WATER-INSOLUBLE POLYMERS AS BINDERS FOR CONTROLLED RELEASE MATRIX AND RESERVOIR PELLETS

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To my family

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List of abbreviations

API	Active pharmaceutical ingredient
CBZ	Carbamazepine
c.l.	Coating level
DBS	Dibutyl sebacate
d.l.	Drug loading
DSC	Differential scanning calorimetry
EC	Ethylcellulose
GIT	Gastro intestinal tract
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methylcellulose
IPA	Isopropanol
K-SR	Kollicoat® SR 30 D
MCC	Microcrystalline cellulose
Meto	Metoprolol tartrate
MFT	Minimum film forming temperature
NP	Nonpareils (sucrose starter cores)
PBS	Phosphate buffer saline
PEG	Polyethylene glycol
PPL	Propranolol HCl
PVA	Polyvinylalcohol
PVP	Polyvinylpyrrolidone
PXRD	Powder X-ray diffraction
SD	Standard deviation
SLS	Sodium lauryl sulfate
TBC	Tributyl citrate
TEC	Triethyl citrate
Theo	Theophylline
W	Water

Chapter 1. Introduction

1. Introduction

1.1 Multiparticulate drug delivery system

The word pellet, is defined as a spherical agglomeration prepared from different starting materials using different techniques. The word pelletization, refers to the agglomeration process which transfers the fine powders and granules into spherical, free flowing units called as pellets (Ghebre-Sellassie, 1989). Pellets as pharmaceutical dosage form have gained increasing attention because of their numerous advantages such as, the uniform distribution throughout the gastrointestinal tract which maximizes the drug absorption and minimizes the side effects or the local irritation (Bechgaard and Nielsen, 1978; Ghebre-Sellassie, 1997). They have low surface area to volume ratio, ideal spherical shape for film coatings, high flowability, low friability and narrow size distribution. Furthermore, they provide high flexibility during formulation development of oral dosage forms. Pellets of different drugs (chemically incompatible, or acting at the same or different sites within the gastrointestinal tract) or of different release rates, can be blended and formulated in a single dosage form (Ghebre-Sellassie, 1989). They can contain drugs with very low loading and high content uniformity, also pellets with high drug loading up to 80% were achievable (Podczeck and Knight, 2006). Pellets are commonly filled into hard gelatin capsules, but can also be compressed into fast disintegrating tablets (Conine and Hadley, 1970; Sandberg et al., 1988; Béchard and Leroux, 1992; Bashaiwoldu et al., 2011).

1.1.1 Pharmaceutical pelletization techniques

There are several techniques available in pharmaceutical industries for pellets preparation (Fig. 1).
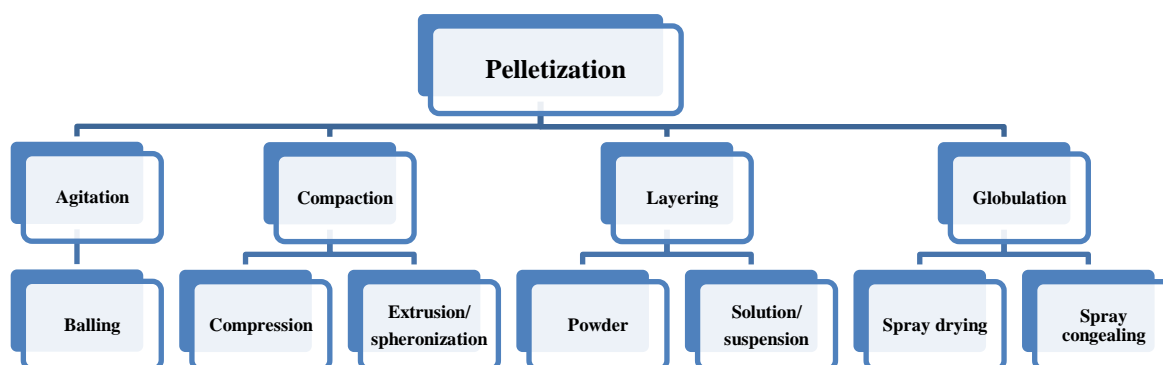
Fig. 1: Classification of pelletization techniques (Ghebre-Sellassie, 1989).

Agitation (balling) process is a pelletization technique in which powders (drug and excipients) are converted upon addition of suitable amount of binding solution or melt, to spherical pellets by continuous rolling motion. When powders come in contact with binder liquid, they start to agglomerate initially with help of liquid bridges, which transfer later on into solid bridges upon liquid evaporation. Similarly, pellets can be formed with the help of melted binder, which solidifies later on upon cooling (Politis and Rekkas, 2011) (Fig. 2).
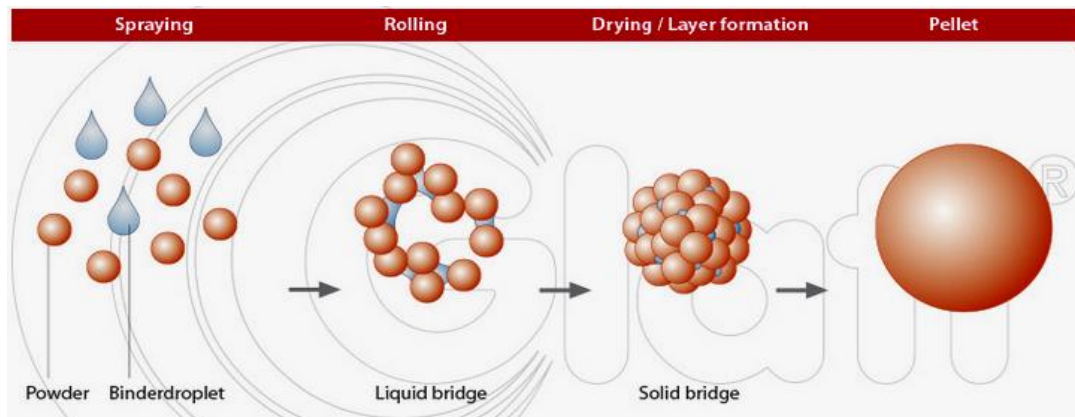
Fig. 2: Schematic presentation of the agitation (balling) technique (Glatt GmbH, 2013).

Pellets prepared by compression technique, are tablets of a very small size that can be considered as spherical pellets. Simply, mixtures of the drug and the excipients are compacted under pressure to prepare pellets of defined size and shape (Ghebre-Sellassie, 1989).

In the spray drying process, solution or suspension of the drug with or without excipients is sprayed into a hot air stream, resulting in highly spherical pellets upon solvent evaporation. Generally, spray-dried pellets tend to have high porosity, therefore, this technique is used to improve the dissolution rate of poorly soluble drugs.

In the spray congealing process, drug is melted, dissolved or dispersed in a hot melt of waxy or fatty materials, and sprayed into cold air stream, where, under suitable processing conditions, this molten materials with drug are transferred into spherical congealed pellets (Cordeiro et al., 2013).

Other pelletization technique, called melt spheronization, in which mixture of the drug and the polymeric carrier is hot-melt extruded (extrusion under elevated temperature at which, the mixture is in molten state). The extrudates are then cut into uniform cylindrical segments, and spheronized also under elevated temperature using traditional spheronizer (Young et al., 2002)**.**

The most commonly used pelletization techniques in the pharmaceutical industries are extrusion/spheronization and solution/suspension drug layering.

1.1.1.1 <u>Extrusion spheronization</u>

This process was first introduced to U.S. market by the reports of (Reynolds, 1970) and (Conine and Hadley, 1970). It is a very important technique for pellets manufacturing even with a high drug loading, and allows a high throughput because of the continuous nature of the extrusion process especially, when combined with multiple spheronizers operating in parallel or in a series. The process involves five steps (Fig. 3):

1- Blending of the dry powders to prepare uniform mixture (mixing).
2- Wet massing of the dry mixture (granulation).
3- Passing the wetted mass through the extruder screen (extrusion).
4- Breaking up the extrudates and rounding the particles into spheres (spheronization)
5- Drying the spheres (drying).

These individual operations can be combined for a continuous process (cascade system). For example, mixing and granulation steps can be performed in one equipment (planetary mixer), or even, mixing, granulation and extrusion operations can be combined in one process using modified extruder as reported by (Goodhart et al., 1973). Additionally, the spheronizer can be designed and located to receive the extrudates directly from the extruder, also, several spheronizers can be connected to one extruder.
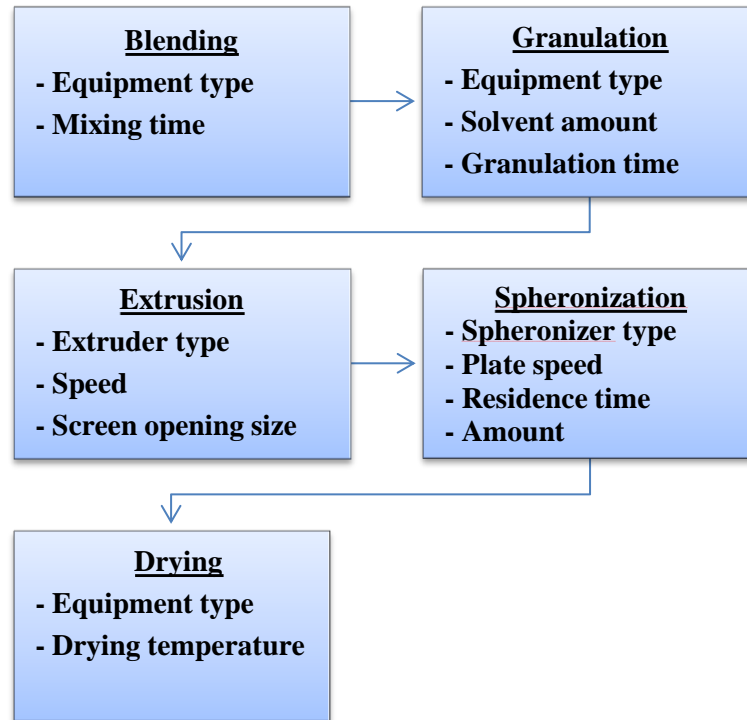
Fig. 3: Processing flow chart of the extrusion/spheronization process containing the individual variables.

For successful extrusion process, the formulation should have a cohesive plastic homogeneous structure with a good flowability and enough lubricant properties that can pass easily through the die (screen) without generating a high amount of heat. The heating produced during extrusion may lead to premature drying of the granules/extrudates or damaging the screen. Furthermore, the wet mass should not adhere to the screws or block the screen. The extrudates should not stick to each other, at the same time they should remain intact and maintain their spaghetti shape after the extrusion (Ghebre-Sellassie, 1989; Fielden and Newton, 1992; Kleinebudde, 1997).

The screen openings size directly determines the diameter of the extrudates, and thereby the mean particle size of the final pellets (Conine and Hadley, 1970). However, the mean pellets size depends also on the formulation (O'Connor et al., 1984).

For successful spheronization process, the extrudates must have sufficient mechanical strength, at the same time; they should be brittle enough to be broken in the spheronizer. On the other hand, they must be sufficiently plastic to enable the cylindrical rods to be spheronized in the spheronizer (Fielden and Newton, 1992; Kleinebudde, 1997).

During the spheronization process, the extrudate is transformed into spherical particles, according to two different suggested mechanisms (Fig. 4):

According to (Rowe, 1985), during spheronization process different shapes of particles can be distinguished which represent different stages. The short rods (cylinders) are first rounded off into cylinders with rounded edges, then to dumb-bell, then forming elliptical particles and finally to perfect spheres (Fig. 4 a).

According to (L. Baert et al., 1993), a twisting of the cylinder occurs after formation of the cylinders with rounded edges, finally resulting in breaking of the cylinder into two distinct spheres (Fig. 4 b).
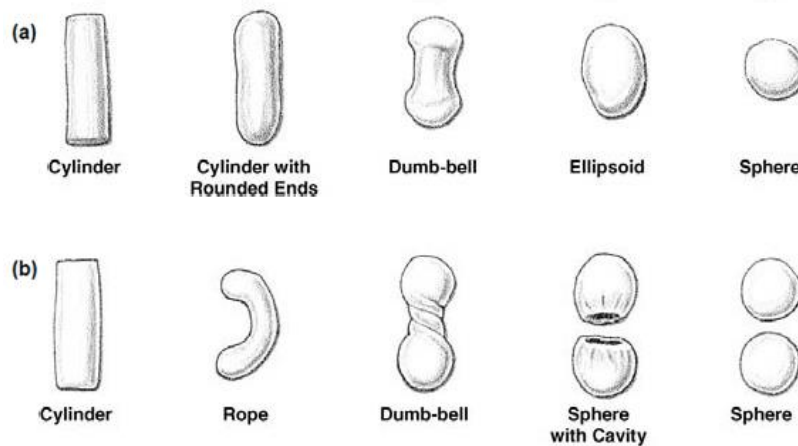
Fig. 4: Mechanism of pellet formation during spheronization process according to (a) Rowe, (b) Baert and Remon.

The processing characteristics of several commercially available excipients were evaluated as spheronization aid (O'Connor et al., 1984). The materials included microcrystalline cellulose, microcrystalline cellulose with carboxymethylcellulose sodium, diabasic calcium phosphate, lactose monohydrate, corn starch and pregelatinized starch. The material properties of these excipients were evaluated in a single-component pellets system (Table 1).

The quality of the pellets produced was dependent on the starting material, especially, the excipients containing microcrystalline cellulose were found to be suitable for spheronization process in single component systems.

Table 1: Processing summary for single-component systems of various matrix materials (Ghebre-Sellassie, 1989)

Excipient	Process			Pellet description
	Granulation	**Extrusion**	**Spheronization**	
Avicel PH types	Yes	Yes	Yes	Spheroids
Avicel RC-581	Yes	Yes	Yes	Spheroids, short rods
Avicel CL-611	Yes	Yes	Yes	Longer rods
Calcium phosphate	No	-	-	-
Lactose	Yes	Yes	No	-
Starch	No	-	-	-
Starch 1500	Yes	No	-	-

Microcrystalline cellulose (MCC) is considered the golden excipient for extrusion spheronization process, because of its binding and rheological properties (Shah et al., 1994). It can absorb high amounts of water, as it has large surface area and high internal porosity (Sonanglio et al., 1995), which imparts the plasticity to the wetted mass, thus, enhances the extrusion spheronization process. According to these properties, pellets prepared via extrusion spheronization using MCC, have a good sphericity, low friability, high density and smooth surface properties. Additionally, relatively wide ranges of water content and processing parameters can be used to produce pellets with acceptable quality, indicating flexibility and robustness of the formulations.

Two theories have been suggested to explain the behavior of MCC during the extrusion spheronization process:

- According to (Fielden et al., 1988), MCC plays a role as a molecular sponge as it absorbs water in high amounts like a sponge. During extrusion, the absorbed water squeezed out of MCC particles and acts as a lubricant, so the resulted extrudates appear dry and brittle, which enhances breaking them during spheronization. At the same time, the plasticization effect of water facilitates spheronization of the pellets.

- In the second theory which called 'crystallite-gel model' (Kleinebudde, 1997), MCC particles form a gel (with a high content of the insoluble solid phase) during extrusion. In presence of water, MCC particles are broken down into smaller units and even partly into single crystals of colloidal size because of the shear stress during granulation and extrusion. The resulting crystallites form a coherent gel-like network

and immobilize the water. Over a particular range of water, which relates to acceptable gel strength, extrusion and spheronization can be done.

In spite of all these excellent properties, MCC also has some disadvantages such as:
- Drug adsorption onto the surface of MCC fibers (Okada et al., 1987).
- Chemical incompatibility with few drugs (Basit et al., 1999).
- Changing of pellets characteristics upon changing the MCC supplier (Newton et al., 1993).
- Lack of disintegration of MCC-based pellets, which leads to prolonged drug release especially with poorly soluble drugs (O'connor and Schwartz, 1985).

To improve the disintegration and/or to increase the drug release from MCC-based pellets, many efforts have been made to find alternatives to microcrystalline cellulose. Such as powdered cellulose (Lindner and Kleinebudde, 1994; Alvarez et al., 2003; Fechner et al., 2003), starch derivatives (Almeida Prieto et al., 2005; Dukić et al., 2007), carrageenan (Bornhöft et al., 2005), chitosan (Santos et al., 2002; Agrawal et al., 2004), hydroxypropyl methylcellulose and hydroxyethyl cellulose (Chatlapalli and Rohera, 1998), polyethylene oxide (Howard et al., 2006), cross-linked polyvinyl pyrrolidone (Liew et al., 2005) and glyceryl monostearate (Basit et al., 1999).

Extrusion spheronization technique as a multi-steps process involves many variables, which may affect on the final pellets quality (Vervaet et al., 1995) such as:
- Moisture content of the granulated mass.
- Type of the granulation liquid.
- Physical properties of the starting materials.
- Extruder type.
- Extrusion speed.
- Properties of the extrusion screen.
- Extrusion temperature.
- Spheronization speed.
- Spheronization time.
- Spheronizer load.
- Drying method.

On the other hand, there are different tests used to evaluate the quality of the pellets such as:

- Size distribution and mean diameter.
- Sphericity.
- Friability and pellet strength.
- Density.
- Flow properties.
- Surface morphology.
- Dissolution testing.

1.1.1.2 Solution / suspension layering

This process involves spraying of successive layers of the drug and binder in form of solution and / or suspension onto the starter cores. The cores usually consist of inert materials such as microcrystalline cellulose, mixture of starch and sucrose or sometimes granules of the same drug.

In this technique, the drug is dissolved or dispersed/ dissolved in a solution of the binder, and sprayed onto the starter cores. As the droplets touch the cores, they spread on the surface and simultaneously solidify forming solid bridges between the core and the initial drug layer and the successive layers of the drug (Fig. 5).
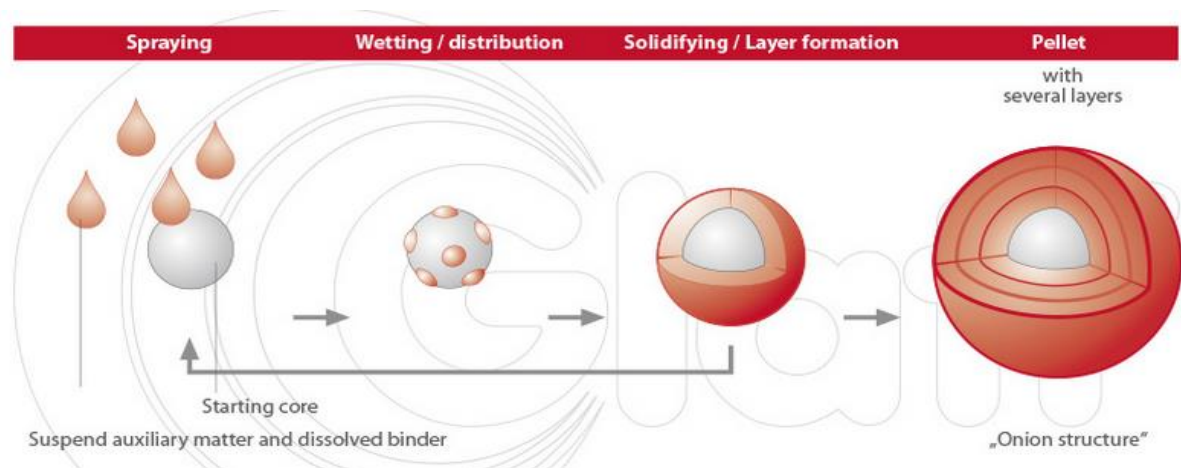
Fig. 5: Schematic presentation of the solution/suspension layering technique (Glatt GmbH, 2013).

Different technologies are being used for drug layering and coating purposes (Christensen and Bertelsen, 1997). Fluidized bed technology is the most preferable and commonly used technique for pellets coating. In this technology, the drug or the coating polymer can be sprayed from the top, from the bottom (using wurster insert) or tangentially (Jones, 1994) (Fig. 6). Because of the unorganized fluidization pattern and the unavoidable spray drying,

top spray mode is considered as less effective in film coating and drug layering, than bottom or tangential modes (Metha et al., 1986; Iyer et al., 1993).

The wurster system is highly preferable for solution and suspension layering, because of its ability to apply high quality films subsequent to the pelletization operation. This technique enables layering of 100-150% w/w solids based on the starting core weight (Ghebre-Sellassie, 1989).

The tangential spraying is especially attractive, because of its ability to apply up to 800% w/w solids in one-step. As the bed in this system is able to expand in two directions, horizontally and vertically, while wurster system, allows only the vertical bed expansion (Ghebre-Sellassie, 1989).

A) **B)** **C)**
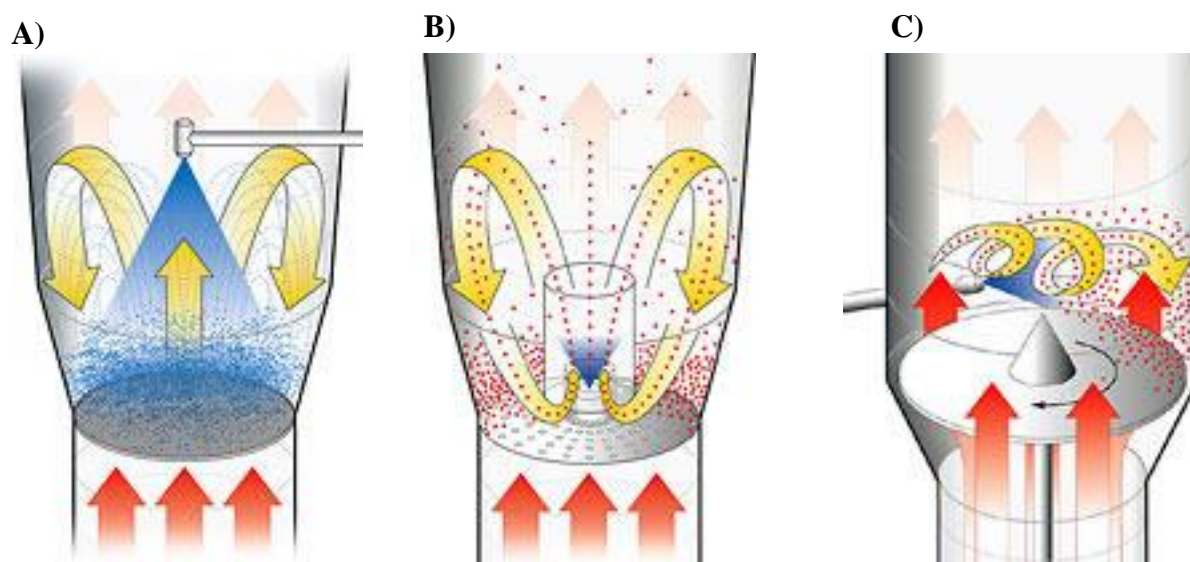
Fig. 6: Schematic presentation of the fluid bed coater with A) top, B) bottom (wurster), and C) tangential spray.

In order to achieve high-quality pellets, different product variables have to be taken into consideration before choosing the process parameter, such as solubility of the drug in the application solvent for solution layering, or solids content for suspension layering. If the viscosity of the spray solution is already high at only 10% solids content, and high drug loaded pellets are required, then, this technique may not be economically desired.

The most critical factor in case of suspension layering is the particle size of the applied drug, the smaller the drug particles, the higher the layering efficiency can be achieved. Generally, it

is very important that the ratio of starting cores diameter to drug particle size should be large. The most preferable particle size for suspension layering is less than 10 microns.

1.1.1.3 <u>Powder layering</u>

Powder layering technique involves the deposition of successive layers of the drug powder and other excipients with the help of binding liquid. The fine drug powder and the binding solution are sprayed simultaneously onto the starter cores at a predetermined controlled rate. Initially, drug particles are bounded to the cores with the help of liquid bridges of the binder solution. The liquid bridges are transformed upon liquid evaporation into solid bridges. Sequential layering of the binder solution and the drug powder allows the formation and growth of the pellets (Ghebre-Sellassie, 1989) (Fig. 7).
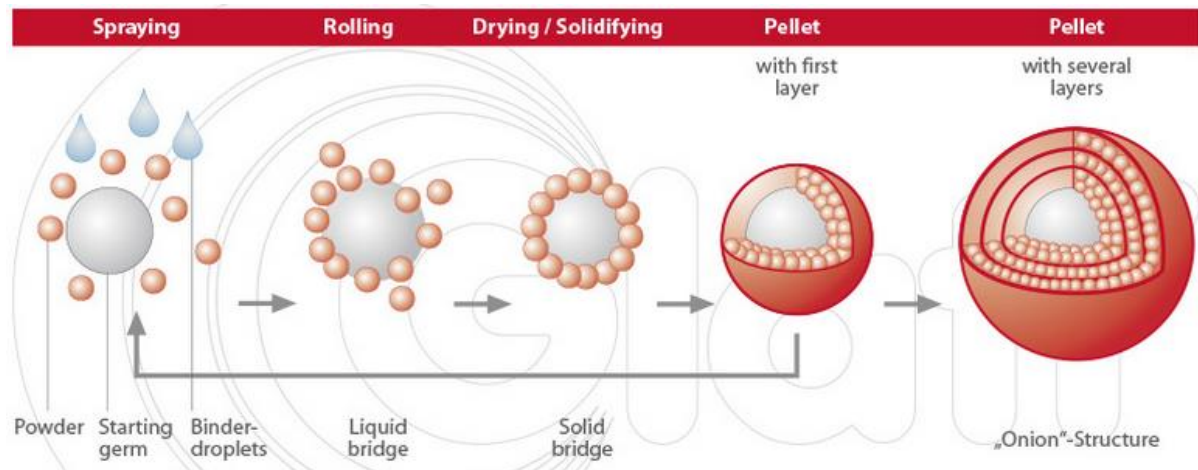
Fig. 7: Schematic presentation of the powder layering technique (Glatt GmbH, 2013).

The main advantage of this process compared to layering with liquid active substances is that the processing time is significantly reduced which leads to a higher efficiency. With optimal process settings, hourly weight gains of up to 300% are possible. Furthermore, it is considered as an environmentally friendly process producing none of the organic or aqueous waste streams.

Usually for powder layering, rotor process is preferable which results in dust-free, very round drug-layered pellets with a narrow particle size distribution.

1.1.2   Binders used for pellet preparation

Binders are adhesive materials that are used in pellets formulations for binding powders and maintaining pellet integrity required for subsequent processing. They can be used either as a solution in a suitable solvent or in dry form. Although dry mixing followed by fluid addition is less efficient than application from solution, however, the later required an additional step for solution preparation and does not allow addition the exact required amount of the binder as it is combined with the solvent.

The majority of binders commonly used for pellets preparation are water-soluble, and include sugars, natural and synthetic polymers. Selection of the best binder for pellet manufacturing is usually determined through a screening process. The most important factors that affect on binder selection are the physiochemical properties of the drug and the preparation technique.

