pellets coated with cellulose acetate butyrate. PBP world meeting, Lisbon, Portugal, # 99, 2014
3. **R. Ali**, R. Bodmeier. Cellulose Acetate Butyrate as a Carrier for Preparation of Highly Drug Loaded Extended Release Matrix Tablets. AAPS Annual Meeting and Exposition, San Diego, USA, # W4026, 2014

CURRICULUM VITAE

8. CURRICULUM VITAE

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