In the case of solution/ suspension layering, it is recommended to use a low-viscosity binder so that the concentration of the drug can be maximized. Usually, amount of the binder when applying the drug from a solution is less compare to suspension, however, the drug layer may be inherently brittle, readily delaminating from the core, or cracking. Therefore, a suitable binder amount is required to avoid these problems.

Binder amount is usually calculated as a percentage based on the drug or based on the total pellet weight. Generally, binders are applied in the concentration range of 2-10% w/w (based on the total pellet weight). For poorly cohesive materials, higher binder amount may be required. Regardless of binder system used, binder amount should be optimized so that the pellets are durable and not friable.

Iyer et al. investigated several binders: PVP, gelatin and HPMC, 5% and 11% w/w in solution layering processes. PVP was tacky and led to uneven surfaces, gelatin and HPMC resulted in rough pellet surfaces at higher binder level (Iyer et al., 1993). Rashid et al. compared low viscous maltodextrin and PVP at concentration of 10-15% as binders for powder layering process. Both binders were effective at higher binder level. PVP resulted in more agglomerations, while, low concentrations of maltodextrin resulted in a low layering efficiency (Rashid et al., 2000). Sinchaipanid et al. used HPMC and HPC as binders for suspension and powder layering. Increasing binder content resulted in lower porosity and pore size, as well as smoother pellet surface. Powder-layered pellets possessed higher pellet

density and smoother surface than did the suspension layered pellets (Sinchaipanid et al., 2004). Suhrenbrock et al. investigated the applicability of the new water-soluble polymer Kollicoat® IR (PVA-PEG graft copolymer) as a binder for suspension drug layering. The required binder amount was 20% based on the drug, and resulted in a layering efficiency between 92.6% and 97.6% even for the coarse drug particles (Suhrenbrock et al., 2011).

During wet granulation step in the extrusion spheronization technique, the liquid bridges hold the powders together initially, however, after liquid evaporation; the binder solid bridges become the main bonding force. Other soluble components may also crystallize and contribute to the bonding mechanisms.

Varshosaz et al. compared PVP and Gelatin/starch at two concentrations as binders for extrusion spheronization technique using two percentages of granulation fluids. 5% of gelatin/starch with 80% of granulation fluid produced more uniform pellets with a narrower particle size range and a high yield of spheres between 710 and l000 µm than the other binder. On the other hand, increasing amount of both binders or percentage of the granulating liquid decreased the drug release significantly (Varshosaz, 1997). Garekani et al. compared different polymers with different viscosity grades as binders for extrusion spheronization technique: PVP K30, PVP K90, HPMC 6cp, HPMC K100LV or HPMC K4M in concentrations of 2, 4 or 6% based on the total pellet weight. Increasing binder viscosity and/or concentration led to decrease pellets yield and sphericity with broader particle size distribution especially with HPMC. Crushing force and elastic modulus of the pellets decreased with increase in PVPs concentration. Drug release rate increased as the concentration of binder increased (Garekani et al., 2012).

Binders can be selected to affect the pellet-release properties. The commonly used water-soluble binder HPMC was shown to improve wettability, dissolution rate and solubility of poorly soluble drugs, as well as preventing recrystallization and thus prolonging supersaturation in different formulations (Usui et al., 1997; Gao et al., 2003; Kennedy et al., 2008). The prolongation in supersaturation was related to the viscosity increase induced by HPMC, also to drug/HPMC interactions.

Similar findings were observed with PVP when used as binder for layering the sparingly water-soluble topiramate. When binder content increased more than 20% w/w in the drug

layer, the physical state of topiramate changed from crystalline to amorphous leading to a dramatic change in the aqueous solubility and dissolution rate, so that the drug release profile changed from zero-order to first-order (Yang et al., 2014).

Hence, increasing concentration of such hydrophilic polymers in the drug layer could have a positive effect on the release of poorly soluble drugs. On the other hand, different water-insoluble polymers can be incorporated in pellets to retard the drug release.

Vila et al. has used different polyacrylic acids (carbopol 974P and 971P) to prepare bio-adhesive pellets of the drug carvedilol by means of extrusion spheronization technique. With 10-20% of these types of carbopol, controlled drug release was achieved in simulated intestinal fluids due to the swelling capacity of carbopol in neutral or basic pH (Vila et al., 1995).

Neau et al. could successfully produce high quality controlled release pellets of the highly soluble drug chlopheniramine maleate via extrusion spheronization technique, by incorporating carbopol 974p as a binder, using calcium chloride in the granulation fluid to reduce the tackiness of the wetted mass (Neau et al., 2000).

Similarly, Bianechini et al. could prolong the release of d-Indobufen using aqueous dispersion of ethylcellulose (Aquacoat® ECD) or Eudragit® RS/RL 30 D with fumaric acid as granulation fluid (Bianechini et al., 1992).

Abbaspour et al. used Eudragit® RS PO and Eudragit® RL PO and their combinations to prepare controlled release pellets containing Ibuprofen via extrusion spheronization technique. Furthermore, he evaluated other pellets properties such as crushing force, elastic modulus, sphericity and surface characteristics (Abbaspour et al., 2005).

Goskonda et al. produced high drug loaded controlled release pellets of the poorly soluble model drug zwitterionic (isoelectric point ~ pH 5.5). The formulation contains Eudragit® RS 30 D, Avicel® RC-591, acetytributyl citrate and fumaric acid to reduce the microenvironmental pH inside the pellets to minimize the drug solubility (Goskonda et al., 1994).

1.2   Controlled release multiparticulate systems

1.2.1   Matrix and reservoir pellets
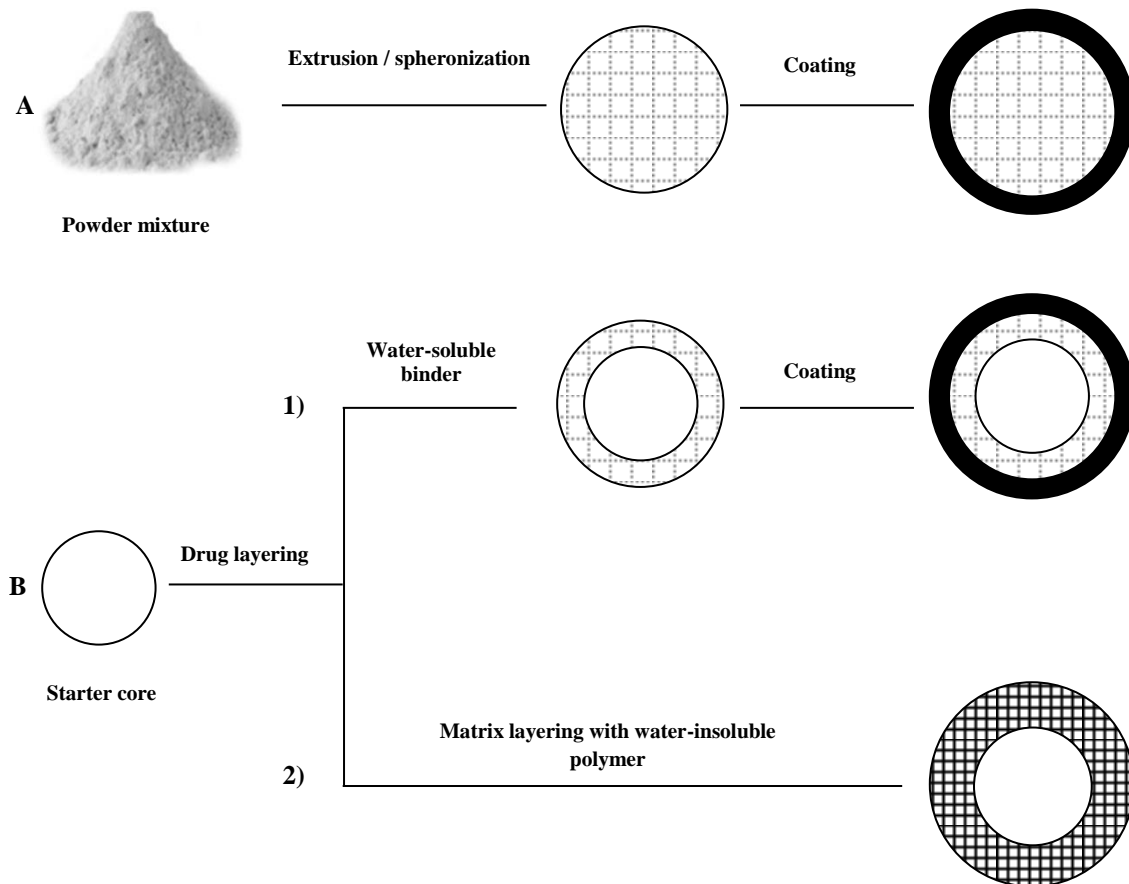
Fig. 8: Schematic presentation of controlled release reservoir- and matrix-pellets.

As shown before, different techniques for pellets preparation are available while, the most commonly used ones are extrusion/spheronization and solution/suspension layering.

Extrusion spheronization technique is usually used to prepare matrix pellets with high drug loading; however, in most cases especially with highly water-soluble drugs, a further coating step with release controlling polymers is required to control the drug release (Fig. 8 A). Alternatively, the release controlling polymers can be incorporated inside the pellets as a binder, which may potentially control the drug release without the need for further coating, or with much thinner coating layer.

Controlled release pellets out of low dose drugs can be prepared by solution/suspension drug layering on starter cores followed by polymer coating (Fig. 8 B_1), this system of pellets called ″reservoir pellets″. It is possible here also to use the water-insoluble polymers as a carrier or

binder for drug layering to prepare controlled release matrix pellets (matrix-layered pellets) (Fig. 8 B_2).

Matrix-layered pellets have several advantages over reservoir pellets such as easy manufacturing and less costs (one-step), higher robustness to mechanical stress (which may damage the coating layer of reservoir pellets resulting in dose dumping). However, they have some disadvantages such as the fast initial release phase, which represents the release of uncovered drug or incompletely covered drug at pellet surface (Huang and Brazel, 2001). Furthermore, high amount of polymer is required in comparison with reservoir pellets, which minimizes the drug loading.

1.2.2   Mechanism of drug release

Drug release mechanism from controlled release multiparticulate system is mainly dependent on system type. Matrix system, where the drug is embedded in the release controlling polymer in one-block, and reservoir system, which consists of a drug depot surrounded by the controlled release polymer. Both types of systems can be subdivided based on the drug concentration, if it is higher or lower than drug solubility in the device.

Nicholas Peppas was the first who introduced an equation, which describes the drug release mechanism from polymeric system (Peppas, 1985).

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

Where: M_t and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; k is a constant including structural and geometric characteristics of the system, and n is a release exponent.

In this model, the value of n characterizes the release mechanism. When the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics. When n = 0.5, Fickian diffusion is the rate-controlling step. Values of n between 0.5 and 1 indicate that both of diffusion process as well as polymer relaxation control the release kinetics (non-Fickian, anomalous or first-order release).

Values of n = 0.5 and 1 are only valid for thin film or slab geometry, while for cylinder, n = 0.45 and 0.89 and for a sphere n = 0.43 and 0.85 (Ritger and Peppas, 1987a, b).

In matrix-layered pellets, where the drug and the polymer are dissolved or dispersed in a suitable solvent and sprayed onto the starter cores, a solid solution (drug dissolved in the polymer) or a solid dispersion (drug dispersed in the polymer) or a combination of both is obtained. If the drug concentration is below drug solubility in the polymer, drug will dissolve in the polymer matrix. In such case, and in the absence of significant changes in the polymer matrix during drug release (such as constant porosity, no swelling, time-independent permeability for the drug), and if perfect sink conditions are maintained throughout the release test, and if drug release is primarily controlled by diffusion through the carrier matrix, the resulting release can be calculated as follows (Crank, 1975):

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} exp\left(-\frac{Dn^2\pi^2 t}{R^2}\right)$$

Where Mt and M∞ are the absolute cumulative amounts of drug released at time t and infinity, respectively; n is a dummy variable, D the diffusion coefficient of the drug within the matrix former, and R the radius of the sphere. This equation was successfully used to quantify drug release from non-degradable controlled release microparticles (Hombreiro-Pérez et al., 2003).

If the drug concentration is higher than drug solubility in the polymer, drug will be dispersed in the polymer matrix. Takeru Higuchi at 1961 has introduced the famous equation, which correlates the square root of time, and the amount of drug released from a thin ointment film with a large excess of drug (Higuchi, 1961).

$$\frac{M_t}{A} = \sqrt{D(2c_0 - c_s)c_s t}$$

Where Mt is the cumulative absolute amount of drug released at time t, A is the surface area of the film exposed to the release medium, D is the drug diffusivity in the carrier material, and c_0 and c_s represent the initial drug concentration and the solubility of the drug in the carrier material, respectively.

The simplicity of this equation gave it a high importance, however, when applying it to controlled drug delivery systems, several assumptions must be fulfilled (Siepmann and Siepmann, 2008), including:

1- Initial drug concentration must be much higher than the drug solubility in the polymer, this is especially important to guarantee that a pseudo-steady state is maintained during release.

2- Drug diffusion takes place only in one direction, which means that the edge effect should be negligible.

3- Drug particle size should be much smaller than thickness of the system.

4- Diffusion coefficient is constant.

5- Perfect sink condition is maintained in the media.

6- The carrier material does not swell or dissolve.

7- No interaction between drug and polymer.

One of the limitations of Higuchi equation is that the prediction is limited to a cumulative drug release of maximum 60%. Above 60%, drug release rate decreases and the linearity is lost. This is due to increased diffusion path length for the drug with time (Tongwen and Binglin, 1998; Siepmann and Peppas, 2011).

The mechanism of drug release from reservoir pellets is quite complicated and dependant on several variables such as cores type, drug solubility and loading, coating type and thickness (Munday and Fassihi, 1989; Ozturk et al., 1990; Kállai et al., 2010).

If the initial drug concentration in the reservoir is below drug solubility in the reservoir (coated pellets with a low drug loading), the released drug is not replaced and drug concentration in the depot (at the inner surface of the coating) continuously decreases with time. Here, if the membrane does not swell or dissolve, if perfect sink condition is maintained and if the drug permeability through the coating remains constant, first order release kinetics result. The drug release can be calculated from the following equation (based on Fick's law of diffusion):

$$\frac{dM_t}{dt} = \frac{ADKc_t}{h}$$

Where M_t represents the absolute cumulative amount of drug released at time t; A is the surface area of the device; D is the diffusion coefficient of the drug within the membrane; K is the partition coefficient of the drug between the membrane and the reservoir; c_t is concentration of the drug in the release medium at time t, and h is thickness of the membrane.

On the other hand, if the initial drug concentration is higher than the drug solubility in the reservoir (high drug loaded coated pellets), the released drug is replaced by the dissolution of undissolved drug, resulting in saturated solutions of the drug at the inner surface of the coating. Also here, if the membrane does not swell or dissolve, if perfect sink condition is maintained and if the drug permeability through the coating remains constant, zero order release kinetics result as long as drug excess is provided, and the drug release can be calculated from:

$$\frac{dM_t}{dt} = \frac{ADKc_s}{h}$$

Where M_t represents the absolute cumulative amount of drug released at time t; A is the surface area of the device; D the diffusion coefficient of the drug within the membrane; K is the partition coefficient of the drug between the membrane and the reservoir; c_s the solubility of the drug in the reservoir, and h the thickness of the membrane.

Practically, many deviations from the previous ideal systems were observed (Ozturk et al., 1990), such as diffusion through water-filled channels created by water-soluble components (Plasticizers and pore former), or, diffusion through micro-cracks in the coating created due to significant hydrostatic pressure build within the reservoir.

Factors which usually affect the permeability of the polymer during coating process are e.g. poor film formation or spray drying of the polymer, the use of non-solvents in the applied polymer solution as well as evaporation of the plasticizers (Lippold and Pagés, 2001; Meier et al., 2004).

The release of phenylpropanolamine HCl from Aquacaot[®] ECD (ethylcellulose-based aqueous dispersion) coated pellets was a combination of osmotically driven release and diffusion through the polymer and/ or aqueous pores (Ozturk et al., 1990).

The release mechanism of rifampicin from ethylcellulose coated nonpareil pellets followed Higuchi diffusion model, and was dependant on plasticizer type and coating thickness (Rao and Murthy, 2002).

In another study, the release from Aquacaot® ECD coated pellets was highly dependent on drug type. Ibuprofen released by diffusion through the coating (due to high affinity to the aqueous dispersion) while, chlorpheniramine maleate diffused through microchannels created due to the osmotic pressure of the core (Bodmeier and Paeratakul, 1994a).

The release of diclofenac sodium from Surelease® (ethylcellulose-based aqueous dispersion) coated pellets was dependant on the coating level. At low coating level, the release occurred through pores and micro cracks, while, at high coating level, drug release was mainly diffusion controlled through intact polymer (Sadeghi et al., 2000).

Inclusion of pore formers has a great influence on the mechanism of drug release from ethylcellulose-coated pellets. At low content of HPMC as pore former, drug release occurred through osmotic pumping, but above a certain value diffusion also contributed to overall drug release (Lindstedt et al., 1989). The addition of small amounts of the newly available water-soluble polymer Kollicoat® IR (PVA-PEG graft copolymer) to the ethylcellulose coatings allowed for a robust controlled drug release, irrespective of the drug solubility or core type. Drug release was mainly controlled by diffusion through the intact polymer (Muschert et al., 2009b).

The plasticizer type can also affect the drug release mechanism. Upon contact with the release medium, water-soluble plasticizers leached out leaving the polymer in glassy brittle state, therefore, the drug diffused through water-filled pores. However, water-insoluble plasticizers kept the polymer in the rubbery state and resulted in a two phase release profile. In the first phase drug was released through pores created by leaching of HPMC and in the second phase pore shrinking occurred leading to a decrease of free volume in the polymer chains. Only in a release medium of high ionic strength, the water-soluble pore former HPMC remained in the coating. Therefore, the drug diffused through a hydrated swollen membrane containing EC, HPMC and insoluble plasticizer (Frohoff-Hülsmann et al., 1999).

1.2.3 Polymers

Several groups of controlled release polymers are available and used as coating materials to control the drug release, such as cellulose ether (ethylcellulose), acrylic polymers and polyvinyl acetate based polymers.

1.2.3.1 <u>Cellulose ether (Ethylcellulose)</u>

Ethylcellulose is a hydrophobic polymer used as binder, film former, masking and time-release agent (in matrix and reservoir systems), water barrier, and rheology modifier. It is a semi-synthetic polymer manufactured by treating the cellulose with an alkaline solution to produce alkali cellulose, which is subsequently reacted with ethyl chloride, resulting in ethylcellulose (Fig. 9) (Dow Cellulosics, 2005). Ethylcellulose is insoluble in gastro-intestinal tract (Siepmann et al., 2007) and assures pH-independent drug release profiles due to its neutral side chains. It is widely used in oral drug delivery as film former, since it is non-toxic, non-allergenic and non-irritant. Ethylcellulose water permeability is very low, and much lower than cellulose acetate (Bindschaedler et al., 1986), therefore, it is usually combined with other water-soluble polymers such as HPMC, HPC (Sakellariou and Rowe, 1995; Chaerunisaa, 2014) or Kollicoat® IR (Muschert et al., 2009a). Ethylcellulose has a high glass transition temperature, between (135-160 °C) depending on the ethoxyl content (which is usually between 44-52%). Therefore, films made from the pure polymer are very brittle and usually require plasticizers (Terebesi and Bodmeier, 2010).
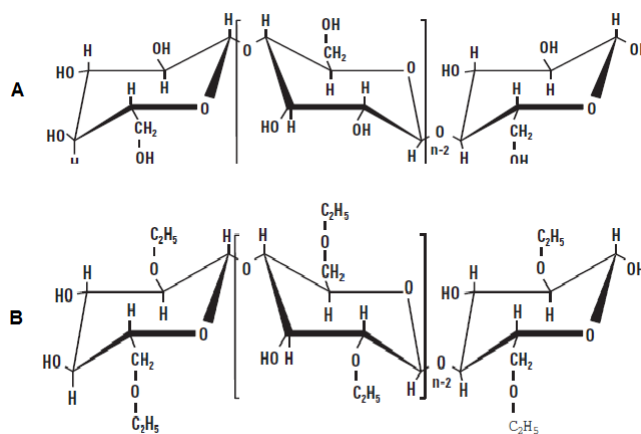
Fig. 9: Chemical structure of A) Cellulose, B) Ethylcellulose (Dow Cellulosics, 2005).

Commercially, ethylcellulose is available in a powder form, under different trade names (Ethocel®, Aqualon®) supplied form different suppliers (Dow and Colorcon, Hercules), and in aqueous dispersion form (Aquacoat® ECD, Surelease®) supplied from (FMC biopolymer, Colorcon).

Ethocel polymers are produced in two ethoxyl types, standard (Std.) grade (ethoxyl content 48.0-49.5%) and medium (Med.) grade (ethoxyl content 45.0-47.0%), also available in a number of viscosity grades depending on the polymer molecular weight.

Aquacoat® ECD is an aqueous dispersion of ethylcellulose, with a solid content of 30% (26% ethylcellulose, 2.4% cetylalcholol, and 1.3% sodium dodecyl sulfate) (FMC Biopolymer). Aquacoat® ECD requires plasticizer to decrease the MFT (81°C) and improve film mechanical properties. Drug release from Aquacaot® ECD coated pellets showed a high curing effect depending on drug type and solubility, curing conditions and plasticizer amount (Bodmeier and Paeratakul, 1994a).

1.2.3.2 Polyvinyl acetate (Kollidon® SR and Kollicoat® SR 30 D)

Kollidon® SR is a co-processed and spray-dried mixture of approximately 80% polyvinyl acetate (PVAc) and 19% polyvinylpyrrolidone (PVP), in addition to, 0.8% sodium lauryl sulphate (SLS) and 0.6% silica as stabilizers (BASF, 2011) (Fig. 10).
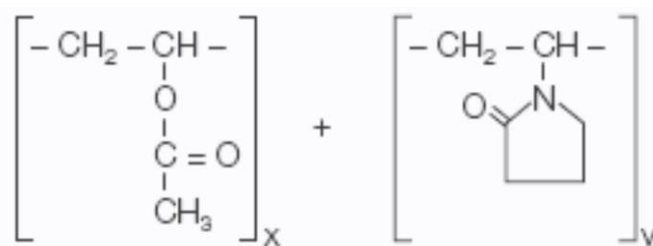
Fig. 10: Chemical structure of Kollidon® SR (BASF, 2011).

It is particularly suitable for preparing of pH-independent sustained release matrix tablets by direct compression. Due to its high plasticity and very good flowability, it enables producing a coherent matrix with low compression force (Hauschild and Picker-Freyer, 2006). Upon contact with the release medium, the water-soluble PVP leaches out creating pores through which the drug releases.

Kollicoat® SR 30 D is an aqueous dispersion of polyvinyl acetate, has a solid content of 30% (27% polyvinylacetate, 2.7% polyvinylpyrrolidone, and 0.3% sodium laurylsulfate) (BASF, 2010). It has a MFT of 18°C and results in brittle films in dry state. Plasticizers are added to improve mechanical properties of the polymer, at the same time, they reduce its MFT depending on the type and amount of plasticizer (Dashevskiy et al., 2004). Since Kollicoat® SR 30 D has no charge or ionizable groups, it results in pH-independent film coatings.

1.2.3.3 <u>Acrylate (Eudragit® polymers)</u>

Eudragit polymers are copolymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups. They are available in a wide range of different physical forms (aqueous dispersion, organic solution, granules and powders) (Evonik, 2007).

Eudragit® RS and Eudragit® RL:

Eudragit® RS, RL are copolymers of ethyl acrylate, methyl methacrylate and a low content of a methacrylic acid ester with quaternary ammonium groups (trimethylammonioethyl methacrylate chloride) (Evonik, 2007) (Fig. 11).
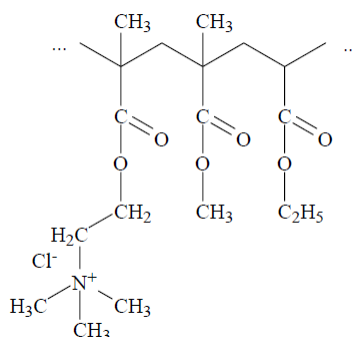
Fig. 11: Chemical structure of Eudragit® RS, RL polymers (Evonik, 2007).

With Eudragit® RL, the molar ratio of the quaternary ammonium groups to the neutral ester groups is 1:20, however, with Eudragit® RS the ratio is 1:40. Since quaternary ammonium groups determine the swellability and the permeability of the films in aqueous media, Eudragit® RL, forms more permeable films with a little delaying action. By contrast, and owing to the reduced content in quaternary ammonium groups, films of Eudragit® RS swell less easily and are only slightly permeable to active ingredients. Eudragit® RS and RL polymers can be mixed in any ratio to produce films with intermediate permeability (Siepmann et al., 2008). Eudragit® RS, RL are water-insoluble swellable polymers, used as matrix carrier (which can be prepared by direct compression or wet granulation or melt extrusion), as well as, as coating material for pellets and tablets. They are available as granules (Eudragit® RS, RL 100), powder (PO), organic solution (12.5%) and aqueous dispersion (30 D).

The aqueous dispersions contain 0.25% sorbic acid as a preservative as well as 0.1% of sodium hydroxide as an alkalizing agent. In order to obtain films of adequate flexibility, 10%

plasticizer (based on dry polymer substance) has to be added to the organic solutions and 20% plasticizer to the dispersions of Eudragit® RS, RL.

Eudragit® RS 30 D, Eudragit® RL 30 D have a minimum film formation temperature of 45 °C and 40 °C respectively.

Eudragit® NE 30-40 D and Eudragit® NM 30 D:

Eudragit® NE, NM are aqueous dispersions of the neutral copolymer based on ethyl acrylate and methyl methacrylate with ratio 2:1 (Fig. 12). Few differences between Eudragit® NE and Eudragit® NM, are summarized in (Table 2).
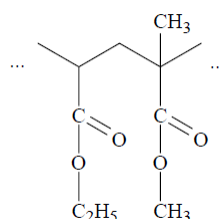
Fig. 12: Chemical structure of Eudragit® NE, NM polymers (Evonik, 2007).

Table 2: Eudragit® NE and Eudragit® NM characteristics

Polymer	Molecular weight, g/mol	Emulsifier,%	Tg (MFT), °C
Eudragit® NE 30 D	800,000	Nonoxynol, 1.5	- 8 (5)
Eudragit® NE 40 D		Nonoxynol, 2.0	
Eudragit® NM 30 D	600,000	Macrogol Stearyl Ether, 0.7	11 (5)

Because of their low MFT (5 °C), no plasticizers are required. They form water-insoluble film, with high flexibility, very low permeability and pH-independent water swellability. These soft polymers are particularly suitable for granulation processes in the manufacturing of matrix tablets and sustained release coatings.

Enteric polymers:

Different enteric polymers are available, that dissolve at different pH, which represent the pH of different parts of the small and large intestines. All are methacrylic acid-based (anionic polymers) and available in different forms (Table 3, Fig. 13).

Table 3: Summary of acrylate-based enteric polymers characteristics

Polymer	Form	Dissolution pH	Chemical structure	Emulsifiers,%	Tg (MFT), °C
Eudragit® L 30 D-55	30% Aqueous dispersion	Above 5.5	Methacrylic acid - ethyl acrylate copolymer 1 : 1	SLS, 0.7, Tween 80, 2.3	96 (27)
Eudragit® L 100-55*	Powder				96
Eudragit® L 100	Powder	Above 6	Methacrylic acid - methyl methacrylate copolymer 1 : 1	SLS, 0.3	> 130
Eudragit® L 12.5	12.% organic solution				
Eudragit® S 100	Powder	Above 7	Methacrylic acid - methyl methacrylate copolymer 1 : 2		
Eudragit® S 12.5	12.% organic solution				
Eudragit® FS 30 D	30% Aqueous dispersion		Methyl acrylate, methyl methacrylate and methacrylic acid 7 : 3 : 1	SLS, 0.3, Tween 80, 1.2	43 (14)

* Eudragit® L 100-55 is a dry substance obtained from Eudragit® L 30 D-55.

Eudragit® L 55   **Eudragit® L, S**   **Eudragit® FS 30 D**
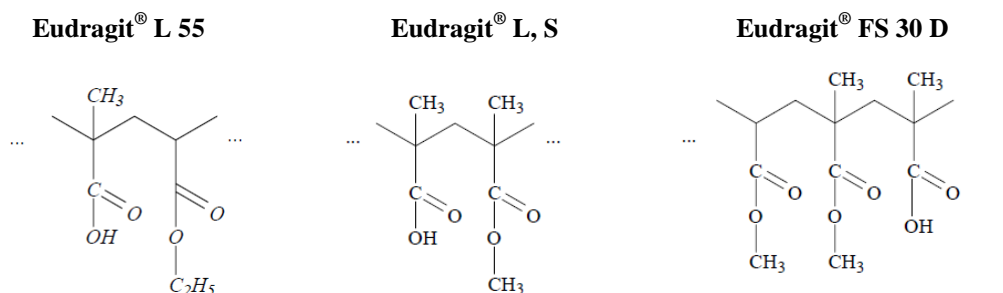
Fig. 13: Chemical structure of acrylate-based enteric polymers (Evonik, 2007).

They assure pH-dependant drug release profiles due to their anionic structure. Furthermore, they provide an ideal protection of the gastric fluid-sensitive drugs and of the gastric mucosa from irritative drugs. On the other hand, different enteric polymers, which dissolve at different pH, can be combined with each other or with extend release polymers to achieve site specific drug delivery within the GI tract (Lecomte et al., 2003; Siepmann et al., 2008).

1.2.3.4 <u>Polymer blends for controlled release</u>

Blending of two (or more) polymers is one of the formulation tools to achieve certain target, which cannot be achieved by using the polymers individually. This target can be desired drug release kinetics, or facilitate film formation in case of aqueous polymer dispersion, or improve mechanical properties and stability of the polymeric coating (Siepmann et al., 2008).

One of the most commonly used polymer blends is Eudragit® RS (low permeability) with Eudragit® RL (high permeability). By varying the blend ratio, different release rates can be achieved (AlKhatib and Sakr, 2003; Kramar et al., 2003).

Phuapradit et al. blended Eudragit® RL with ethylcellulose or cellulose acetate. In both cases, the permeability of the resulting film increased significantly; however, in much higher extent in case of ethylcellulose. On the other hand, the mechanical strength of the polymeric film decreased upon addition of Eudragit® RL (Phuapradit et al., 1995).

Different water-soluble polymers have been added to the poorly permeable ethylcellulose to improve its permeability, such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol-polyethylene glycol graft copolymer (PVA-PEG graft copolymer) (Nesbitt, 1994; Frohoff-Hülsmann et al., 1999a; Tang et al., 2000; Rohera and Parikh, 2002).

Blends of GIT-insoluble and enteric polymers are particularly interesting for coating of weakly basic drug exhibiting highly pH-dependent solubility. The principal is, to compensate the dropping in drug solubility in high pH-media, by simultaneous increase in coating permeability upon dissolving the enteric polymer. Thus, pH-independent sustained release profile can be achieved. Several blends (GIT-insoluble : enteric polymers) were successfully applied as coating for different weakly basic drugs and resulted in pH-independent sustained release profile. Such as Eudragit® NE 30 D : Eudragit® L (Amighi and Timmermans, 1998), Kollicoat® SR 30 D : Kollicoat® MAE 30 DP (Dashevskiy et al., 2004b), Eudragit® RS : HPMCAS with help of fumaric acid to provide an acidic microenvironment inside the pellets (Munday, 2003).

Eudragit® NE 30 D being highly flexible polymer was added to Eudragit® RL 30 D to improve the mechanical stability of the coating. As the tablet core was highly swellable, a

highly flexible coating was required to resist the mechanical stress generated from the core (Deshpande and Shah, 1997).

Beckert et al. blended the highly brittle enteric polymer Eudragit® L 30 D-55 with the highly flexible sustained release polymer Eudragit® NE 30 D, to reduce damage of the coating and thus surviving the enteric release property upon pellets compression (Beckert et al., 1996). Similarly, Dashevskiy et al. showed that, addition of 30% of Kollicoat® EMM 30 D to the enteric polymer Kollicoat® MAE 30 DP, could reduce the film damage during compression significantly, at the same time, did not affect the enteric release properties (Dashevskiy et al., 2004a).

Sometimes, enteric polymers can be added to GIT-insoluble polymers to reduce the tackiness during coating. For example, addition of 15% Eudragit® L 30 D-55 to Eudragit® NE 30 D prevented effectively pellets agglomeration during coating and storage, simultaneously, reduced the curing time required to achieve a stable film (Zheng and McGinity, 2003). On the same principle, Eudragit® L 100 increased significantly the storage stability of Eudragit® RS 30 D coated pellets (Wu and McGinity, 2003).

Interestingly, ethylcellulose was incompatible with most GIT-soluble and enteric cellulose derivates, although they have the same cellulosic backbone. Blends of ethylcellulose and cellulose acetate phthalate (CAP) or hydroxypropyl methylcellulose acetate phthalate (HPMCP) showed phase separation. However, CAP and HPMCP showed plasticizing effects on ethylcellulose, which can be attributed to polymer-polymer interactions via carboxybenzoyl groups. These interactions also lead to an incomplete enteric polymer leaching out of the films at high pH (Sakellariou et al., 1986; Sakellariou and Rowe, 1991; Sakellariou, 1995).

It is important to mention, that by blending of two polymers several considerations have to be taken into account especially when the polymers are in the aqueous dispersion form (Siepmann et al., 2008). Generally, anionic polymers (such as Eudragit® L and Eudragit® S) can be blended in any ratio with neutral polymers (Eudragit® NE), while with cationic dispersions (e.g., Eudragit® RS, Eudragit® RL), interactions between the ionic groups of the polymers can occur, resulting in flocculation.

In addition to the compatibility of the ionic groups of the components when using aqueous polymer dispersions, also the size of the polymer particles in the coating formulations can play a significant role in the resulting system and drug release properties. Blends of Aquacoat® ECD (ethylcellulose aqueous dispersion with average particle size of 200 nm) and an enteric polymer such as HPMCAS (particle size=5 μm) or Eudragit® L (particle size 80 nm) were used to coat theophylline pellets. Although, in phosphate buffer pH 7.4 both enteric polymers are soluble, nevertheless, the release from ethylcellulose with Eudragit® L was much faster than with HPMCAS. As the particles of Eudragit® L were much smaller than HPMCAS, they could distribute more homogeneously between ethylcellulose particles. Consequently, the ethylcellulose structures remaining after enteric polymer leaching at high pH were mechanically much weaker in case of Eudragit® L than HPMCAS, resulting in more crack formation and faster drug release (Siepmann et al., 2005).

Furthermore, the type of plasticizer and its affinity to the polymers to be blended may play an important role for the resulting coating properties and drug release. In contrast to TEC, DBS had a higher affinity to ethylcellulose than to Eudragit® L, resulting in potential redistributions of this plasticizer within the polymeric blend and changes in the release profiles during storage (Lecomte et al., 2004).

1.2.4 Tabletting of controlled release pellets

Controlled release pellets can be administered orally either filled into hard gelatin capsules, or compressed into fast disintegrating tablets. Most recently, there has been an increasing interest in the development of multiparticulate dosage forms in the form of tablets, as they are mechanically stronger, can be divided, dispersed into water prior to intake and produced at lower cost and higher rate when compared to capsules (Chambin et al., 2005; Murthy Dwibhashyam and Ratna, 2008).

Compaction of pellets is a high challenging area, therefore, only few pellets-containing tablet products are available, such as Beloc® ZOK, Antra® MUPS. The main challenges during pellets compression include damaging of the release-controlling polymer because of the stress applied for compression, which leads to lose the controlled release property (Altaf et al., 1998). Furthermore, the pellets may fuse together resulting in a further release retardation because of decreasing the surface area and increasing disintegration time of the tablets (Dashevskiy et al., 2004a). In addition, segregation of the pellets from tabletting excipients can occur prior to compression resulting in content uniformity problems (Hosseini et al., 2013).

For successful production of controlled release pellets-containing tablets, several formulation and process variables have to be taken into consideration (Fig. 14).

Pellets core	Release controlling polymer	Tableting excipients
• **Composition** • **Shape** • **Size** • **Porosity and density** • **Loading in the tablet**	• **Nature** • **Amount/thickness** • **Plasticizers** • **Thermal treatment**	• **Nature** • **Particle size** • **Amount**

Fig. 14: Formulation variables of pellets compression.

The preferable mechanical properties of the pellets core are that they should be strong enough to withstand the compression force, at the same time, they should have some degree

of plasticity to accommodate changes in shape and deformation during compression (Beckert et al., 1998; Schwartz, 1994). Therefore, the core should contain ideally materials that undergo plastic deformation such as microcrystalline cellulose.

Maganti and Çelik compared compaction properties of pellets, mainly consist of MCC and some other excipients, with that of powder from which the pellets were made. The powders exhibited plastic deformation during compression and resulted in strong tablets, while the pellets showed elastic deformation and brittle fragmentation and thus, lower strength tablets were resulted. This was due to the lower contact area of the pellets compare to powders (Maganti and Çelik, 1993).

Incorporation of soft materials such as polyethylene glycol 6000 or some waxy materials such as glyceryl behenate (Compritol) into pellets of microcrystalline cellulose, led to an improve in pellets compressibility. This is due to increasing the plastic deformation of the pellets during compression (Nicklasson and Alderborn, 1999; Iloanusi and Schwartz, 1998).

Cured ibuprofen pellets containing Eudragit® RS/RL, underwent a plastic deformation without any fracture upon compression (Abbaspour et al., 2005). The plastic behavior of these pellets was due to the structural deformation of Eudragit® polymers from glassy to rubbery state upon curing. The higher drug loaded pellets (80% w/w) exhibited brittle properties even after curing, because of lack of the Eudragit® polymer in their structure.

Shape of the pellets to be compressed also plays an important role in tablet forming ability (Johansson and Alderborn, 2001).Tablets formed from granules of an irregular shape had a closer pore structure than those formed from spherical pellets of equal intragranular porosity, and the granules seemed to deform to a higher degree during compression. Furthermore, tablets formed from irregular granules were stronger than those formed from the pellets.

The pellets size can also affect the compaction properties. The smaller the pellets, the less affected by compression, as they were significantly stronger, relative to their size, than the larger pellets (Haslam et al., 1998). In another study, the larger pellets were more elongated and deformed than the smaller pellets. This was because of decreased number of force transmission points with the larger pellets, thus, increased the force applied on each individual pellet (Johansson et al., 1998). In the case of pellets coated at the same coating

level, the larger pellets were more resistant to compression, because of increased coating thickness due to the decrease in surface area (Bechard and Leroux, 1992).

Porosity of the pellets to be compressed seems to be a very important factor that affects the compaction behavior. Coated pellets of a high porosity were highly deformed upon compression; however, the drug release was unchanged. While, the lower porosity pellets suffered from damage of the coating, thus, increased drug release, although, they were less deformed (Tunón et al., 2003). Furthermore, increasing the pellets porosity, led to an increase in the degree of deformation and densification during compression, thereby, increased the compressibility of the pellets (Nicklasson et al., 1999).

As mentioned before, different groups of controlled release polymers are available and used as coating materials, such as cellulose ethers (ethylcellulose), acrylic polymers and polyvinyl acetate based polymers. Compared to ethylcellulose films, acrylic polymer films were more flexible and therefore more suitable for coating of pellets to be compressed into tablets. Films prepared from ethylcellulose dispersions were of lower puncture strength and elongation values than those prepared from organic solutions. The enteric dispersion Eudragit® L 30 D, resulted in brittle films in dry state, but in very flexible films in the wet state, because of the plasticization effect of water (Bodmeier and Paeratakul, 1994b). Films of Eudragit® NE 30 D were very flexible with a high elongation value, and the drug release from coated pellets was not affected by compression (Łunio et al., 2008).

The plasticizer type and ratio have also a great influence on mechanical properties of the polymeric films. Eudragit® RS 30 D films plasticized with water-insoluble plasticizers showed a much higher flexibility in the wet state than the corresponding films plasticized with water-soluble plasticizers (Bodmeier and Paeratakul, 1994b). This was because of leaching of the water-soluble plasticizers upon contact with the release medium, leaving the polymer in a brittle state. Unplasticized Kollicoat® SR 30 D coatings were brittle and damaged during compression. The addition of only 10% w/w triethyl citrate as a plasticizer improved the flexibility of the films significantly and therefore were not affected by pellets compaction (Dashevskiy et al., 2004a).

Thickness of the coating has to be considered also when developing pellets-containing tablet formulation. Beckert et al. compared different enteric coatings regarding their performance

upon compression. The higher the coating level, the less drug which was librated after compression (Beckert et al., 1996). Sawicki and Łunio have found that Kollicoat® SR 30 D coated pellets with thickness of 35 µm have deformed by compression with significant increase in drug release. Increasing film thickness to 50 µm, decreased the deformation upon compression remarkably (Sawicki and Łunio, 2005).

The tableting excipients must fill the voids between the pellets acting as a cushion to prevent the fusion and to protect the polymeric coating during compression. They can be either as a powder or in form of agglomerations such as granules. The granules are more preferable, as they are of closer size to the pellets, so, less risk of segregation (Murthy Dwibhashyam and Ratna, 2008). The protection effect of an excipient depends on the particle size and the plastic elastic properties. Wagner et al. compared different tableting excipient regarding their protection efficiency during pellets compression (Wagner et al., 2000). The order of least damage to the coating was: polyethylene glycol 3350 < microcrystalline cellulose < crospovidone < lactose < dicalcium phosphate. Vergote et al. prepared placebo beads of different excipients and mixed with film-coated pellets, to evaluate them as cushioning and protective agents during pellets compression. Only the tablet formulations containing wax/starch beads provided good protection to the film coat (Vergote et al., 2002). Hosseini et al. applied a cushion layer based on microcrystalline cellulose on the top of ethylcellulose coated pellets. The cushion layer facilitated segregation-free direct compression of the pellets without damaging the highly brittle coating ethylcellulose (Hosseini et al., 2013).

1.2.5 Biorelevant dissolution testing

Dissolution testing is an official evaluation method for solid oral dosage forms. The pharmacopeial methods were initially developed for immediate release dosage forms and then extended to modified release dosage forms. The typical dissolution testing is usually used for assessing batch-to-batch consistency (QC test), as guidance for development of new formulations and as a tool to prove the product quality after certain changes such as the formulation or manufacturing process.

The use of dissolution test was later on extended for bioavailability prediction. i.e. to predict the in vivo performance of products from in vitro test by a proper correlation, so called in vitro/in vivo correlation (IVIVC) (Uppoor, 2001; Royce et al., 2004; Emami, 2006). Selection of the test conditions, which can reflect the in vivo drug release is highly challenging, and requires a high knowledge in the GIT physiology. The test conditions should be based on physicochemical characteristics of the drug substance, at the same time, should cover all possible variables, which can be faced in the GIT. Physiological conditions vary wildly along the gastrointestinal (GI) tract. These variations are related to intersubject variability such as disease states, physical activity level, stress level and food ingestion (Dressman et al., 1998).

Different biorelevant media have been developed to mimic the physiological conditions in the gastrointestinal tract (Dressman et al., 1998; Klein et al., 2004; Stippler et al., 2004; Vertzoni et al., 2004; Kalantzi et al., 2006; Jantratid et al., 2008). There are four standard biorelevant dissolution media that are typically used for in vitro dissolution:

- Simulated gastric fluid (SGF).
- Simulated intestinal fluid (SIF).
- Fasted state simulated intestinal fluid (FaSSIF).
- Fed state simulated intestinal fluid (FeSSIF).

Each media represents various pH and or components associated with the gastrointestinal tract. For example, SGF represents the pH and the components observed in the stomach (pH 1.2). SIF mimics the intestinal tract (pH 6.8), and FaSSIF, FeSSIF are for the fasted or fed conditions in the intestine, respectively.

1.3 Research objectives

- To investigate the effect of binder type (water soluble vs. insoluble) and granulation fluid (aqueous vs. organic) on properties and drug release from pellets prepared by extrusion spheronization technique.

- To investigate the applicability of the water-insoluble polymers as binders for drug layering as an alternative to water-soluble binders to control drug release, furthermore to evaluate the performance of the pellets upon compression into tablets.

- To investigate the feasibility to control and to adjust the release of two drugs, having different aqueous solubilities, layered on the same pellet as a multilayer matrix pellet.

- To investigate the applicability of the aqueous polymer dispersions as binders (carriers) for drug layering to the control drug release, furthermore to evaluate the performance of the pellets upon compression into tablets.

Chapter 2. Materials and methods

2. Materials and methods

2.1 Materials

Model drugs

Metoprolol tartrate, diprophylline, propranolol HCl, paracetamol, theophylline, verapamil HCl, ibuprofen and carbamazepine (BASF SE, Ludwigshafen, Germany).

Polymers

Hydroxypropyl methylcellulose (HPMC) (Methocel® E5, Colorcon, Dartford Kent, UK), polyvinylpyrrolidone (PVP) (Kollidon® 30, BASF SE, Ludwigshafen, Germany), vinylpyrrolidone-vinyl acetate copolymer (Kollidon® VA 64, BASF SE, Ludwigshafen, Germany), PEG 6000-vinylcaprolactam-vinyl acetate graft copolymer (Soluplus®, BASF SE, Ludwigshafen, Germany), ethylcellulose (EC) (Ethocel® 10-20-45-100 cp, Colorcon, Dartford Kent, UK), ethylcellulose aqueous dispersion (Aquacoat® ECD, FMC BioPolymers, Cork, Ireland), ethyl acrylate and methyl methacrylate copolymer with a low content of a methacrylic acid ester with quaternary ammonium groups, granules and aqueous dispersion (Eudragit® RS 100, Eudragit® RS 30 D, Evonik Industries AG, Darmstadt, Germany), ethyl acrylate and methyl methacrylate copolymer aqueous dispersion (Eudragit® NE 30 D, Evonik Industries AG, Darmstadt, Germany), co-spray dried polyvinyl acetate-vinylpyrrolidone (Kollidon® SR, BASF SE, Ludwigshafen, Germany), polyvinyl acetate aqueous dispersion (Kollicoat® SR 30 D; BASF SE, Ludwigshafen, Germany), methacrylic acid and ethyl acrylate copolymer, powder and an aqueous dispersion (Eudragit® L 100-55, Eudragit® L 30 D-55, Evonik Industries AG, Darmstadt, Germany), methacrylic acid and methyl methacrylate copolymer (Eudragit® S 100, Evonik Industries AG, Darmstadt, Germany), methyl acrylate, methyl methacrylate and methacrylic acid copolymer (Eudragit® FS 30 D, Evonik Industries AG, Darmstadt, Germany).

Fillers

Microcrystalline cellulose (MCC, Avicel® PH-101, 102, FMC BioPolymers, Philadelphia, PA, USA). MCC 101 was used as a pelletization aid for extrusion spheronization, while, MCC 102 was used as a pellets tableting aid.

Pellets

Sucrose nonpareils beads 710-850 μm (NP, Suglets®, NP Pharm S.A., Bazainville, France), MCC beads (Cellets® 780, Harke Pharma, Mühlheim a.d.R., Germany).

Plastcizers

Triethyl citrate (TEC) (Citroflex® 2; Morflex, Greensboro, NC, USA), tributyl citrate (TBC) (Citroflex® 4; Morflex, Greensboro, NC, USA).

Surfactants

Polyoxyethylene sorbitan monooleate (Tween® 80; Sigma-Aldrich Chemie GmbH, Steinheim, Germany), sodium lauryl sulfate (SLS) (Roth GmbH & Co. KG., Karlsruhe, Germany).

Solvents

Isopropanol, water.

Other excipients

Talc (Luzenac pharma, Europe, Toulouse, France), magnesium stearate (Pharma veg®, Baerlocher, Germany), sodium chloride (NaCl) (Roth GmbH & Co. KG., Karlsruhe, Germany).

2.2 Methods

2.2.1 Pellets preparation

2.2.1.1 <u>Extrusion spheronization</u>

The ingredients API, MCC 101 and the binder, were premixed with different ratios (Table 6) in a planetary mixer (Kitchen Aid, model KSM90, Michigan, USA). The required amount of granulation fluid (Table 6) for wet massing was added using plastic pipette gradually along 5 minutes during mixing, then the wetted mass was granulated for further 3 minutes. The extrusion was done immediately after granulation process using radial screen extruder (Caleva model 10, Caleva LTD, Dorset, UK), equipped with a 15 cm screen, with holes diameter of 1 mm. Extrusion speed was adjusted to 50 rpm. The extrusion was done twice to ensure a better densification of the wet mass, thus, more robust extrudates. 50-80 g of the extrudates were then spheronized for 5 minutes at speed of 1740 rpm using (Caleva spheronizer model 120, Caleva LTD, Dorset, UK), fitted with a 12 cm cross hatch friction plate. The pellets were then dried at 50 °C overnight in a conventional oven (Heraeus D-6450 Hanau, Thermo Scientific, Germany).

2.2.1.2 <u>Solution / suspension layering</u>

Table 4 and 5 summarize the composition of layering solution/dispersion and the variable process parameters for drug layering with organic solution of the polymers, and with the aqueous polymer dispersions, respectively. Drug layering was performed in a fluidized bed coater (Miniglatt, Glatt AG, Binzen, Germany, or, Aeromatic Strea-I, Binzen, Germany). In Miniglatt, the following process parameters were used for all drugs: starting core 60g, air pressure 0.2 bar, spray pressure 0.9 bar, nozzle diameter 0.5 mm, final drying 10 minutes. While, in Aeromatic: starting core 400 g, air flow = 60-80 m^3/h, spray pressure 1.2 bar, nozzle diameter 1.2 mm, final drying 10 minutes. Product temperature and spraying rate were dependent on the drug (Table 4, 5).

In the case of carbamazepine layering with different aqueous dispersions, additional stabilizer was added to the polymer dispersion before addition of the drug. While, for theophylline and metoprolol tartrate layered with high ratios of Kollicoat® SR 30 D, no stabilizer was required (Table 5).

Table 4: Composition of layering solution/suspension and the variable process parameters for layering with organic polymer solutions

Drug	Polymer ratio, % w/w based on the drug	Solvent, isopropanol: water	Layering method	Total solid content, % w/w	Product temperature, °C	Spray rate, g/min	
						Miniglatt	Aeromatic strea
Carbamazepine	5 - 40	88:12	Suspension	20	30-35	2-3	-
Ibuprofen	20	88:12	Solution	12.5	25-30	-	6-9
Verapamil HCl	20	96:04	Suspension	12.5	35-40	2-3	-
Theophylline	5 - 40	88:12	Suspension	20	30-35	2-3	-
	60 - 100			14	30-35	1-2	-
Propranolol HCl	20	88:12	Suspension	20	30-35	-	7-12
		70:30	Solution	12.5	35-40	-	7-12
	160-200	88:12	Suspension/ solution	10	35-40	0.7-1.2	-
Diprophylline	180	88:12	Suspension/ solution	10	35-40	0.7-1.2	-
Metoprolol tartrate	20	88:12	Solution	12.5	55-60	-	6-10
	160-200	96:04	Suspension/ solution	10	35-40	0.7-1.2	-

Table 5: Composition of layering solution/suspension and the variable process parameters for layering with aqueous polymer dispersions

Drug	Aqueous dispersion	Polymer ratio, % w/w based on the drug	Plasticizer, % w/w based on polymer	Stabilizer, % w/w based on the drug	Total solid content, % w/w	Product temperature, °C	Spray rate, g/min (Miniglatt)
Carbamazepine	Kollicoat® SR 30 D	20	TEC, 5	SLS, 5	20	30-35	2-3
	Eudragit® NE 30 D		-		12.5		
	Aquacoat® ECD		TBC, 20		20		
	Eudragit® RS 30 D		TBC, 0-10-20	PVP K30, 5	20		
Theophylline	Kollicoat® SR 30 D	100-400	TEC, 5	-	18-26 [*]		0.7-1.2
Metoprolol tartrate		400-700			16.7-18.0 [*]		

[*] Depending on drug : polymer ratio (the amount of the drug was added to the 15% w/w polymer dispersion).

2.2.2 Pellets characterization

2.2.2.1 <u>Size distribution</u>

Pellets size distribution was analyzed using mechanical sieving (Analysette 3 Pro, Fritsch, Rudolstadt, Germany). Approximately 50 g of each batch were shaken for 3 minutes at amplitude of 0.8 mm, using a series of the following sieves: 450, 850 and 1180 μm.

2.2.2.2 <u>Sphericity</u>

Macroscopic pictures of the pellets were done using light macroscope (Inteq® informationtechnik, GmbH, Berlin, Germany). The pellets sphericity was evaluated by measuring the aspect ratio (n=10). The aspect ratio of each individual pellet is the ratio between the longest and the shortest diameter.

2.2.2.3 <u>Bulk density</u>

Bulk density was determined (n=3) by measuring the volume and the weight of uncoated pellets using volumetric cylinder.

2.2.2.4 <u>Crushing force of single pellets</u>

Crushing force of single pellets was measured using the texture analyzer (TA.XT plus, Winopal Forschungsbedarf GmbH, Ahnsbeck, Germany). 20 pellets were placed individually on a stainless steel plate and compressed with a cylindrical stainless steel probe (diameter: 2 mm) with a load cell of 5 kg, starting height 3 mm, test speed of 0.1 mm/s, trigger force 0.1 g, elongation 0.4 mm and return speed 5 mm/s. Force-distance diagrams were recorded and evaluated with regard to maximal force and displacement.

2.2.2.5 <u>Water swellability</u>

Swelling studies were done (n=3) simply using the volumetric method. 10 g of pellets were poured freely in a volumetric cylinder, excess amount of water (same amount was used for all the batches) was added, and pellets volume was noted after 0.5 - 2 hour. The swelling was calculated as follows:

$$Swelling \, \% = \frac{Volume_{wet} - Original \, volume}{Original \, volume} \, x \, 100$$

2.2.3 Pellets coating

Pellets coating was performed in a fluidized bed coater (Miniglatt, Glatt GmbH, Binzen, Germany) fitted with wurster insert. 60 g pellets were coated with ethylcellulose organic solution (Isopropanol : water 88:12) with a solid content (7% w/w for EC 10cp, EC 20cp and 5% w/w for EC 45cp, EC 100cp), to achieve coating levels of 2.5, 5, 10 and 20%. The coating conditions were as follows: inlet temperature = 50 °C, product temperature = 35-40 °C, spray pressure = 0.9 bar, air pressure = 0.2 bar and spray rate = 0.6-1.0 g/min, final drying 10 minutes.

2.2.4 Pellets curing

Pellets curing was done at 60 °C and 60 °C/75% relative humidity (RH) for 24 hours in petri dishes in an oven. The 75% RH was attained using saturated solution of sodium chloride in desiccators at 60 °C. In case of Eudragit$^{®}$ RS 30 D layered pellets, the curing effect was studied additionally at different time points.

2.2.5 Pellets compression

Tableting excipients (Avicel$^{®}$ PH 102 47.5% w/w, Ac-Di-Sol$^{®}$ 2% w/w and magnesium stearate 0.5% w/w) were mixed manually using mortar and pistil for 5 minutes. Pellets:tableting excipients 50:50 were weighed individually for each tablet and mixed in eppendorf tubes for 30 seconds. The tablets were prepared on an instrumented single punch tablet press (Korsch EK0, Korsch Pressen GmbH, Berlin, Germany) with different compression forces (10-20 kN). Biplane tablets of 8 mm diameter and 180 mg weight (90 mg pellets) were obtained. Hardness of the tablets was measured with a hardness tester (Multicheck, Erweka GmbH, Heusenstamm, Germany). The effect of pellets compression on drug release was evaluated by comparing the release profiles of uncompressed and compressed pellets using the similarity factor F2.

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

Where f_2 is similarity factor, n is the number of observations (release points), R_t is the percentage of drug released from reference formulation (uncompressed pellets), and T_t is the percentage of drug released from test formulation (compressed pellets).

2.2.6 Differential scanning calorimetric (DSC) studies

DSC studies were performed using a differential scanning calorimeter (DSC-822e Mettler-Toledo, Switzerland). 10-15 mg of the samples were weighed accurately in a 40 μl aluminum pan. All tests were run under a nitrogen atmosphere at a scanning rate of 10 °C/min from 25 °C to 200 °C.

2.2.7 Powder X-ray diffraction (PXRD) studies

X-ray studies were done using Philips PW 1830 X-ray generator with a copper anode (Cu Kα radiation, λ = 0.15418 nm, 40 kV, 20 mA) fixed with a Philips PW 1710 diffractometer (Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). The scattered radiation of the samples was detected with a vertical goniometer (Philips PW 1820, Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). A scanning rate of 0.02 2θ per second over the range of 4-40 2θ at ambient temperature was used to determine each spectrum.

2.2.8 Drug solubility studies

Excess amounts of carbamazepine were placed in 20 ml screw cap glass vials with 10.0 g of phosphate buffer solution (PBS) pH 6.8, PBS pH 6.8 + sodium lauryl sulfate (0.25% w/v) or PBS pH 6.8 + Tween® 80 (0.25% w/v) (n=3). The slurries were stirred magnetically at ~200 rpm at 37 °C for 10 min, to insure wetting and dispersion of the drug, and then placed in a horizontal shaker (GFL 3033) (75 rpm, 37 °C) for 48 h. Samples were taken and filtered through a 0.22 μm CME-syringe-filter and analyzed for drug concentration UV-spectrophotometrically (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) (λ = 285 nm) after appropriate dilution. Blanks of drug-free mediums containing different surfactants were treated and measured likewise.

2.2.9 Drug release

The drug release from pellets and tablets was investigated in an USP II paddle apparatus (VK 7000, Vankel Industries, Edison, NJ, USA) at 50-150 rpm using 900 ml 0.1 N HCl or PBS pH 6.8 at 37∘C with an optional addition of 0.25% w/v Tween® 80 or 0.25% w/v SLS. NaCl was used also to adjust the osmolality of the media to 600 mosmol/kg. At predetermined time points, samples were withdrawn and quantified UV-spectrophotometrically (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) at the following wavelengths: (metoprolol tartrate: 221 nm, propranolol HCl: 289 nm, diprophylline: 272 nm,

paracetamol: 245 nm, theophylline 271 nm, verapamil HCl: 278 nm, ibuprofen: 222 nm and carbamazepine: 285 nm). F2 similarity factor was also used to evaluate the difference in drug release between different formulations.

2.2.9.1 <u>Video monitoring during drug release</u>

The video monitoring of pellets during drug release was performed using a light macroscope (Inteq® informationtechnik, GmbH, Berlin, Germany) supplied with an image analyzing software (IQ Easy measure®, Inteq® informationtechnik, GmbH, Berlin, Germany), to observe a possible cracking or rupturing of the ethylcellulose coating layer during drug release.

Chapter 3. Results and discussion

3. Results and discussion

3.1 Comparison of water -soluble and -insoluble polymers used as binders in pellets prepared by extrusion spheronization

3.1.1 Preliminarily studies and processability

Preliminarily experiments were performed to optimize binder content, amount and composition of the granulation fluid, spheronization speed and time. Regarding to binder ratio, formulations with binder contents from 0% to 15% w/w based on the total pellet weight were prepared. Formulations containing < 5% w/w binder resulted in friable extrudates, which turned into fine powder and/or very small pellets during the spheronization process. Furthermore, the yield of the desired size fraction of pellets (850-1180 µm) was low. On the other hand, formulations with > 10% w/w binder resulted in robust extrudates, which were difficult to break/ spheronize. Therefore, dumbbell-shaped pellets or short rods (small pieces of extrudates) were obtained (Fig. 15).

A)   B)
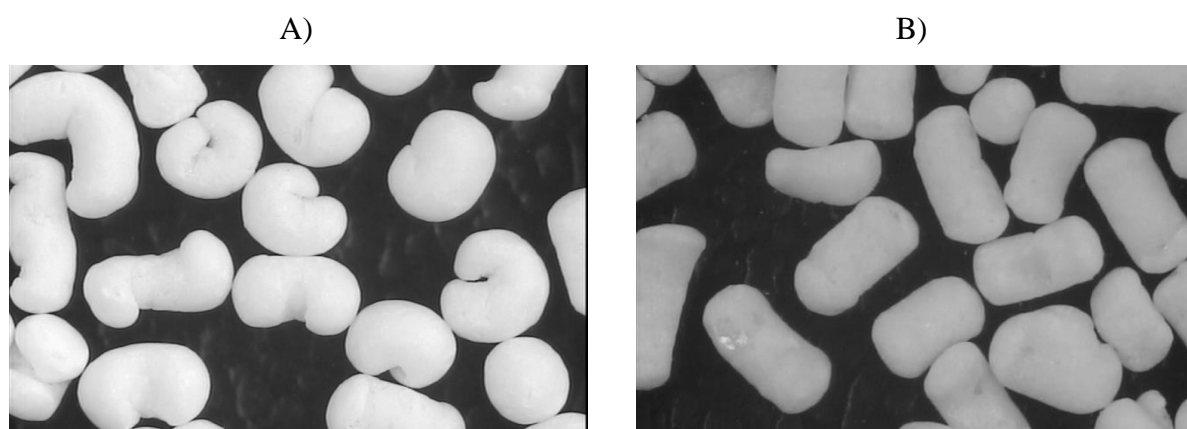
Fig. 15: Dumbbell-shaped pellets A) and short rods B) with 12% and 14% w/w ethylcellulose respectively.

Formulations prepared with the water-soluble binder HPMC E5, deionized water was used as granulation fluid. While, those prepared with the water-insoluble binder ethylcellulose, a mixture of isopropanol:water 70:30 was chosen as granulation fluid. Since this ratio can still dissolve ethylcellulose, and at the same time, contains the highest possible amount of water (which is necessary for the plasticizing and binding effect of the filler MCC). To eliminate any effect caused by different granulation fluids, pellets were prepared with the binder HPMC E5, using isopropanol:water 70:30 as a granulation fluid.

The amount of granulation fluid which can be used, is highly dependent on the solubility and the ratio of the components (drug and filler) (Sousa et al., 2002). Therefore, amount of the granulation fluid was adjusted carefully at each drug loading to get a suitable wet mass for the extrusion and spheronization processes (Table 6). Excessive wet massing (high amount of granulation fluid) resulted in high quality extrudates (long and robust); however, they agglomerated during spheronization. On the other hand, poor wet massing (low amount of granulation fluid) resulted in friable extrudates and a high amount of fine powders during spheronization.

Table 6: Ingredients and granulation fluid ratio of different formulations

Ingredients, %			Granulation fluid, %
API	**Binder**	**Filler (Microcrystalline cellulose 101)**	
5	5	90	80
25	5	70	60
25	10	65	50
45	5	50	45

There was a high correlation between microcrystalline cellulose amount in the formula and the required amount of granulation fluid (Fig. 16). The more Microcrystalline cellulose in the formula, the higher the amount of granulation fluid needed. This is because of this excipient possesses a high surface area (particle size 50 μm) and high internal porosity (Sonanglio et al., 1995), so it absorbs high amounts of water and imparts binding and plastic properties. Presence of an additional binder imparted additional binding properties and therefore, with higher binder content (10% w/w), less amount of granulation fluid was required (Fig. 16).
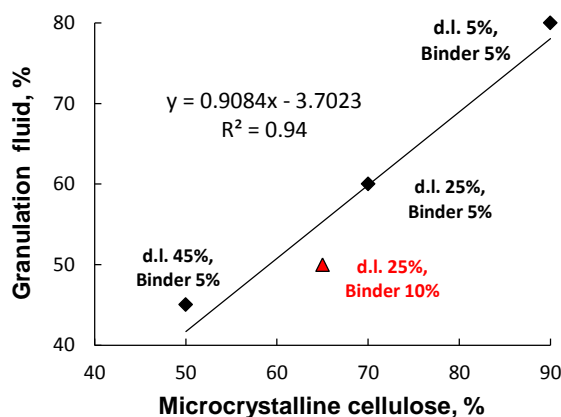

Fig. 16: Relationship between microcrystalline cellulose amount and required amount of the granulation fluid.

The spheronization process was also optimized regarding to spheronization speed and residence time in the spheronizer. The higher spheronization speed and the longer process time, the more spherical and homogenized size pellets were obtained (L Baert et al., 1993). On the other hand, long residence time in the spheronizer and/or high spheronization speed could lead to the formation of a high amount of fines (Wan et al., 1993). This is the case especially when organic solvents are used as granulation fluids, as they might evaporate with time, leaving a more brittle friable mass, which turns quickly into powders. A moderate spheronization speed of 1740 rpm and spheronization time of 5 min were kept constant for all formulations.

3.1.2   Pellets characterization

3.1.2.1 <u>Size distribution</u>

The pellets were sieved and sorted into four size fractions: < 425μm, 425-850μm, 850-1180 μm and > 1180 μm (Fig. 17). Majority (60-90%) of the pellets were of the size fraction 850-1180 μm, which was consistent with the sieve opening size of the extruder (1000 μm). Therefore, this size fraction was chosen for further studies. Pellets prepared with HPMC E5 as a binder had a more homogeneous size distribution than those prepared with ethylcellulose, attributed to its better binding efficiency. Some amount of fines < 425 μm was observed with pellets prepared with ethylcellulose as a binder. This could be due to partial evaporation of the granulation fluid (isopropanol:water) during the spheronization process, leaving dry and friable extrudates and resulting in some fines. With high binder ratio (10% w/w) or high drug loading (45% w/w), few agglomerates > 1180 μm were observed, attributed to increased cohesiveness of the wetted mass.
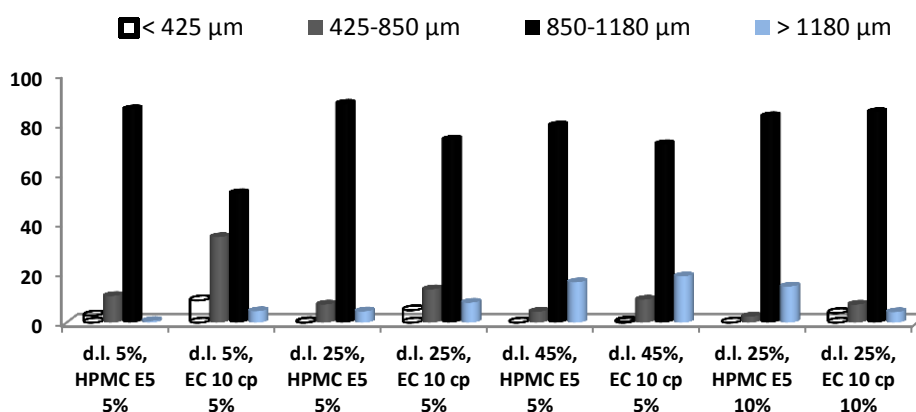
Fig. 17: Pellets size distribution of different formulations with different drug loadings and binder contents (d.l.: drug loading).

3.1.2.2 <u>Sphericity</u>

Macroscopic pictures of different pellet formulations (Fig. 18) were made using a light macroscope and the aspect ratio of all pellet formulations was calculated (Table 7). The aspect ratio of each individual pellet is the ratio between the longest and shortest diameter. There were no remarkable differences between different batches, regarding sphericity and aspect ratio (Table 7).

d.l. 5%, HPMC 5%	d.l. 5%, EC 5%
d.l. 25%, HPMC 5%	d.l. 25%, EC 5%
d.l. 45%, HPMC 5%	d.l. 45%, EC 5%
d.l. 25%, HPMC 10%	d.l. 25%, EC 10%

Fig. 18: Macroscopic pictures of different pellets (d.l.: drug loading).

Table 7: Pellet formulations and characterization

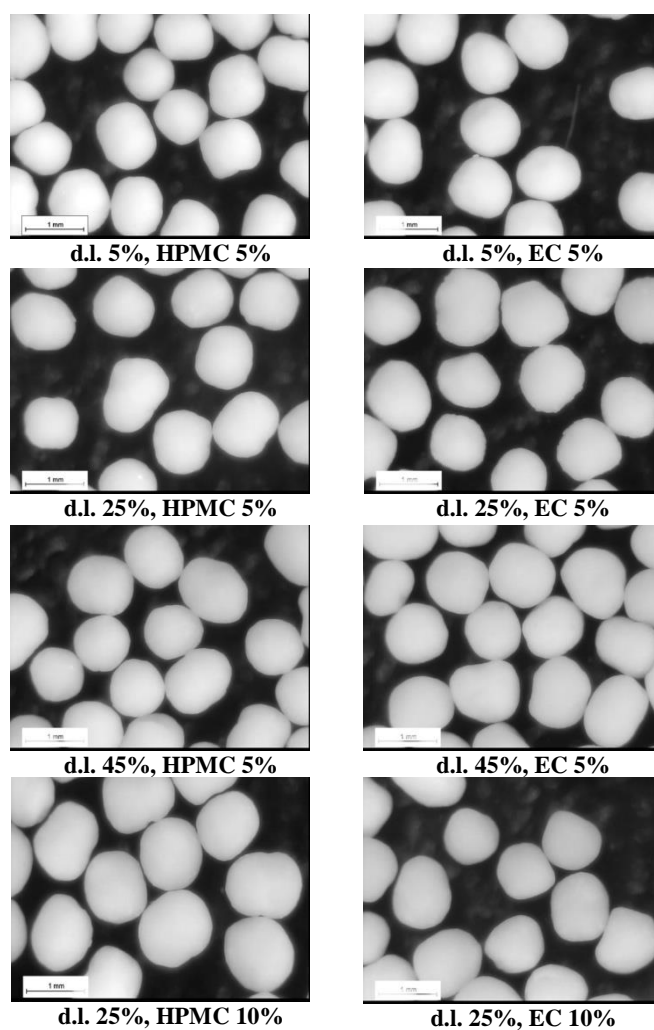| Drug loading, %	Binder		Granulation fluid		Aspect ratio	Bulk density, g/ml	Crushing force, N	Water swellability, %
	Type	%	Type	%				
5	HPMC E5	5	Water	75	1.10	0.82	8.16	75.0
25		5		60	1.12	0.79	8.50	70.0
45		5		45	1.05	0.75	8.61	62.5
25		10		50	1.08	0.77	11.39	68.0
25		5	IPA:W 70:30	65	1.04	0.59	4.55	27.3
5	EC 10 cp	5	IPA:W 70:30	80	1.10	0.73	5.14	26.6
25		5		60	1.14	0.65	4.51	22.4
45		5		45	1.14	0.67	4.87	13.2
25		10		50	1.09	0.70	5.94	15.0
25		5 (as solution)		60	1.08	0.55	3.25	12.0

IPA: isopropanol, W: water

3.1.2.3 <u>Bulk density</u>

Density of pellets can be considered as a main indicator of their porosity, which plays a significant role in their compactibility, as the degree of pellet deformation increases with increasing pellet porosity (Johansson et al., 1995). For pellets prepared with extrusion spheronization, the composition of the granulation fluid used for wet massing step can affect remarkably the density of the final pellets (Millili, G.p., Schwartz, J.B., 1990). All formulations prepared with isopropanol:water as a granulation fluid were of lower bulk density (higher porosity) than those prepared with water (Table 7). This was attributed to the effect of surface tension and dielectric properties of the granulation liquids on the contraction and densification of the pellets during drying (Berggren and Alderborn, 2001; Dreu et al., 2005).

3.1.2.4 <u>Crushing force of single pellets</u>

Mechanical strength of pellets is a result of cohesive strength of powder particles and solid bridges (created by the binder) (Wang et al., 1996). On the other hand, porosity of the pellets is one of the main factors affecting the hardness of pellets (Millili, G.p., Schwartz, J.B., 1990). As expected, pellets prepared with isopropanol:water as granulation fluid had lower density (higher porosity) and a much lower crushing force than those prepared with water (Table 7). HPMC-pellets prepared with isopropanol:water as granulation fluid had almost the same crushing force as EC-pellets prepared with the same granulation fluid. This indicates that the granulation fluid is the main factor, which influences the pellet hardness. Increasing drug loading, did not affect either density or crushing force, as the same MCC:granulation fluid ratio was used for all formulations (with same binder content) (Table 6, Fig. 16). Increasing binder content (5% vs.10% w/w) led to an increase in the cohesive strength inside the pellet, thereby increase the crushing force. Applying ethylcellulose as solution in the granulation fluid resulted in pellets with a minimal crushing force (Table 7). Probably, because of the low density of these pellets.

3.1.2.5 <u>Water swellability</u>

The pellets prepared with water as granulation fluid showed a much higher (3-4 times) water swellability (size increase) than those prepared with isopropanol:water, at all drug loadings and binder contents (Table 7). This could be explained as follows: As the pellets prepared with isopropanol:water have higher porosity, swelling of microcrystalline cellulose particles upon contact with dissolution medium will fill the pores inside the pellet without increasing the total volume of the pellet significantly. However, in the case of nonporous (less porous) pellets prepared with water, swelling of microcrystalline cellulose particles will lead to an increase of the total volume of the pellets.

3.1.3 Drug release

3.1.3.1 <u>Effect of drug solubility</u>

Drug release from pellets prepared with ethylcellulose as binder, was slower than those prepared with HPMC for all tested drugs (Fig. 19).

With the poorly soluble drug carbamazepine, drug release from ethylcellulose pellets was much slower than those prepared with HPMC using the same granulation fluid (isopropanol:water) (same porosity) (Fig. 19 A). This reflects a further retardation effect induced by ethylcellulose solid bridges, which covered the drug partially and retarded its release. However, the less porous HPMC pellets prepared with water, released the drug in the same rate of those prepared with (ethylcellulose/isopropanol:water) (Fig. 19 A). Pellets prepared with ethylcellulose as organic solution had a faster release rate than those prepared with ethylcellulose as a powder (Fig. 19 A). This could be also due to the high porosity (low density) of these pellets. Another possible reason could be that, ethylcellulose, being applied from a thick solution, did not distribute homogeneously and therefore, did not cover the drug effectively, in comparison with the fine powder form.
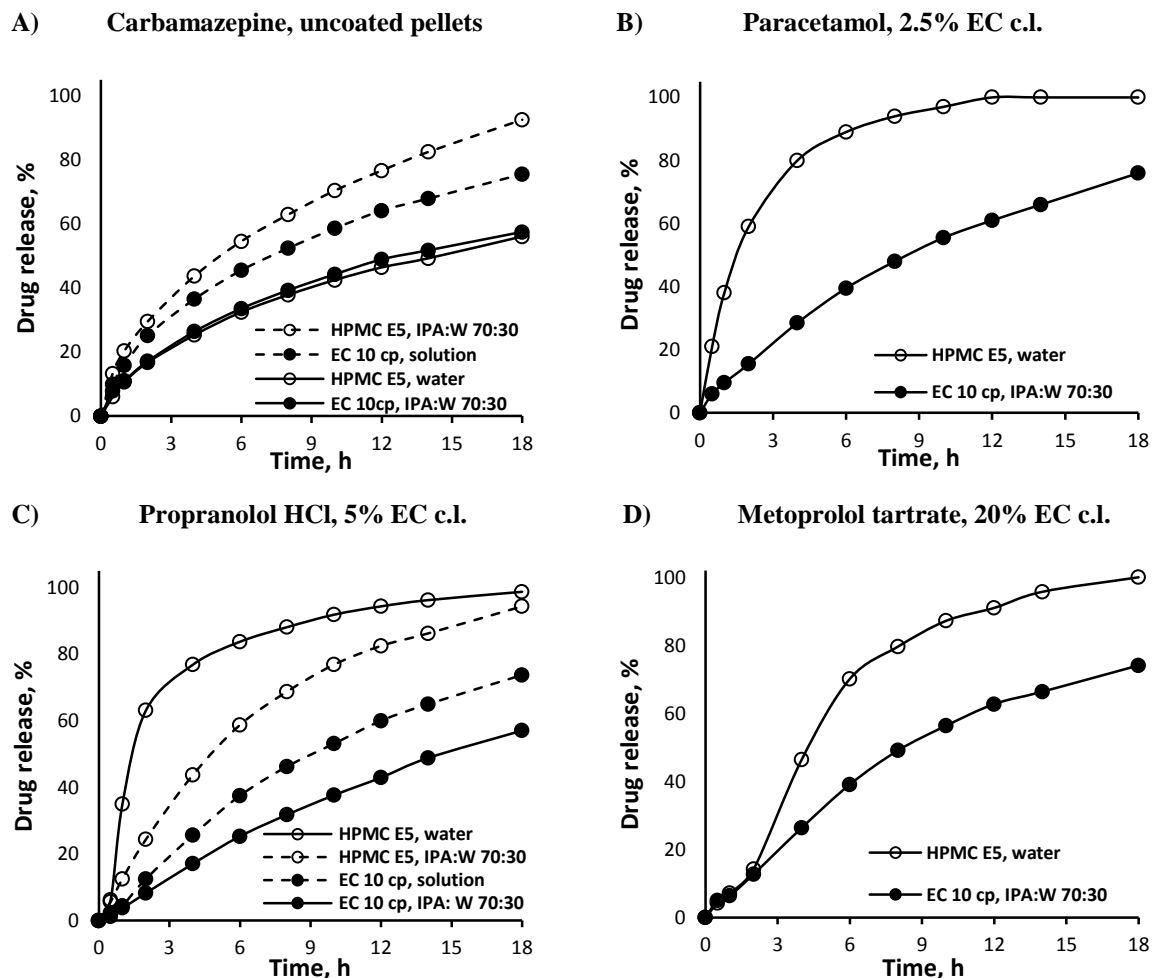
Fig. 19: Effect of binder type, granulation fluid on drug release (drug loading 25% w/w, binder content 5% w/w).

For higher solubility drugs, paracetamol, propranolol HCl and metoprolol tartrate, the release after coating was also much slower from pellets prepared with EC (Fig. 19 B, C, D respectively). This was due to:

➢ The additional release retardation effect induced by ethylcellulose.

➢ Rupturing of the ethylcellulose coating layer of pellets prepared with (HPMC/water), which was not seen with the pellets prepared with (ethylcellulose/isopropanol:water) (Fig. 20).

HPMC/water pellets

Time 0   30 min

2 h   6 h

EC/IPA:W pellets

Time 0   30 min

2 h   6 h

Fig. 20: Macroscopic pictures of propranolol HCl pellets (5% EC c.l.) during drug release at different time points.

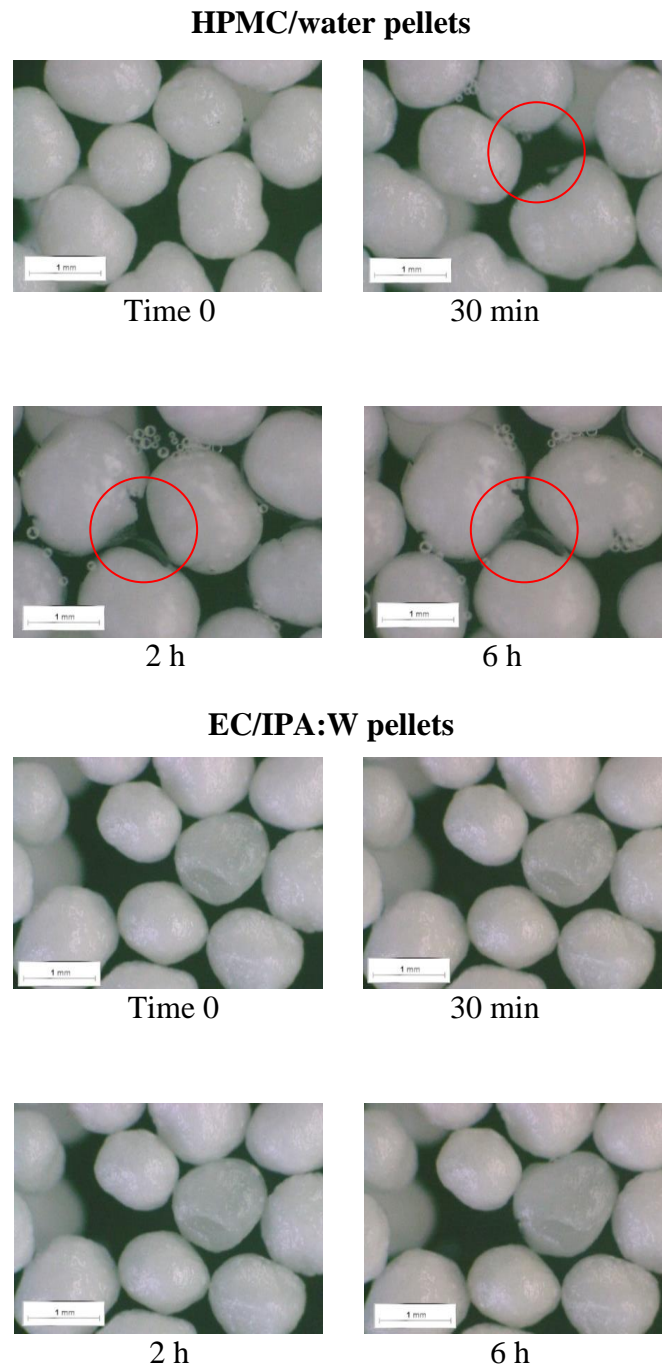Coating rupture of pellets prepared with (HPMC/water) during drug release can be attributed to the high water swellability of these pellets (increase of pellet volume) (Table 7), which creates a high internal pressure on the coating. However, pellets prepared with (ethylcellulose/isopropanol:water), did not swell dramatically upon contact with the release medium (less size increase), therefore, their coating layer remained intact (less cracked) (Fig. 20, 21).
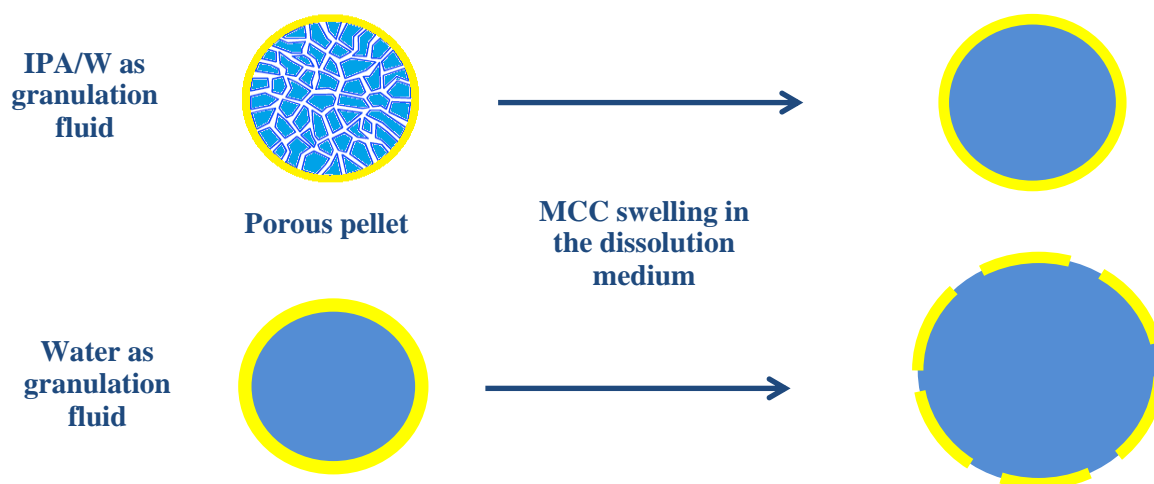

Fig. 21: Schematic presentation of swelling behavior of pellets prepared with different granulation fluids, and its influence on the outer coating.

Pellets prepared with (HPMC/isopropanol:water) released propranolol HCl more slowly than those prepared with (HPMC/water) (higher porosity, less swelling, less coating cracking). But, the drug release was still much faster than from pellets prepared with (ethylcellulose/isopropanol:water) (Fig. 19 C), which confirms the retardation effect of ethylcellulose used as binder.

3.1.3.2 Effect of drug loading

Increasing drug loading led to a decrease in drug release with both binder types (Fig. 22 A). This could be attributed to decrease surface area/dose ratio. Furthermore, the higher the drug loading the less MCC was used in the formulation, i.e. less size increase of the pellets (Table 7), therefore, less cracking of the coating layer and slower drug release. As discussed before, size increase of the pellets and cracking of the coating layer were more pronounced for pellets prepared with (HPMC/water). Therefore, the decrease in drug release rate upon increasing the drug loading was more pronounced for pellets prepared with (HPMC/water) than for those prepared with (ethylcellulose/isopropanol:water) (Fig. 22 A). On the other hand, increasing drug loading (5 vs. 25 vs. 45% w/w) with the same binder content (5%

w/w), led to decrease binder/drug ratio, which reduced the binder effect, i.e. reduced the difference in drug release between ethylcellulose and HPMC pellets (Fig. 22 B).
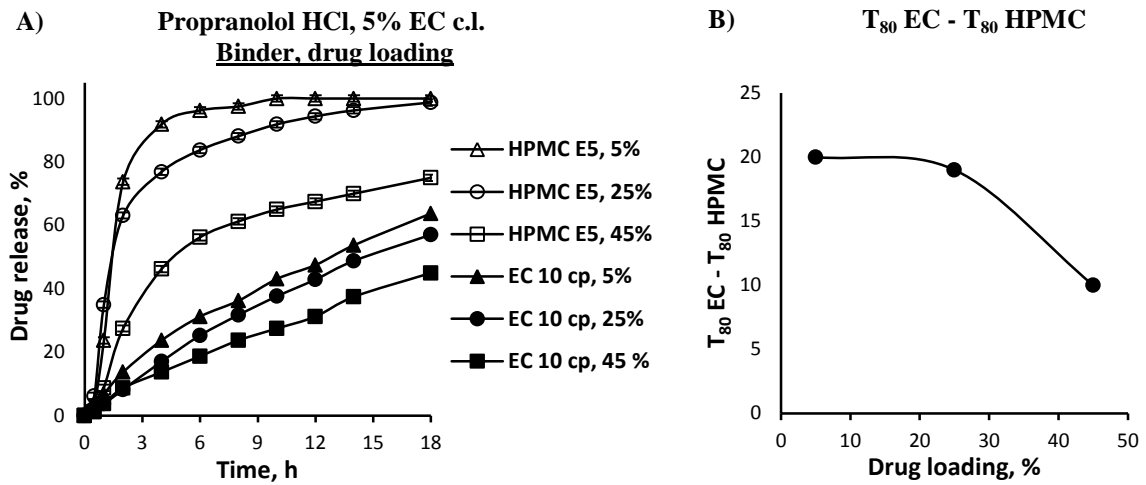
Fig. 22: Effect of drug loading (w/w based on total pellet weight) on drug release (binder content 5% w/w).

3.1.3.3 Effect of binder content

Increasing the HPMC content led to an increase in the carbamazepine release from uncoated pellets (pore forming effect), however, increasing the ethylcellulose content decreased the drug release (further retardation effect correlated with polymer amount) (Fig. 23). Propranolol HCl release from coated pellets was not affected significantly upon increase of the binder content, as the drug release is mainly controlled by the coating layer, which was not affected by increase of the binder content.
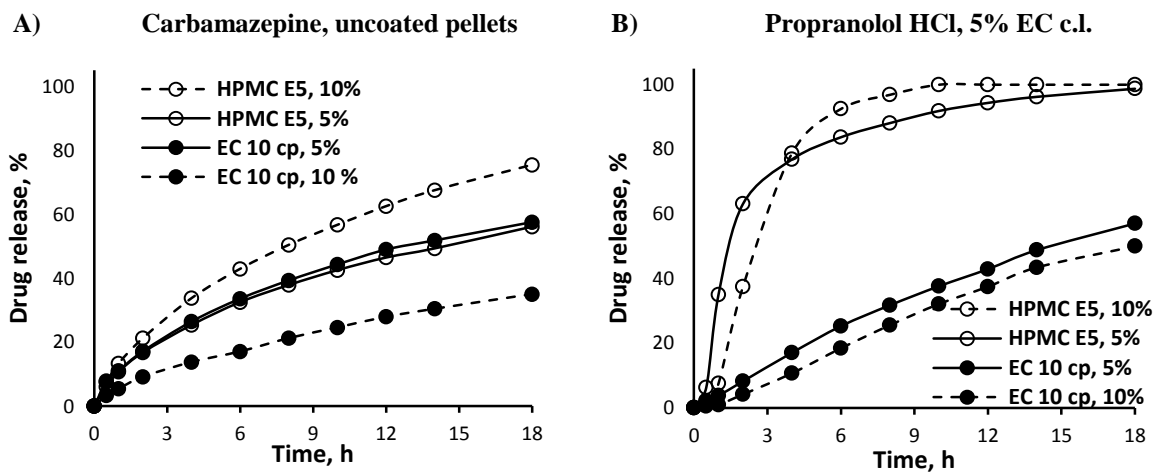

Fig. 23: Effect of binder content (w/w based on total pellet weight) on drug release (drug loading 25% w/w).

3.1.3.4 <u>Effect of coating level</u>

Increasing the coating level (thickness) led to a decrease in drug release from pellets prepared with both binders (Fig. 24 A). Leveling effect of the coating (decreasing the release rate upon increasing the coating level) was more pronounced with EC-pellets, as the coating was less cracked during drug release. Therefore, the difference in drug release between HPMC- and EC-pellets increased by increasing the coating level (Fig. 24 B). Interestingly, pellets prepared using HPMC as a binder required 4 times higher coating level to achieve the same release rate as EC-pellets (10% vs. 2.5% c.l.) (Fig. 24 A).
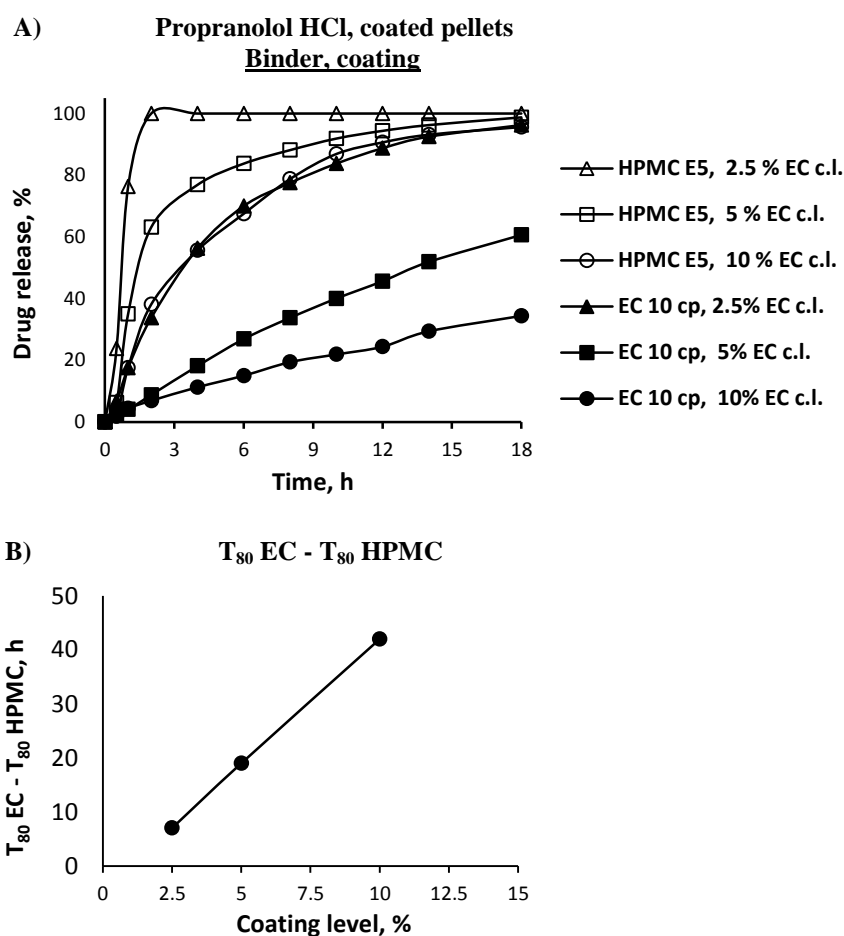
Fig. 24: Effect of coating level on drug release (drug loading 25% w/w, binder content 5% w/w).

3.1.3.5 <u>Effect of ethylcellulose molecular weight</u>

There is a high dependence of the mechanical properties of ethylcellulose on its molecular weight, the higher the molecular weight, the stronger ethylcellulose coating layer is obtained (Marucci et al., 2013; Rowe, 1992). Low molecular weight polymers are relatively weak and may rupture easily upon exposure to any internal pressure (osmotic pressure or swelling of pellets core). Because of the presence of microcrystalline cellulose in all formulations, the

prepared pellets have the tendency to swell (increase in size) upon contact with the release medium (Table 7). This leads to remarkable rupture of the ethylcellulose coating layer and thus faster drug release, especially with pellets prepared with (HPMC/water) (Fig. 20). Therefore, using a higher molecular weight of ethylcellulose as a coating, led to a remarkable decrease in drug release with both binders (Fig. 25 A). The decrease in drug release was more pronounced with pellets prepared with (HPMC/water), as they had higher tendency to swell than the pellets prepared with (ethylcellulose/isopropanol:water).
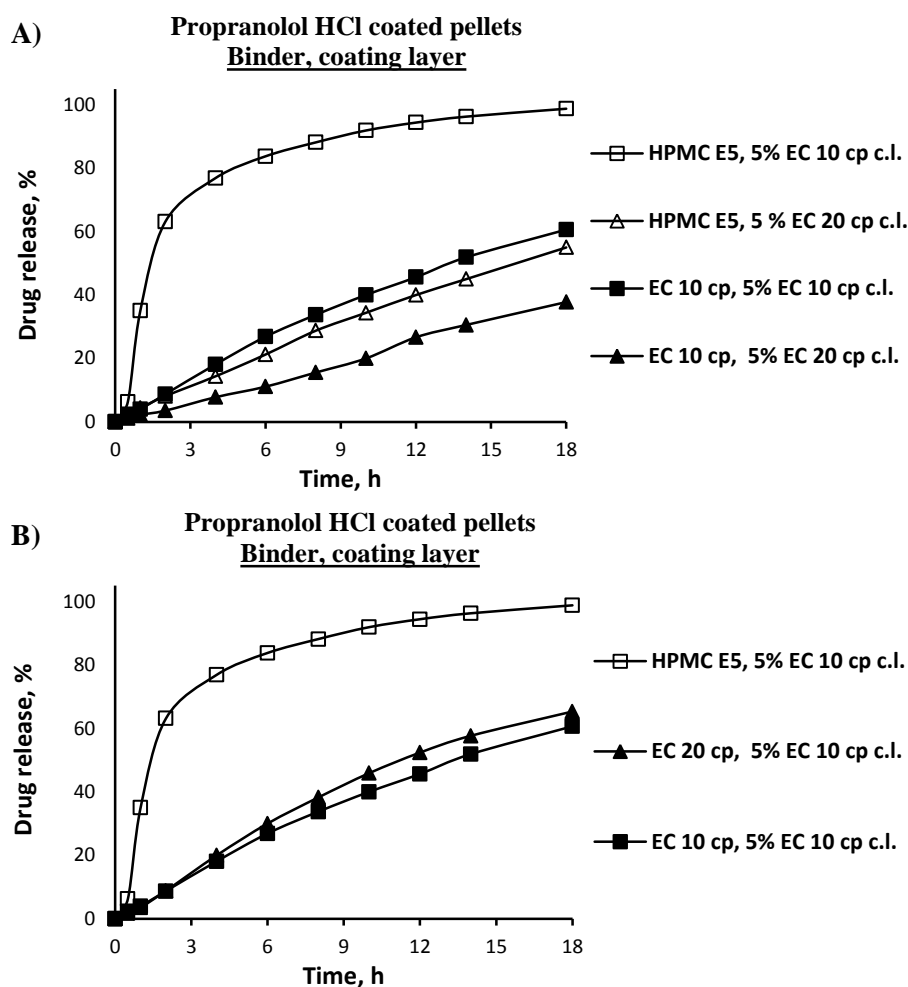
Fig. 25: Effect of molecular weight of ethylcellulose on drug release, A) as coating, and B) as binder (drug loading 25% w/w, binder content 5% w/w).

The molecular weight of ethylcellulose used as binder, had no influence on drug release (Fig. 25B). This is due to: first, the swelling of pellets prepared with (ethylcellulose/isopropanol:water) is less pronounced, second, the ethylcellulose here is present as unconnected solid bridges inside the pellets, therefore a further cracking will not

induce a remarkable increase in drug release, when compared with cracking of the continuous coating layer.

3.1.3.6 <u>Other hydrophilic polymers as binders</u>

In case of poorly soluble drugs such as carbamazepine, MCC-based pellets prepared by extrusion spheronization technique showed a prolonged drug release profile even with the hydrophilic binder HPMC E5 and without retarding coating layer (Fig. 19A). This could be attributed to lack of pellet disintegration and adsorption of the drug to MCC as reported by (Thommes and Kleinebudde, 2008). For this reason, several efforts have been made to find an alternative filler to MCC to increase the release of poorly soluble drugs out of this system (Howard et al., 2006; Charoenthai et al., 2007; Thommes and Kleinebudde, 2007; Verheyen et al., 2009). Nevertheless, MCC remained the ″golden″ excipient for pellets preparation with the extrusion spheronization technique. Several hydrophilic polymers were used as binder instead of HPMC, as an attempt to increase the carbamazepine release from MCC-based pellets prepared by extrusion spheronization. All tested hydrophilic polymers increased carbamazepine release in comparison with HPMC E5 (Fig. 26), as they might dissolve faster and leach out of the pellets providing a pore forming effect. Another possibility to increase the drug release is to increase the porosity of the pellets by using a non-aqueous granulation fluid (organic solvent), as shown before (Fig. 19A).

Carbamazepine uncoated pellets
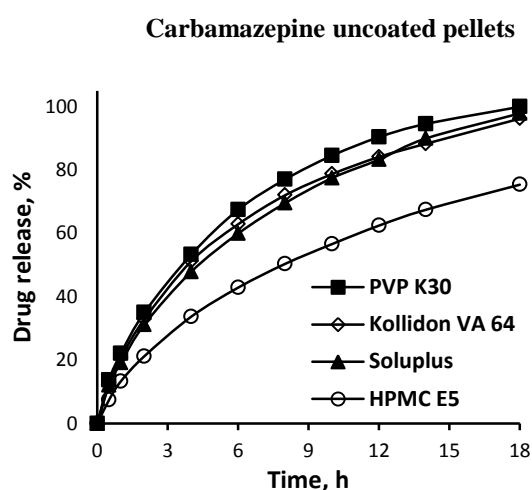
Fig. 26: Effect of different hydrophilic polymers used as binder on carbamazepine release (drug loading 25% w/w, binder content 10% w/w).

3.2 Comparison of water-soluble and -insoluble polymers used as binders in drug-layered pellets

The typical manufacturing procedure of controlled release multiparticulate systems includes drug layering on neutral cores using water-soluble binders, followed by coating with the release-controlling polymers. In the literature, different water-soluble binders such as HPMC, PVP, gelatin and PVA-PEG graft copolymer have been used for drug layering and were evaluated regarding viscosity and stickiness, drug layering efficiency and roughness of the final pellet surface (Suhrenbrock et al., 2011; Yang et al., 2014; Sinchaipanid et al., 2004). Drug release from these pellets layered using water-soluble binders was very fast, therefore, a further coating step was required to control the drug release. Several groups of release controlling polymers are available and used as coating materials, such as cellulose ethers, acrylic polymers and polyvinyl acetate-based polymers. The objective of this study was to investigate the effect of binder type (water-soluble vs. -insoluble) used for drug layering on drug release from controlled release pellets as a further formulation tool to control drug release.

3.2.1 Effect of drug solubility

A) **Carbamazepine uncoated pellets**

B) **Ibuprofen uncoated pellets, pH 5.5**

C) **Ibuprofen uncoated pellets, pH 6.8**

Fig. 27: Effect of binder type on drug release from uncoated pellets (drug loading 25% w/w, binder content 20% w/w based on the drug).

With the poorly soluble drugs (carbamazepine: 0.2 mg/ml, ibuprofen pH 5.5: 0.7 mg/ml, ibuprofen pH 6.8: 3.3 mg/ml), extended drug release profiles were already achieved without further polymer coating by using water-insoluble polymers as binders for drug layering. In contrast to an immediate release from pellets layered with the most commonly used water-soluble binder HPMC (Fig. 27). Carbamazepine release retardation was in the order of ethylcellulose 10 cp > Eudragit® RS > Kollidon® SR (Fig. 27A). The faster release from Kollidon® SR and Eudragit® RS layered pellets, was because of leaching of the water-soluble components, PVP and quaternary ammonium groups (HCl salts), respectively. The difference in drug release rate between ethylcellulose and HPMC layered pellets decreased as the drug solubility increased (Fig. 27 A vs. B vs. C).

A) **Theophylline coated pellets**
2.5% EC/HPC 78/22 c.l.

B) **Propranolol HCl coated pellets**
5% EC c.l.

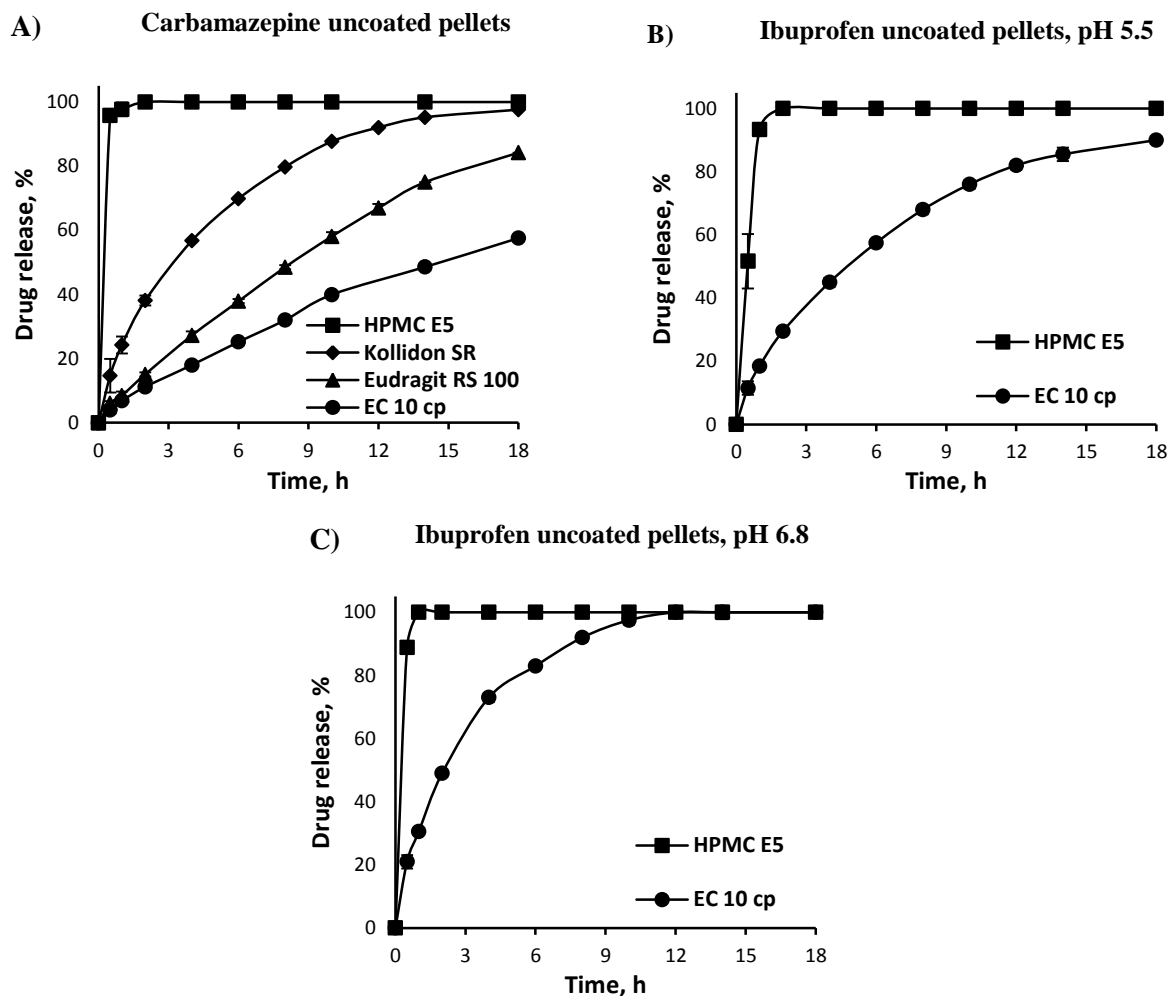**C)** **Metoprolol tartrate coated pellets**
20% EC 10 cp c.l.
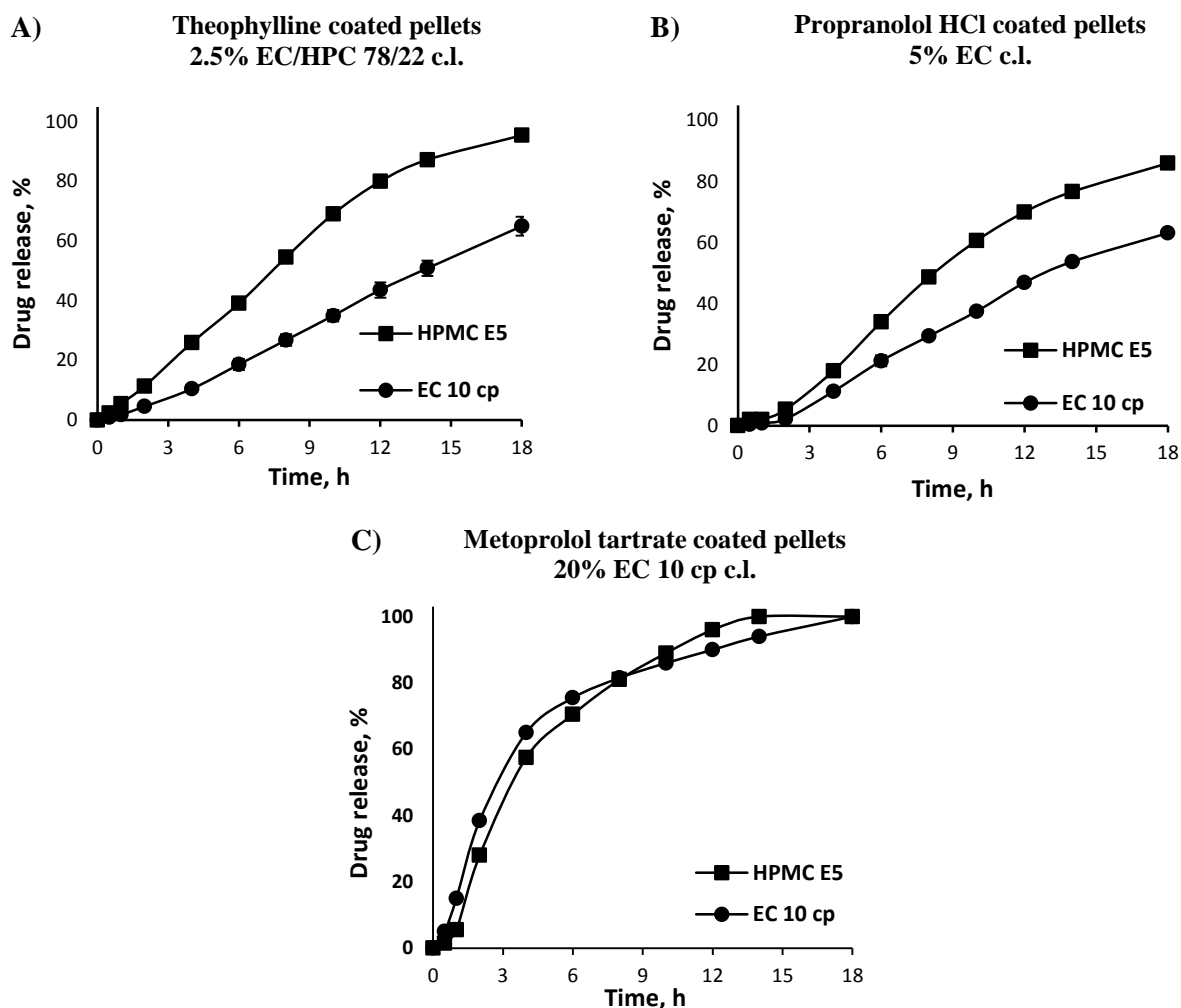
Fig. 28: Effect of binder type on drug release from coated pellets (drug loading 25% w/w, binder content 20% w/w based on the drug).

For higher soluble drugs (theophylline: 10 mg/ml, propranolol HCl: 220 mg/ml, metoprolol tartrate > 1000 mg/ml), drug release from uncoated pellets was very fast (100% release within 15 min) with both binder types (data not shown), due to the high solubility of these drugs. Therefore, the release was further studied after coating the pellets with EC, or EC/HPC (as pore former) at a suitable coating level (Fig. 28). For theophylline and propranolol HCl pellets, the water-insoluble binder ethylcellulose resulted in a much slower release rate than the water-soluble binder HPMC, i.e. a lower coating level was required to achieve the same release rate when ethylcellulose was used as a binder instead of HPMC (Fig. 28 A, B). For metoprolol tartrate pellets, no effect of binder type on drug release was seen, because of its high solubility (Fig. 28 C).

3.2.2   Effect of starter core type

Drug release mechanism from controlled release pellets is complicated and can be affected by different pellet properties (Wesselingh, 1993). The core type is one of the most important properties which may affect the drug release (Kállai et al., 2010). Ethylcellulose, being a highly brittle polymer, can easily rupture under mechanical stress generated internally by the pellets core, or externally upon pellets compression into tablets (Bodmeier and Paeratakul, 1994; Bodmeier, 1997). Two types of cores are usually used for pellets preparation, nonpareil sugar, and microcrystalline cellulose-based cores.
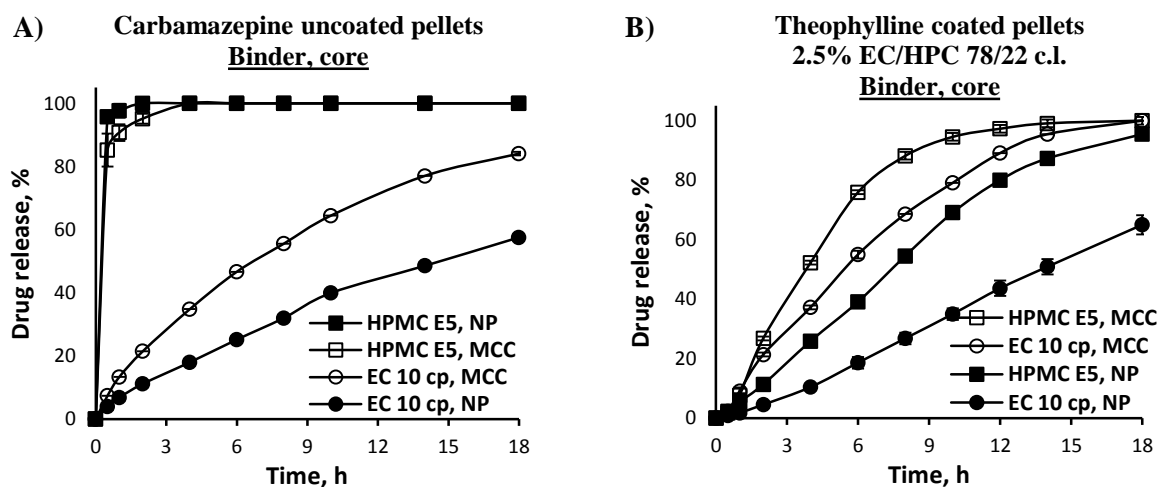
Fig. 29: Effect of core type on drug release (drug loading 25% w/w, binder content 20% w/w based on the drug).

Carbamazepine release from EC-layered pellets was much faster with MCC cores compare to NP cores. This could be attributed to the high swelling capacity of MCC cores in water (30% size increase within 30 minutes), which created a high pressure on the EC/drug layer, leading to swelling-induced cracking of the EC/drug layer, resulting in increased drug release. Carbamazepine release from HPMC-layered uncoated pellets was not affected by the core type, as the release was very fast with both cores (Fig. 29 A). Theophylline release from coated pellets was much faster with MCC than with NP-based cores with both binder types (Fig. 29 B). However, the EC-coated EC-drug layered pellets were more affected (F2 MCC vs. NP: 22) than the EC-coated HPMC-drug layered pellets (F2 MCC vs. NP: 32). For this reason, the difference in drug release between EC- and HPMC-layered pellets decreased with MCC cores compare to NP cores.

3.2.3 Effect of drug loading

A) **Carbamazepine uncoated pellets**
Binder, drug loading

- HPMC E5, 5%
- HPMC E5, 25%
- HPMC E5, 45%
- EC 10 cp, 5%
- EC 10 cp, 25%
- EC 10 cp, 45%

B) **Theophylline coated pellets**
2.5% EC/HPC 78/22 c.l.
Binder, drug loading

- HPMC E5, 5%
- HPMC E5, 25%
- HPMC E5, 45%
- EC 10 cp, 5%
- EC 10 cp, 25%
- EC 10 cp, 45%

C) **Propranolol HCl coated pellets**
5% EC c.l.
Binder, drug loading

- HPMC E5, 5%
- HPMC E5, 25%
- HPMC E5, 45%
- EC 10 cp, 5%
- EC 10 cp, 25%
- EC 10 cp, 45%
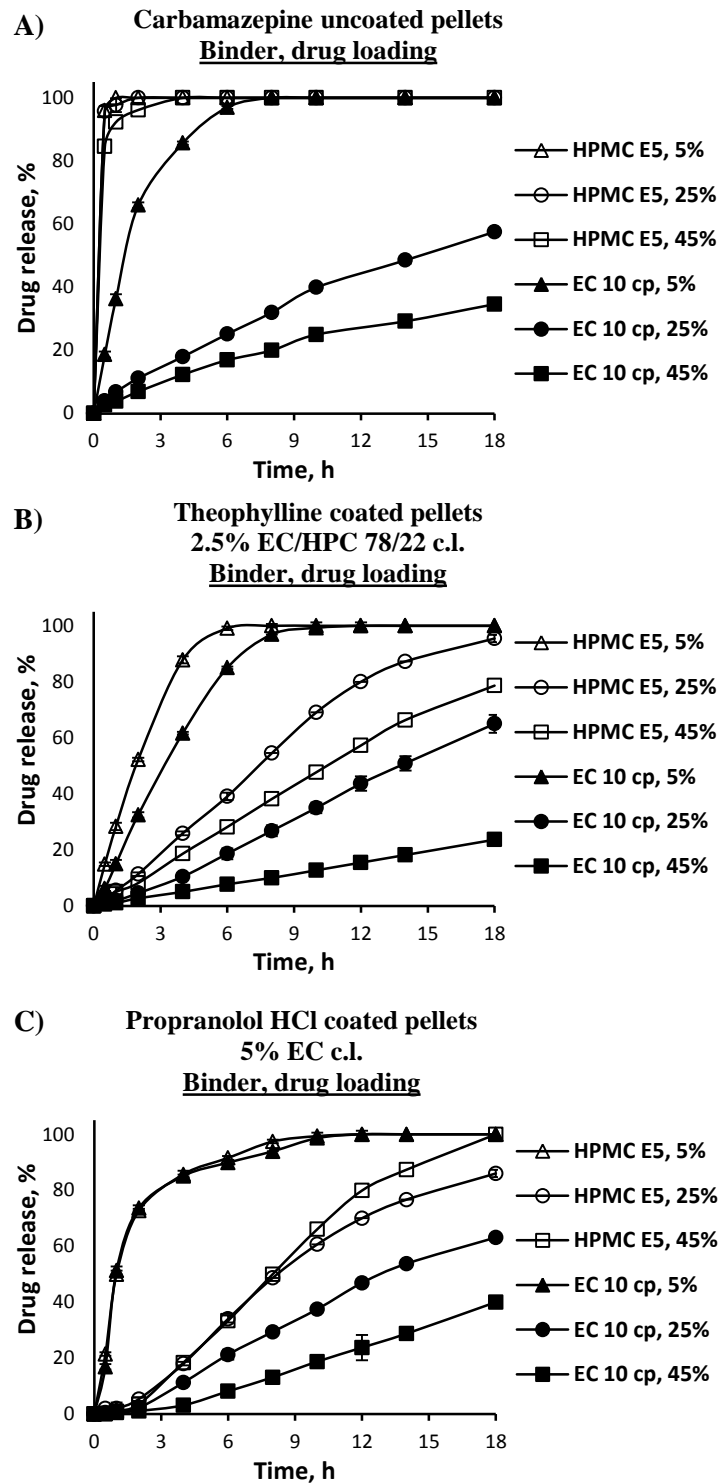
Fig. 30: Effect of drug loading on drug release (binder content 20% w/w based on the drug).

Increasing the drug loading led to a decrease in drug release from both coated and uncoated pellets with both binders (Fig. 30 A, B, C). This is due to a decreased surface area/dose ratio. In the case of ethylcellulose layered pellets, the ethylcellulose present in the drug layer plays a role as matrix former, and the drug has to diffuse through this matrix to be released out of

the pellets. Therefore increasing the drug loading (thicker EC/drug layers) led to increase the diffusion path length and thereby decreased the drug release.

For this reason, the effect of drug loading was more pronounced with EC- than HPMC-layered pellets, thus, the difference in drug release between EC- and HPMC-layered pellets (T_{80} EC – T_{80} HPMC) increased by increasing the drug loading (Fig. 31).

Fig. 31: Effect of drug loading on the difference in drug release between EC- and HPMC-layered pellets, represented by T_{80} EC – T_{80} HPMC.
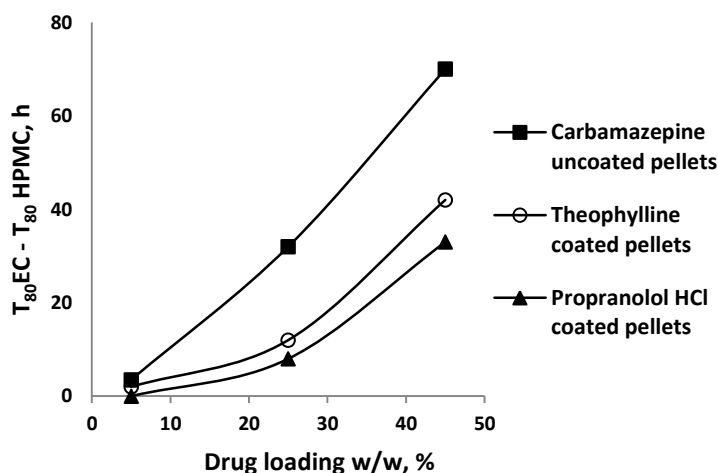
3.2.4   Effect of binder content

In this part, the drug loading was kept constant (25% w/w, based on the total pellet weight), however, the binder content was varied (5, 20, 40% w/w based on the drug). Increasing the binder content resulted in different effects on the drug release, for coated compared to uncoated pellets, and for EC- compared to HPMC-layered pellets (Fig. 32).

In the case of uncoated carbamazepine pellets, increasing the amount of ethylcellulose as binder led to a decrease in drug release, as a further retardation effect correlated with the polymer content. However, increasing the amount of HPMC as binder, did not affect the drug release, as the release with all tested amounts was very fast (100% release within 0.5 hour) (Fig. 32A). In the case of coated theophylline pellets, increasing the amount of ethylcellulose as binder, led to a slight decrease in drug release. However, increasing the amount of HPMC as binder, led to an increase in drug release dramatically (Fig. 32 B). This can be attributed to the swellability of HPMC in water, which creates a high pressure on the thin (2.5% c.l.) and brittle ethylcellulose coating layer, leading to further cracking and increased drug release.

A)   **Carbamazepine uncoated pellets**

Legend:
- HPMC E5, 5%
- HPMC E5, 20%
- HPMC E5, 40%
- EC 10 cp, 5%
- EC 10 cp, 20%
- EC 10 cp, 40%

B)   **Theophylline coated pellets**
2.5% EC/HPC 78/22 c.l.

Legend:
- HPMC E5, 40%
- HPMC E5, 20%
- HPMC E5, 5%
- EC 10 cp, 5%
- EC 10 cp, 20%
- EC 10 cp, 40%
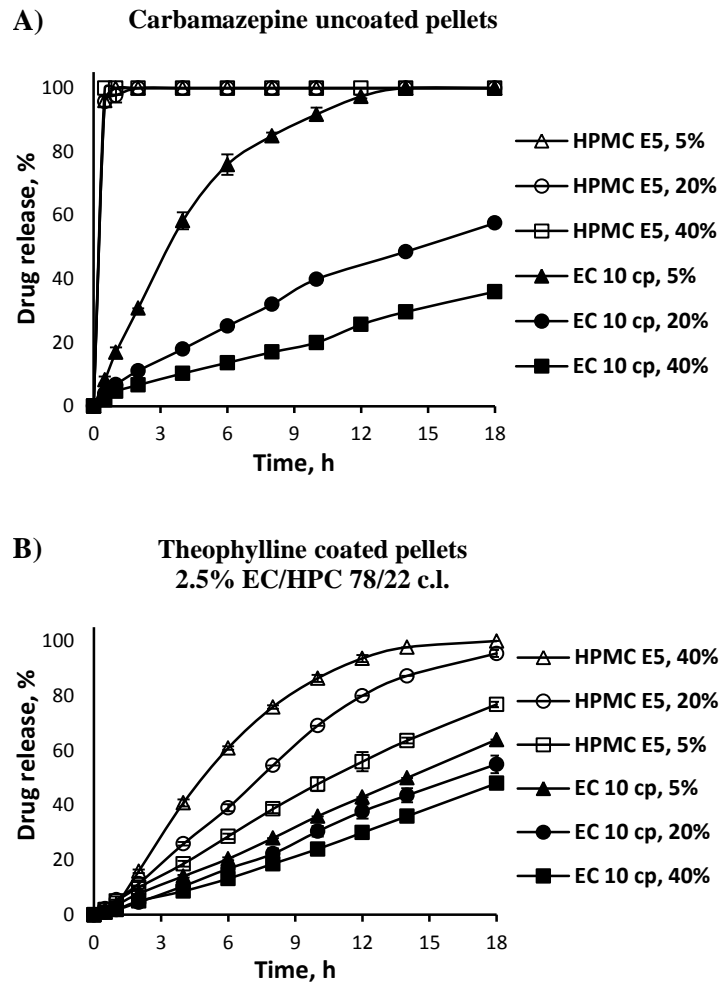
Fig. 32: Effect of binder content (w/w based on the drug) on drug release (drug loading 25% w/w).

As a summary, the difference in drug release rate between EC- and HPMC-layered pellets (T_{80} EC − T_{80} HPMC) increased with increasing the binder content with both coated and uncoated pellets (Fig. 33).

Legend:
- Carbamazepine uncoated pellets
- Theophylline coated pellets

Fig. 33: Effect of binder content on the difference in drug release between EC- and HPMC-layered pellets, represented by T_{80} EC − T_{80} HPMC.

3.2.5 Effect of coating level

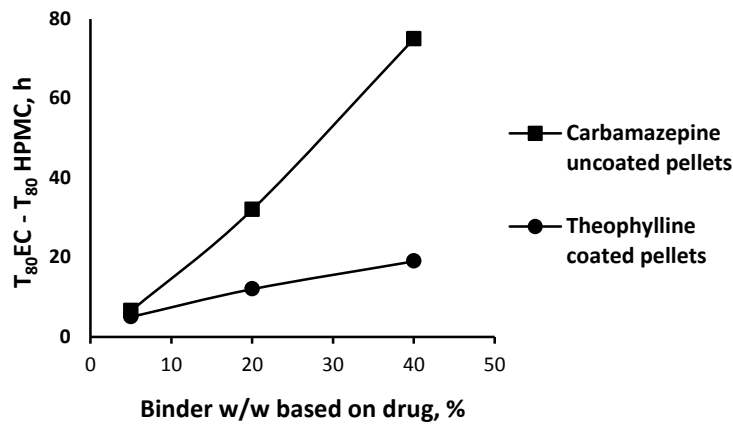The propranolol HCl release from uncoated pellets was very fast with both binders (Fig. 34), attributed to the high aqueous solubility of this drug. Furthermore, with uncoated pellets, the drug layer is in direct contact with the release medium, which dissolves the drug quickly, thereby minimizing the retardation effect of ethylcellulose present in the drug layer. Therefore, applying a top coating on the pellets, which decreases the exposure of the drug layer to the release medium, led to a decrease in drug release, and enlarged the retardation effect induced by ethylcellulose in the drug layer (Fig. 34). Therefore, increasing thickness of the coating layer (coating level) led to increase the difference in drug release between EC- and HPMC- layered pellets (T_{80} EC − T_{80} HPMC) (Fig. 35). Interestingly, HPMC-layered pellets required approximately twice the coating level required for EC-layered pellets to achieve the same release rate (10% vs. 5% EC c.l.) (Fig. 34).
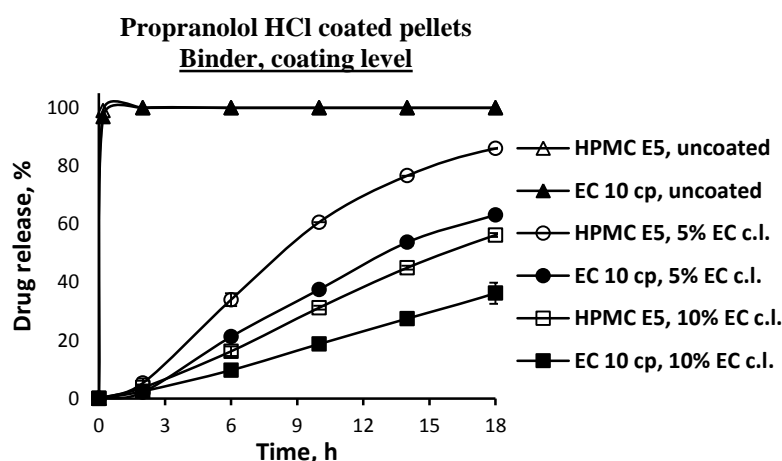

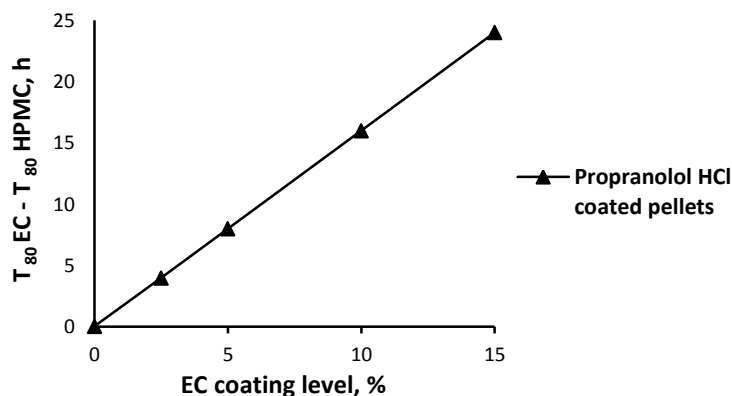**Fig. 34:** Effect of coating level on drug release (drug loading 25% w/w, binder content 20% w/w based on the drug).

Fig. 35: Effect of coating level on the difference in drug release between EC- and HPMC-layered pellets, represented by T_{80} EC − T_{80} HPMC.

3.2.6 Effect of ethylcellulose molecular weight

As discussed before, the higher molecular weight of ethylcellulose used as coating was more resistant to the pressure created by swelling of the MCC-based pellets prepared by extrusion spheronization, and therefore decreased the drug release. However, no remarkable effect of ethylcellulose molecular weight on drug release was seen when used as a binder. Also for the system of drug-layered pellets, ethylcellulose with different molecular weights (viscosity grades) was used as coating material and as a binder for drug layering, as well.

As a coating:

A) **Propranolol HCl coated pellets**
5% EC c.l.
Binder, coating layer

B) **Metoprolol tartrate coated pellets**
20% EC c.l.
Binder, coating layer

Fig. 36: Effect of molecular weight of ethylcellulose used as coating on drug release (drug loading 25% w/w, binder content 20% w/w based on the drug).

No influence of molecular weight of ethylcellulose used as a coating on propranolol HCl release, with both binder types (Fig. 36A). However, with the higher soluble metoprolol tartrate, the drug release decreased dramatically with both binder types upon increasing the molecular weight (viscosity grade) of ethylcellulose (Fig. 36B). This is because with such extremely highly soluble drug, cracking of the coating layer represents the main mechanism

of drug release because of the high osmotic pressure created by the drug. Therefore, increasing toughness of the coating layer (by increasing the molecular weight of ethylcellulose) led to an increase in the resistance to the osmotic pressure, thus, less cracking and a slower drug release.

As a binder:

A) **Propranolol HCl coated pellets 5% EC 10 cp c.l.**

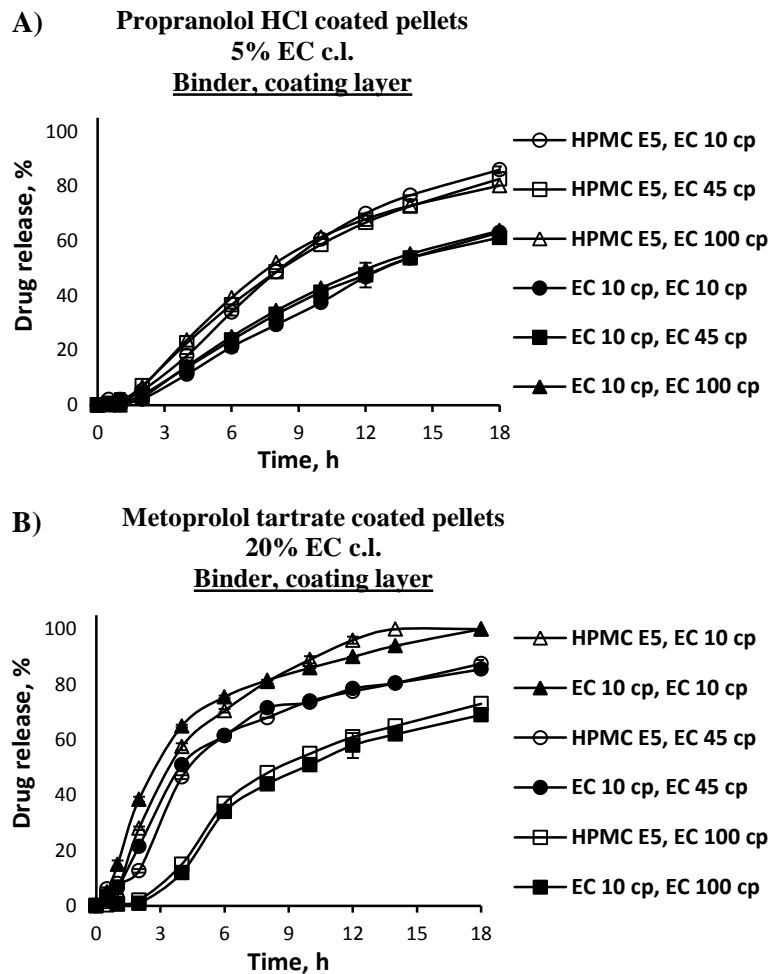**B)** **Metoprolol tartrate coated pellets 20% EC 10 cp c.l.**
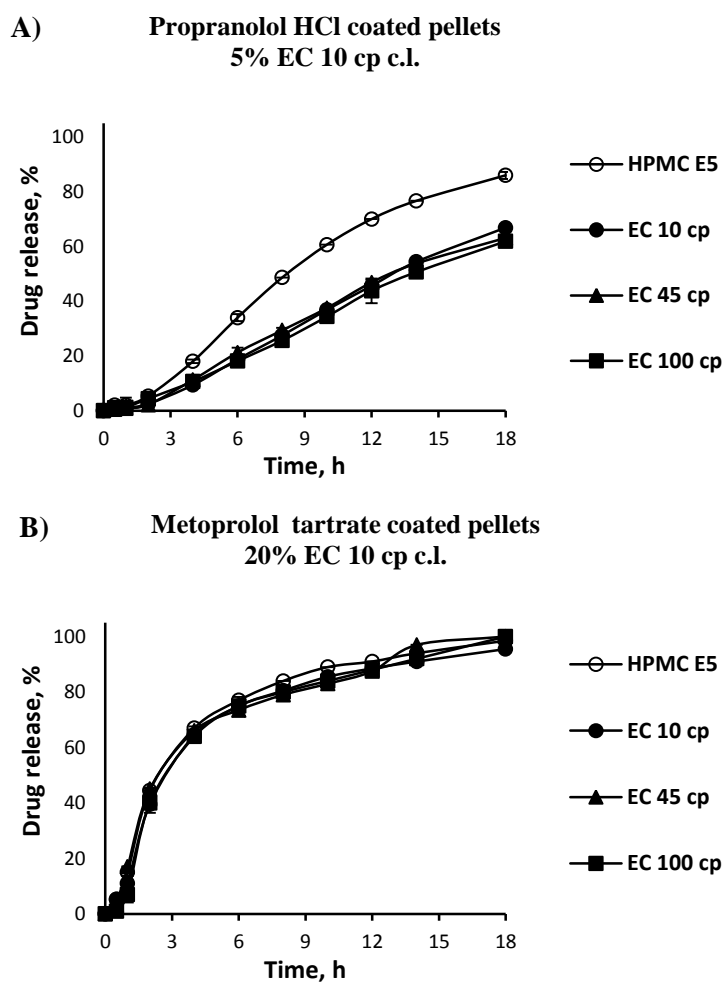

Fig. 37: Effect of molecular weight of ethylcellulose used as binder on drug release (drug loading 25% w/w, binder content 20% w/w based on the drug).

There was no influence of the molecular weight of ethylcellulose used as a binder on the release of both drugs (Fig. 37).

3.2.7 Effect of layering method (solution vs. suspension)

Drug layering can be carried out either from a solution or a suspension of the drug (Ghebre-Sellassie, 1989a). Solution drug layering may require a lower amount of binder, especially if the drug solution is sticky enough to adhere to the starter cores. However, if the drug solution is extremely sticky or has a high viscosity, this could lead to sticking of the pellets to each other (agglomeration) or to the wall of the coating chamber (Opota et al., 1999). Furthermore, the recrystallized drug may have another crystalline form with different aqueous solubility or less stability than the original form. Therefore, suspension drug layering is more preferable (Jones, 1989). Propranolol HCl was layered from a solution in (isopropanol:water 70:30), and a suspension in (isopropanol:water 88:12) using both HPMC E5 and EC 10 cp as binders. Additionally, the drug was dissolved in the corresponding solvents and recrystallized (upon drying in the oven) and then tested regarding to solubility and crystalline form using PXRD, and compared with the original drug. There was no effect of the layering method on drug release with both binders (Fig. 38), as the crystalline form (Fig. 39) and the solubility (Table 8) of the recrystallized drug were identical to the original drug.
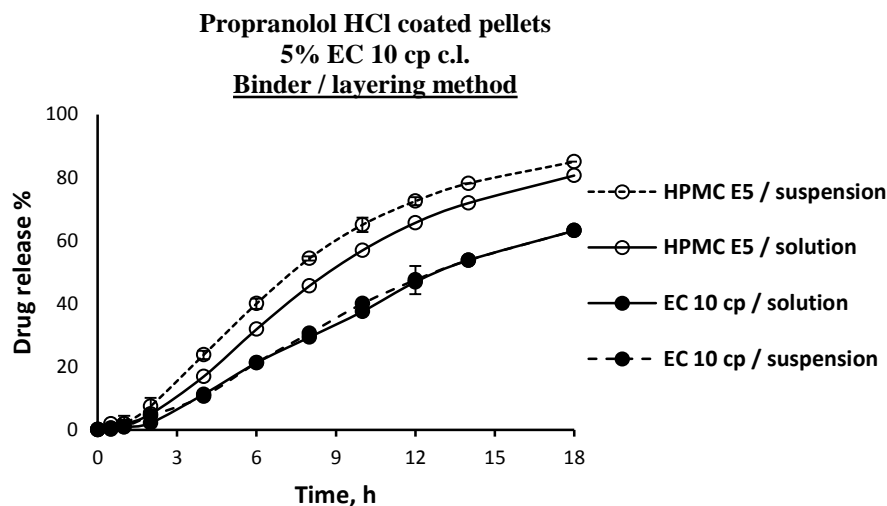
Fig. 38: Effect of drug layering method on drug release (drug loading 25%w/w, binder content 20% w/w based on the drug).
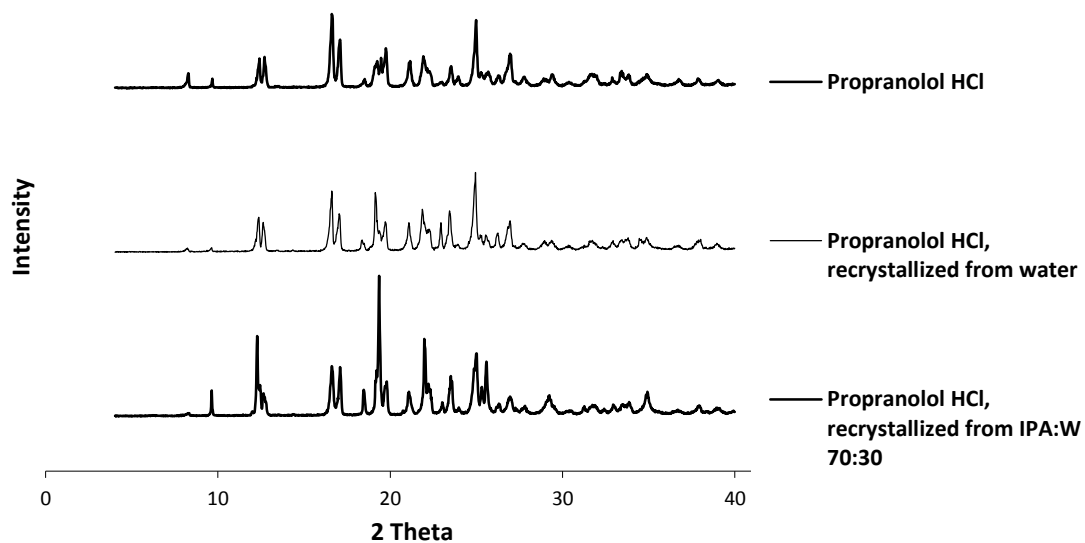
Fig. 39: PXRD of propranolol HCl original powder and the recrystallized one from different solvents.

Table 8: Solubility in 0.01 N HCl of propranolol HCl original powder and the recrystallized one from different solvents

	Original powder	**Recrystallized powder**	
		From water	**From IPA:W 70:30**
Solubility mg/ml	220	250	240

3.2.8 Enteric polymers as binders

Targeting of the drug release to the small intestine is a beneficial approach to avoid local irritation of the stomach, and to protect acid sensitive drugs, or for the local treatment of intestine or colon (Wilding, 2000; Cole et al., 2002; Ashford and Fell, 1994). According to the United State Pharmacopoeia (USP) under the monograph 711, delayed-release dosage forms should not release in the acid stage (2 hours in 0.1 N HCl) more than 10% of the labelled amount of the drug, followed by immediate release in the simulated intestinal fluids. An enteric release profile of carbamazepine without coating was achievable only at high amount (40% w/w based on the drug) of the anionic polymers Eudragit® L100 55 or Eudragit® S 100 used as binders (Fig. 40). In PBS pH 6.8, the release was very fast with Eudragit® L100 55 as it dissolves completely at this pH (above pH 5.5) (Evonik, 2007), however, with Eudragit® S 100 which dissolves at pH 7 (Evonik, 2007), the release was sustained over 12 hours.

Binder, content
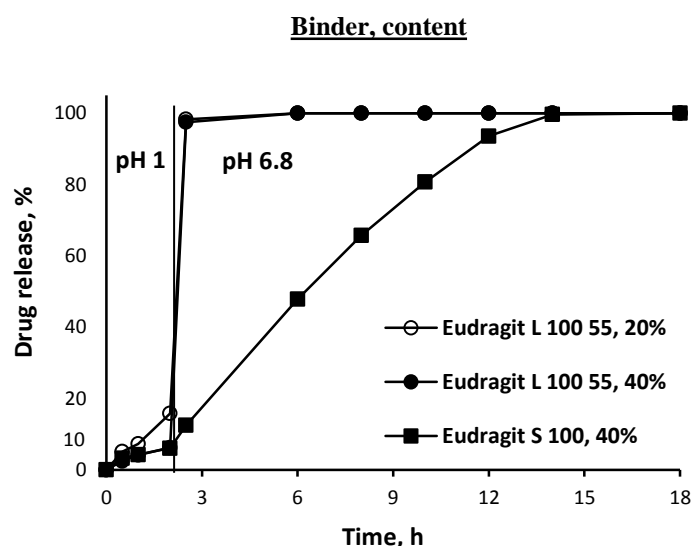
Fig. 40: Carbamazepine release from pellets layered with enteric polymers as binder (drug loading 25% w/w).

In some chronic diseases such as ulcerative colitis, the inflammation was seen along the whole colon (Hu et al., 1999). Therefore, extending the drug release in the high pH-fluids is required to ensure delivery of the drug to all parts of intestine and colon.

A combination of ethylcellulose and Eudragit® L100 55 was able to prevent the release in pH 1 ($\leq$ 10% release within 2 hours) and to retard it in PBS pH 6.8 (Fig. 41).

Ethylcellulose + Eudragit L 100 55

Fig. 41: Effect of ethylcellulose:Eudragit® L 100 55 ratio on carbamazepine release (drug loading 25% w/w).

Sometimes, a blend of two polymers can be used to facilitate the adjustment of desired release patterns, especially for drugs with a pH-dependent solubility (Siepmann et al., 2008). For example, weakly basic drugs demonstrate pH-dependent release from extended release formulations. At low pH they are freely soluble and have a fast release rate, however, the release decreases dramatically at higher pH (Thoma and Ziegl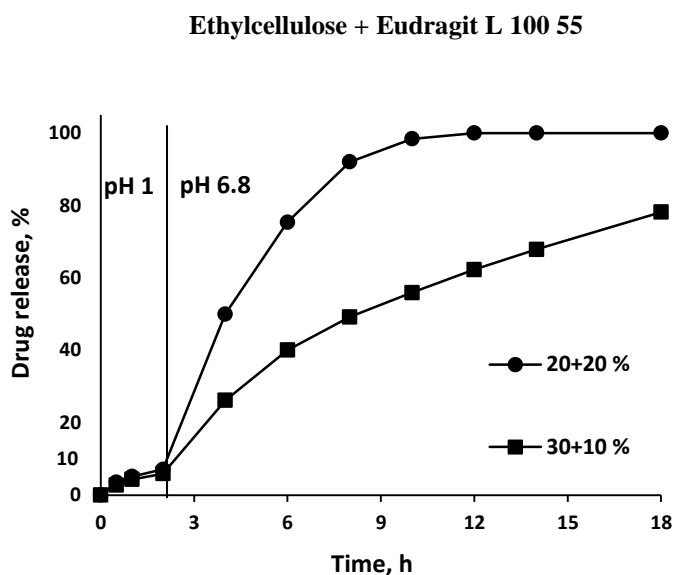er, 1998; Cha et al., 2009). Several approaches have been used to overcome the pH-dependent release of these drugs, such as incorporation of organic acids in the drug cores to maintain an acidic microenvironment to keep the drug in the more soluble form regardless of pH of the release medium (Thoma and Ziegler, 1998; Espinoza et al., 2000). However, addition of the organic acids to the formulation may not be always possible, as they might be incompatible with some drugs. Therefore, the approach which is more commonly used to achieve pH-independent extended release, is the coating with a combination of sustained and enteric release polymers (Dashevskiy et al., 2004; Körber et al., 2011). In the intestinal fluids, the enteric polymer leaches out, increasing the permeability of the coating layer to compensate the decrease in aqueous solubility of the basic drug in high pH media. Verapamil HCl was chosen as a weakly basic model drug, the solubility in pH below 6 is more than 100 mg/ml, while, in pH 6.8 it drops to approximately 3 mg/ml (Streubel et al., 2000).
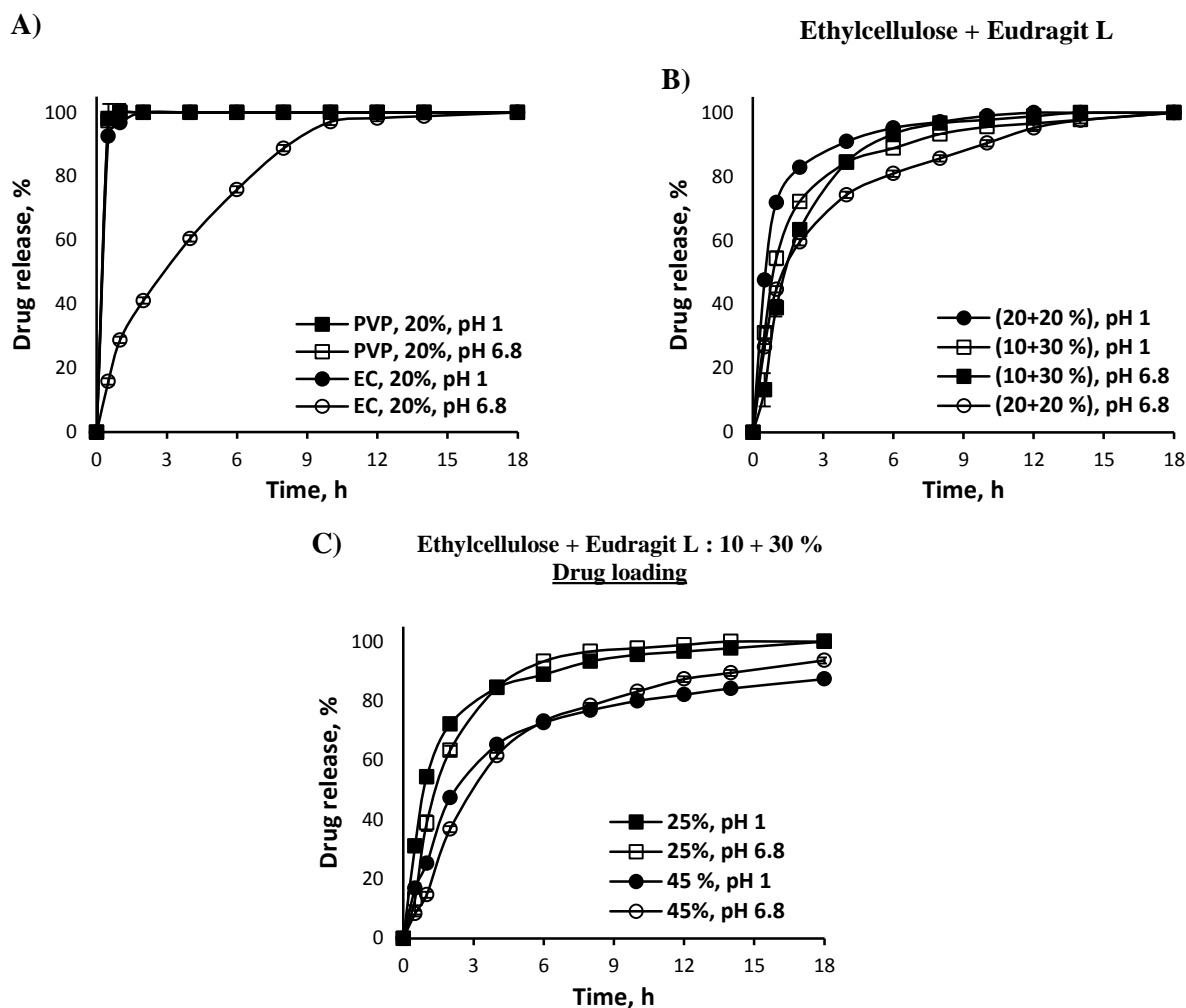
A)

Ethylcellulose + Eudragit L

B)

C)   **Ethylcellulose + Eudragit L : 10 + 30 %**
Drug loading

Fig. 42: Verapamil HCl release from uncoated pellets layered using different binders (w/w based on the drug) and combinations thereof.

The release of verapamil HCl from uncoated pellets layered with the water-soluble binder PVP was very fast and independent of pH of the release medium. However, the release from ethylcellulose-layered pellets was relatively slower and highly pH dependent. The release in PBS pH 6.8 was much slower than in pH 1, because of the reduced drug solubility at elevated pH (Fig. 42A). A reduction of the difference in drug release between pH 1 and pH 6.8 was achieved by using combination of ethylcellulose and Eudragit® L100 55 as binder for drug layering (Fig. 42 B). The combination ratio of (ethylcellulose+Eudragit® L 10+30% based on the drug) resulted in a comparable release rate in both media. The achieved pH-independent release was relatively fast ($t_{80} \approx 4h$), therefore, a further retardation tool was required to retard the drug release. This target could be achieved (as shown before) either by increasing ratio of the polymer blend used as a binder, or by increasing the drug loading. For high dose drugs like verapamil HCl (120-180 mg/day), the second approach is more preferable. As expected, the pH-independent release profile was maintained and further extended at higher drug loading (Fig. 42 C).

3.2.9 Pellets performance upon compression

Controlled release multiparticulate systems are usually administered orally either filled into hard gelatin capsules, or compressed into fast disintegrating tablets. Pellets compression usually involves a high risk of damaging the release retarding film and hence changing the release characteristics (Altaf et al., 1998). The degree of damage depends mostly on the mechanical properties of the polymer (Bodmeier, 1997). For example, ethylcellulose is considered as a highly brittle polymer, which can be damaged easily under stress leading to the loss of extended release characteristics (Bansal and Vasireddy, 1993; Bodmeier and Paeratakul, 1994; Dashevskiy et al., 2004). However, acrylic polymers are more flexible than ethylcellulose and are therefore more preferable for coating of the pellets intended to be compressed into tablets (Bodmeier and Paeratakul, 1994b). Sometimes, addition of certain amount of a flexible polymer can result in more flexible and mechanically more stable films (Cuppok et al., 2011).

Drug release from ethylcellulose- layered pellets increased dramatically (F2 < 50) upon compression with both core types (Fig. 43), attributed to the brittleness of ethylcellulose. The increase in drug release upon compression was less pronounced with MCC cores compare to nonpareils (Fig. 43 B vs. A). This is probably because with MCC cores, the polymer was damaged in both uncompressed (during dissolution test upon swelling of the MCC cores) and compressed pellets (during compression). Furthermore, there was no influence of compression force (10 vs. 20 KN) on drug release regardless of starter core type (Fig. 43).
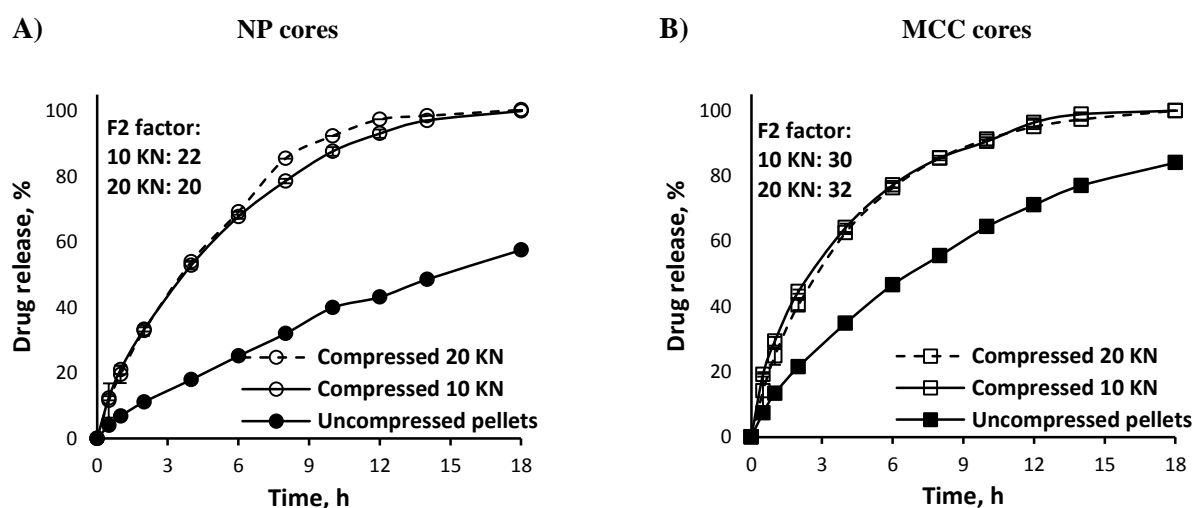

Fig. 43: Effect of compression on carbamazepine release from ethylcellulose-layered pellets (pellet content 50% w/w).

The higher molecular weight ethylcellulose 100 cp used as binder was more resistant to rupture, therefore, the drug release was less affected by compression (Fig. 44).
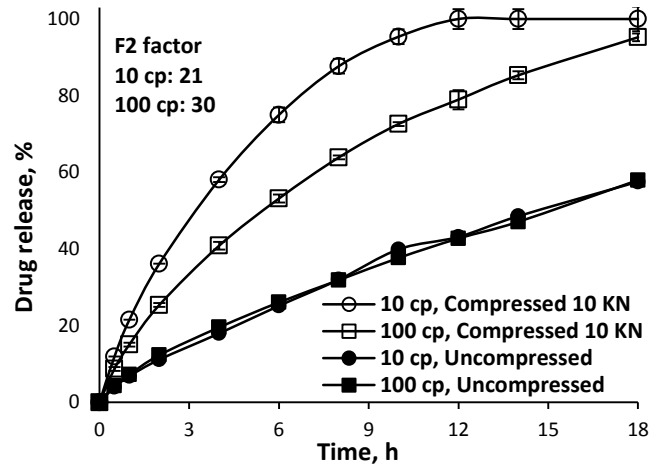
Fig. 44: Effect of compression on carbamazepine release from pellets layered with different grades of ethylcellulose (pellet content 50% w/w).

Although the acrylic polymers are considered as flexible polymers, drug release from Eudragit® RS- layered pellets increased remarkably upon compression (F2 < 50). Probably because of the low amount of Eudragit® RS (20% w/w, based on the drug), forming very thin, and thus very weak solid bridges. Therefore, increasing Eudragit® RS amount to (40% w/w based on the drug) led to more robust bridges and less changes upon compression (F2 > 50) (Fig. 45).

Fig. 45: Effect of Eudragit® RS content (w/w based on the drug) on carbamazepine release from uncompressed and compressed pellets (pellet content 50% w/w).

The drug release from pellets layered using the flexible polymer Kollidon® SR was not affected by compression (Fig. 46).
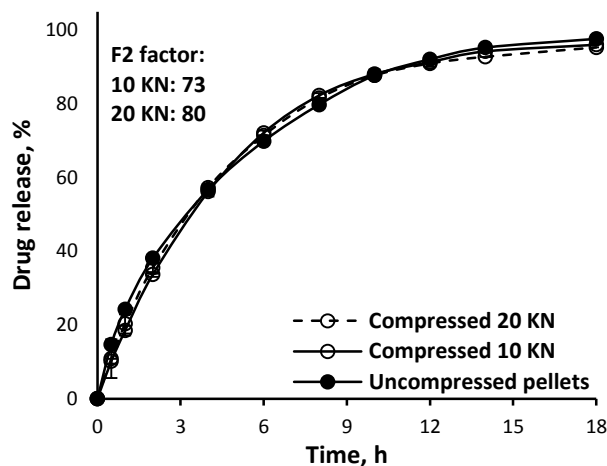
Fig. 46: Effect of compression on carbamazepine release from Kollidon® SR-layered pellets (pellet content 50% w/w).

Ethylcellulose- layered pellets released the drug slowly, however, the drug release increased dramatically upon compression (F2 factor: 22) (Fig. 43). On the other hand, relatively faster drug release was seen with Kollidon® SR-layered pellets, but it was unaffected by compression (Fig. 46). Therefore, to combine the retardation efficiency with the flexibility, mixtures of ethylcellulose and Kollidon® SR with different ratios were used as binders for carbamazepine layering. As expected, increasing the ratio of Kollidon® SR in the combination, resulted in a faster drug release which was however less affected by compression (Fig. 47 A, B).
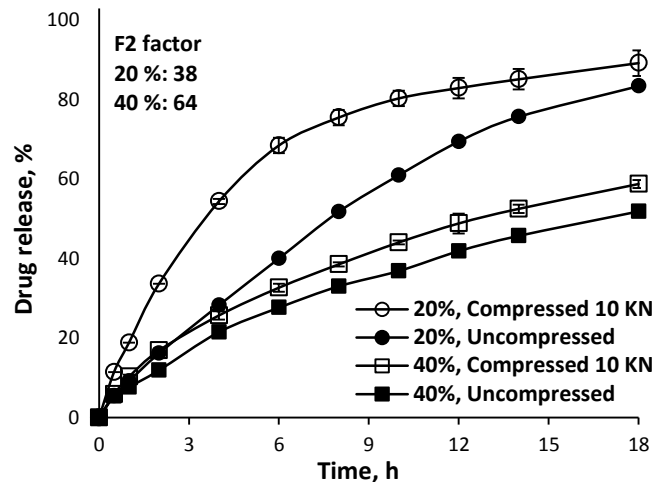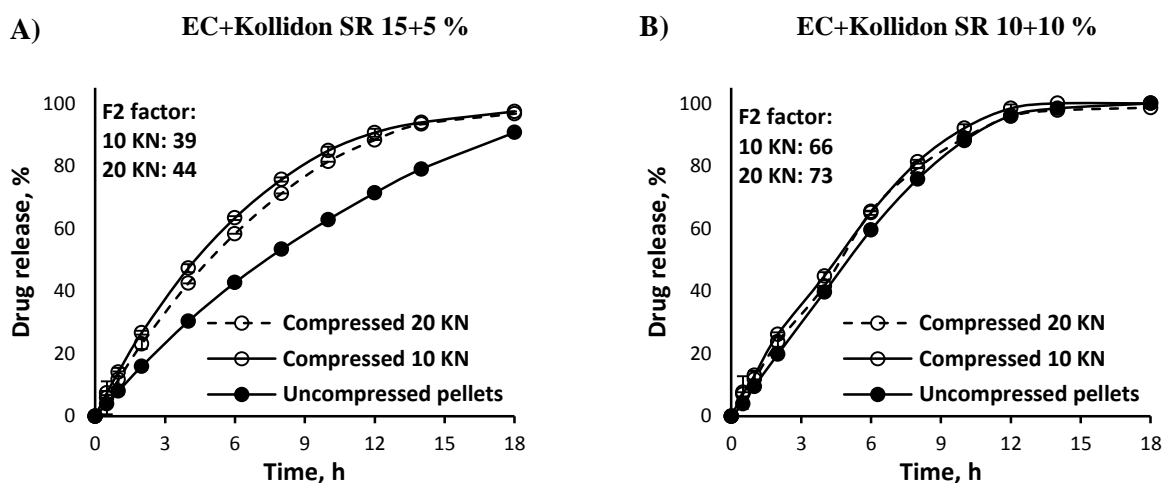

Fig. 47: Effect of ethylcellulose:Kollidon® SR blend ratio (w/w based on the drug) on carbamazepine release from uncompressed and compressed pellets (pellet content 50% w/w).

3.2.10 Effect of dissolution test conditions

Several efforts have been paid to develop a biorelevant dissolution media which can simulate the GIT fluids (Al-Behaisi et al., 2002; Sunesen et al., 2005; Jantratid et al., 2009) as an attempt to predict the in vivo performance of the dosage form, and to establish an in-vivo in-vitro correlation (IVIVC). In this study, few modifications on the pharmacopeial dissolution test conditions were made to mimic the gastrointestinal environment such as pH, osmolality and surface tension of the release media.

The osmolality was adjusted to 600 mosmol/kg using sodium chloride. Surface tension of the release medium was adjusted using different surfactants (sodium lauryl sulfate, polysorbate 80) in a concentration of 0.25% w/v, as recommended by several researchers (Shah et al., 1989; Galia et al., 1998). The results were evaluated using the F2 similarity factor (Table 9).

Drug release from pellets prepared with all tested polymers was unaffected (F2 > 50) by pH, except for Eudragit® RS- layered pellets, which showed a decreased drug release in 0.1 N HCl compare to PBS pH 6.8. This was attributed to the decreased permeability of Eudragit® RS in 0.1 N HCl media, because of the common ion effect, as the quaternary ammonium groups in the acrylic polymer are in hydrochloride salt form. For the same reason, increasing osmolality of the release media to 600 mosoml/kg using NaCl, led to a decrease in the drug release from Eudragit® RS- layered pellets, while, the release from pellets layered with other polymers was independent of osmolality.

Presence of surfactants in the release media can potentially increase the wettability and thereby the accessibility of water to the dosage form, leading to a faster drug release (Raiwa, 2011). The addition of Tween® 80 to the release media led to increased carbamazepine release from Eudragit® RS- and ethylcellulose-layered pellets while pellets layered with Kollidon® SR were not affected. Robustness of drug release from Kollidon® SR-layered pellets could be correlated to its high permeability, as the polymer contains high amount (20% w/w) of the water-soluble polyvinyl pyrrolidone. The addition of sodium lauryl sulfate to the release media, led to a significant increase in the drug release from all formulations, due to the significant increase of carbamazepine solubility (Table 10).

Table 9: Effect of dissolution test conditions on carbamazepine release from pellets layered with different polymers (20% w/w based on the drug), represented by F2 similarity factor

Polymer	F2 similarity factor			
	pH	Osmolality, mosmol/kg	Surfactants PBS pH 6.8 with vs. without	
	1 vs. 6.8	600 vs. 100	0.25% w/v Tween® 80	0.25% w/v SLS
Ethocel® 10	86	74	(+) 35	(+) 19
Eudragit® RS 100	(-) 39	(-) 44	(+) 36	(+) 20
Kollidon® SR	83	75	64	(+) 36

(+) the drug release increased, (-) the drug release decreased.

Table 10: Solubility of carbamazepine in PBS pH 6.8 in the presence of different surfactants

	PBS pH 6.8	PBS pH 6.8 + 0.25% w/v Tween® 80	PBS pH 6.8 + 0.25% w/v SDS
Carbamazepine solubility, mg/ml	0.22	0.29	0.71

3.3 Matrix layering with ethylcellulose for controlled release pellets of single drug and drug combination

As shown before, the use of water-insoluble polymers as binders (5-40% w/w based on the drug) for drug layering was an effective tool to control the drug release. With poorly soluble drugs, controlled release was already achieved without an additional coating step. With higher soluble drugs, a further coating layer was necessary to retard the release, however, a much less coating level was required for pellets prepared with water-insoluble binders than those prepared with water-soluble ones.

Matrix-layered systems have gained increasing interest recently because of several advantages over reservoir systems, such as easy manufacturing, less costs (one step process) and less risk of dose dumping (if the coating accidentally ruptured or damaged). This system is also applicable for drug combination, to prepare one dosage form containing two different drugs, which increases patient compliance and reduces production costs.

In this study, matrix layering with ethylcellulose for controlled release pellets of single drug, or drug combination (Fig. 48), and factors affecting drug release were investigated.
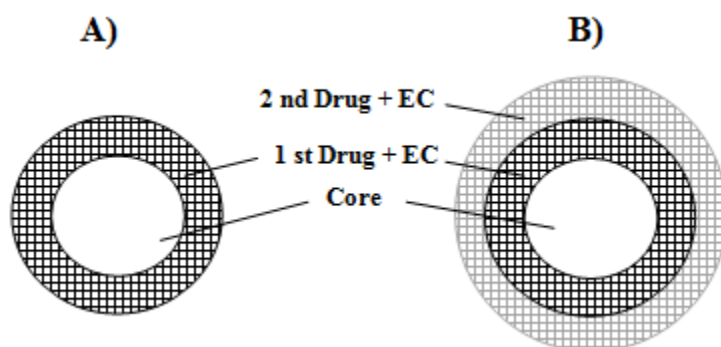
Fig. 48: Schematic presentation of A) single-layer matrix pellet, and B) multilayer matrix pellet.

3.3.1 Effect of drug:polymer ratio and drug solubility

Controlled drug release was achieved with all drugs using different ratios of drug:ethylcellulose (Fig. 49). With the poorly soluble drug carbamazepine, the release was already controlled with small amounts of ethylcellulose (drug:ethylcellulose 1:0.1-0.2) (Fig. 49 A). The more soluble drugs required more ethylcellulose to control the release (Fig. 49 B-D). Surprisingly, the freely soluble propranolol HCl (aqueous solubility ≈ 200 mg/ml), required similar amounts (even more) of ethylcellulose, which were required for the very soluble metoprolol tartrate (aqueous solubility > 3000 mg/ml) (Fig. 49 C vs. D). This might be attributed to the surface activity of propranolol HCl, which can potentially increase the permeability of ethylcellulose (as it is embedded within ethylcellulose), thereby increase the drug release. The surface activity of propranolol HCl was investigated and proven by (Apichatwatana, 2011).

Fig. 49: Effect of drug:ethylcellulose ratio on drug release (drug loading 15% w/w).

To confirm the effect of drug solubility and/or surface activity on drug release, the release of propranolol HCl was compared with the release of diprophylline at the same drug:EC ratio and the same drug loading. Diprophylline has almost the 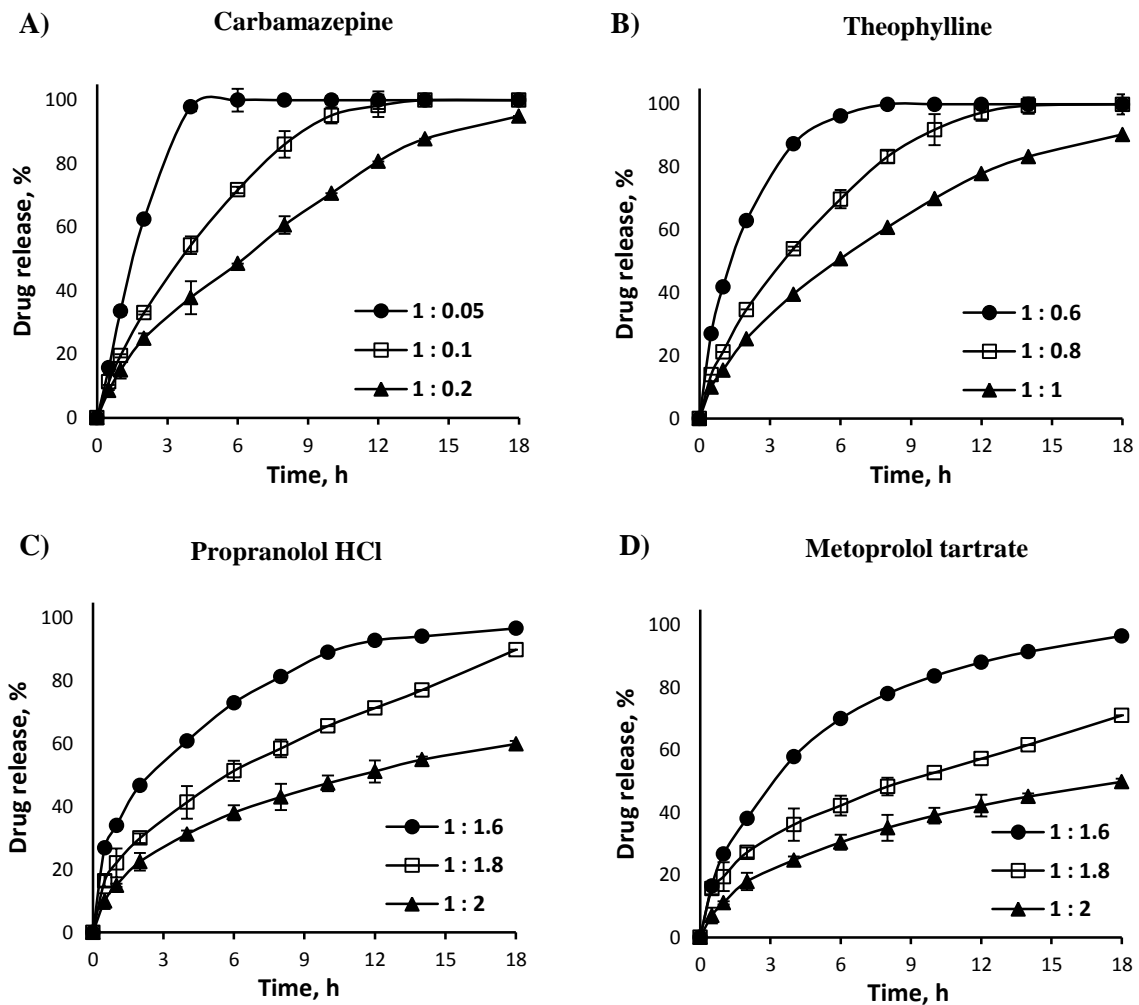same aqueous solubility as propranolol HCl ($\approx$ 200 mg/ml), however, without surface activity (Apichatwatana, 2011). As expected, the release of diprophylline was much slower than propranolol HCl (Fig. 50).

Drug : ethylcellulose 1:1.8
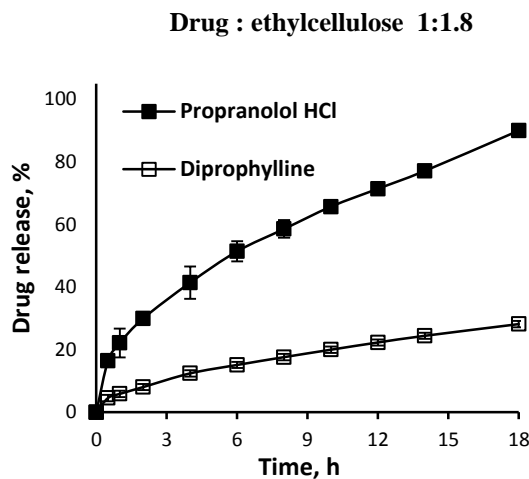
Fig. 50: Effect of drug type on the release from ethylcellulose-layered pellets (drug loading 15% w/w).

3.3.2   Effect of drug loading

A decrease in the drug release was observed upon increasing the drug loading (Fig. 51), as it is associated with decreasing surface area/dose ratio, as well as increasing the diffusion path length. Different release rates were achieved with different drugs having different aqueous solubilities, by varying drug:ethylcellulose ratio, and drug loading. On the other hand, it is important to consider, that the more ethylcellulose used, the less drug can be loaded, i.e. the higher drug solubility the more ethylcellulose is required to control the release, thus, the less drug can be introduced by this system.

For drug layering in the fluid bed using bottom spray model, the maximum weight increase, which can be achieved is 150% w/w based on the starter core weight (Ghebre-Sellassie, 1989). On the other hand, the maximum amount of pellets, which can be filled in one capsule (size 0), is approximately 500 mg.

Based on these assumptions, the maximum dose of drug which can be introduced at each drug:ethylcellulose ratio was calculated (Table 11).

A) Carbamazepine:EC 1:0.1

B) Theophylline:EC 1:0.8

C) Propranolol HCl: EC 1:1.8

D) Metoprolol tartrate: EC 1:1.8
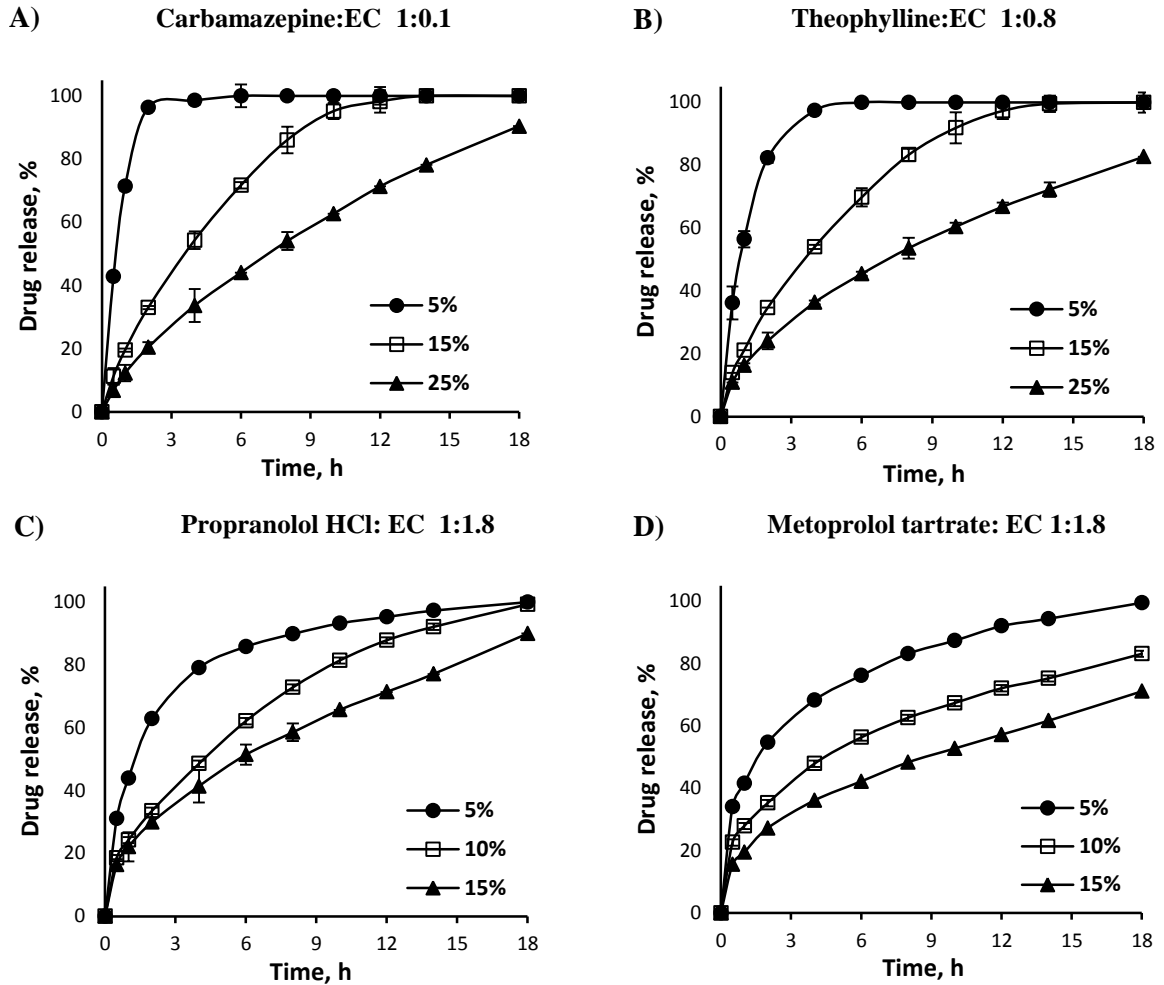
Fig. 51: Effect of drug loading on drug release.

Table 11: The maximum drug loading and the maximum dose at each drug: ethylcellulose ratio

Drug : EC ratio	Maximum drug loading [*], w/w % based on the total pellet weight	Maximum dose [**], mg	Drug : EC ratio	Maximum drug loading, w/w % based on the total pellet weight	Maximum dose, mg
1:0.05	57.0	285.0	1:1	30.0	150.0
1:0.1	54.5	272.5	1:1.2	27.5	137.5
1:0.2	50.0	250.0	1:1.4	25.0	125.0
1:0.4	43.0	215.0	1:1.6	23.5	117.5
1:0.6	37.5	187.5	1:1.8	21.5	107.5
1:0.8	33.5	167.5	1:2	20	100.0

[*]: Assuming that the highest achievable weight increase using bottom spray technique is 150% w/w based on starter core weight.

[**]: Assuming that the highest amount of pellets which can be filled in one capsule is 500 mg.

3.3.3 Solid state characterization

In matrix-layered pellets, the drug is dissolved or dissolved/dispersed in a solution of the matrix-forming polymer, depending on solubility of the drug in the polymer solvent. Upon solvent evaporation, if the drug has high affinity to the polymer, it may dissolve partially or completely in the polymer. Depending on solubility of the drug in the polymer, a solid solution (drug dissolved in the polymer) or solid dispersion (drug dispersed in the polymer) or combination of both can be obtained.

One of the most commonly used techniques to discriminate between solid solution and solid dispersion, is differential scanning calorimetry (DSC). In the case of solid dispersion, usually a clear melting peak of the drug crystals appears. Therefore, appearance of a melting peak is a direct indicator of the solid dispersion, however, absence of drug melting peak from the DSC chromatogram does not reflect necessarily a solid solution state. In some cases, the polymeric carrier may hinder the recrystallization of the drug, which stays in amorphous form after solvent evaporation, and the amorphous form does not show any melting peak. Other possibility is that the drug crystals dissolve in the molten polymer during the heating phase of DSC experiment before reaching the melting point of the drug. For this reason, it is recommended to run a physical mixture of the drug and the polymer as a standard, which reflects validity of the DSC method.

To characterize the solid state of the drug in the polymeric matrix, casted films of the layering solution/suspensions were prepared and tested with DSC. In addition, physical mixtures of the drugs and the polymer were tested in parallel.

For the slightly and very slightly soluble theophylline and carbamazepine, it was visually easy to notice that the majority of the drug is dispersed and not dissolved in the polymeric solution; therefore, no DSC test was performed for these drugs.

A clear melting peak was observed in both physical mixture and casted film for both propranolol HCl and metoprolol tartrate at two drug:ethylcellulose ratios 1:1 and 1:2 (Fig. 52 A, B), which indicates a solid dispersion state.
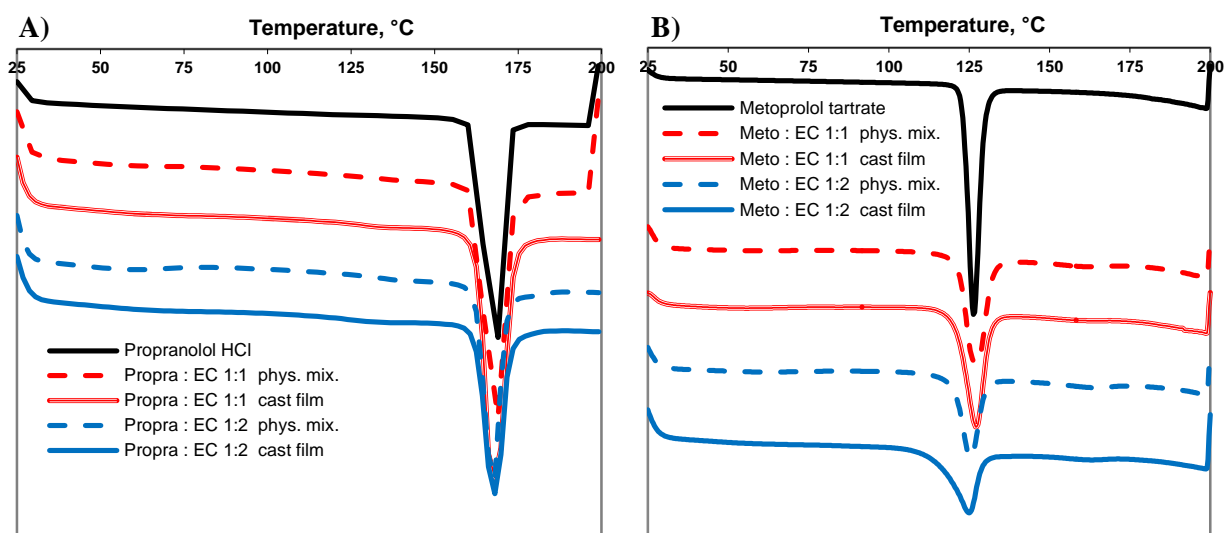
Fig. 52: DSC curves of physical mixtures and casted films of drug and EC.

To quantify the amount of the drug which has dissolved in the polymer (or transferred into amorphous form), enthalpy of fusion of the drug in both physical mixture and casted film was compared (Table 12). The enthalpy of fusion of the drug in casted film was lower than in physical mixture, however, the difference was very small (approx. 3% for propranolol HCl and 7% for metoprolol tartrate) regardless to drug:ethylcellulose ratio (Table 12).

The low ratio of drug, which was dissolved in the polymer, could be due to the poor solubility of the drugs in the chosen organic solvent, thus, if the drug was not dissolved completely in the organic solution of the polymer, there would not be any chance to be dissolved in the polymer upon solvent evaporation.

Table 12: Enthalpy of fusion of the drug in physical mixture and casted film

	Enthalpy of fusion, mJ	Difference Cast film vs. phys. mix. %
Propra:EC 1:1 phys. mix.	- 1359.55	3.18
Propra:EC 1:1 cast film	- 1316.35	
Propra:EC 1:2 phys. mix.	- 1347.82	3.49
Propra:EC 1:2 cast film	- 1300.71	
Meto:EC 1:1 phys. mix.	- 980.51	7.14
Meto:EC 1:1 cast film	- 910.50	
Meto:EC 1:2 phys. mix.	- 1177.08	6.60
Meto:EC 1:2 cast film	- 1099.34	

3.3.4 Release adjustment of drug combination

The objective of this study was to investigate the feasibility to control and to adjust the release of two drugs, having different aqueous solubilities, from multilayer matrix pellet. Furthermore, to understand the factors, which can influence the release of each drug. The layering order was based on the principal that the higher soluble drug was layered first onto the cores, then, the lower soluble drug was layered on top. The thinking behind that was, when the lower soluble drug is layered on top, it may have a release controlling effect on the higher soluble first drug. Based on this principal, three different combinations resulted out of three drugs (Fig. 53). Each drug was layered using suitable amount of ethylcellulose, based on the results of single-layer matrix pellets.
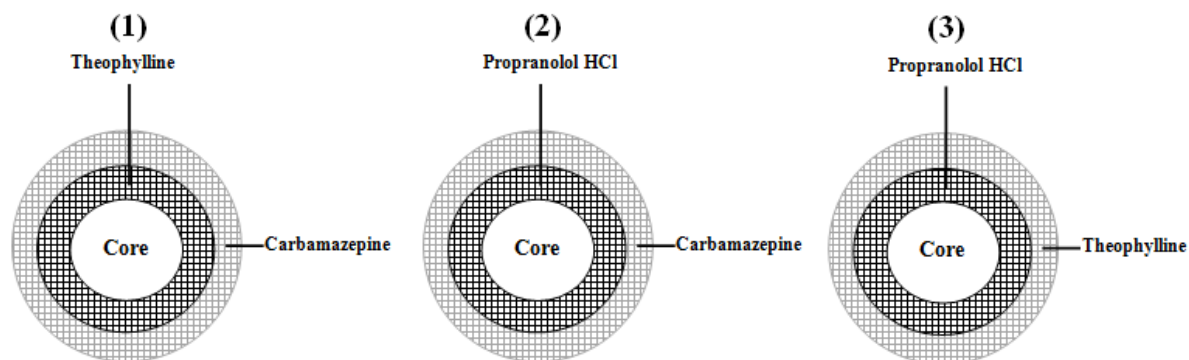
Fig. 53: Schematic presentation of different drug combinations.

In the first combination, the higher soluble theophylline was layered first onto the cores, then, carbamazepine was layered on top. Controlled release of both drugs was achieved from multilayer matrix pellet. Theophylline release was delayed and slower than carbamazepine (Fig. 54), due to the retardation effect of carbamazepine layer. Addition of the pore-former HPC (25% w/w based on ethylcellulose amount) to carbamazepine layer, led to an increase in the release of both drugs significantly (Fig. 54 A, B vs. Fig. 55 A, B), however, in higher extent for theophylline, that it matched carbamazepine release (Fig. 55 A, B). Increasing the drug loading of both drugs (from 10% to 20% w/w based on the total pellet weight), resulted in a decrease of their release rate (Fig. 55 A vs. B).

Increasing theophylline loading only (from 10% to 20% w/w based on the total pellet weight) led to a decrease in its release only without affecting the release of carbamazepine (top layer) (Fig. 55 A vs. C). However, increasing carbamazepine loading, led to a decrease in the release of both drugs, because of the retardation effect of carbamazepine (being layered on top) on theophylline (Fig. 55 A vs. D).

A)

B)

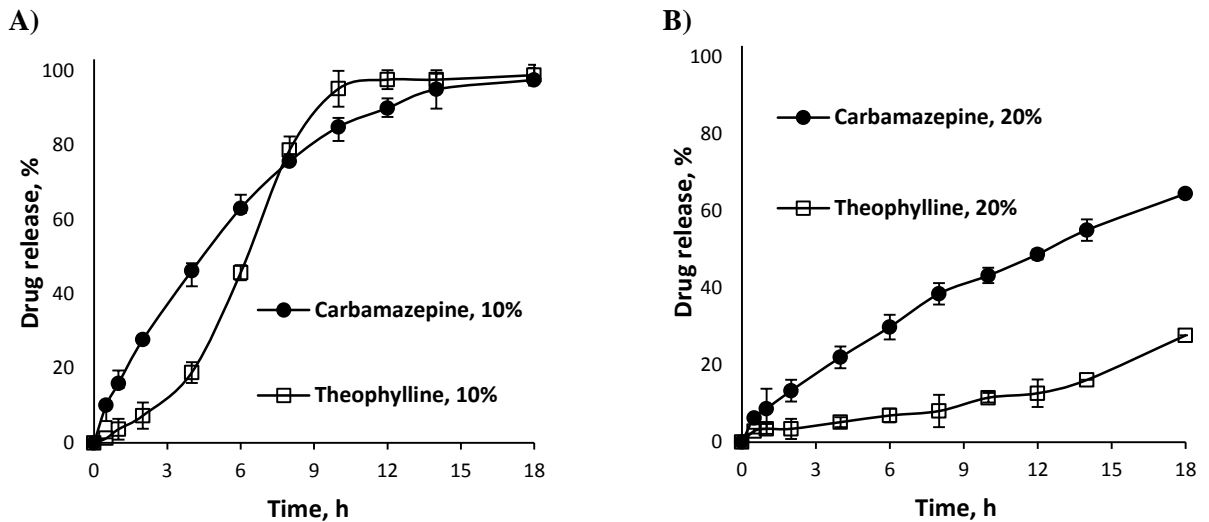**Fig. 54:** Drugs release from multilayer matrix pellet (same loading 10% w/w), first layer theophylline:EC 1:0.6, top layer carbamazepine:EC 1:0.2.

A)

B)

C)

D)
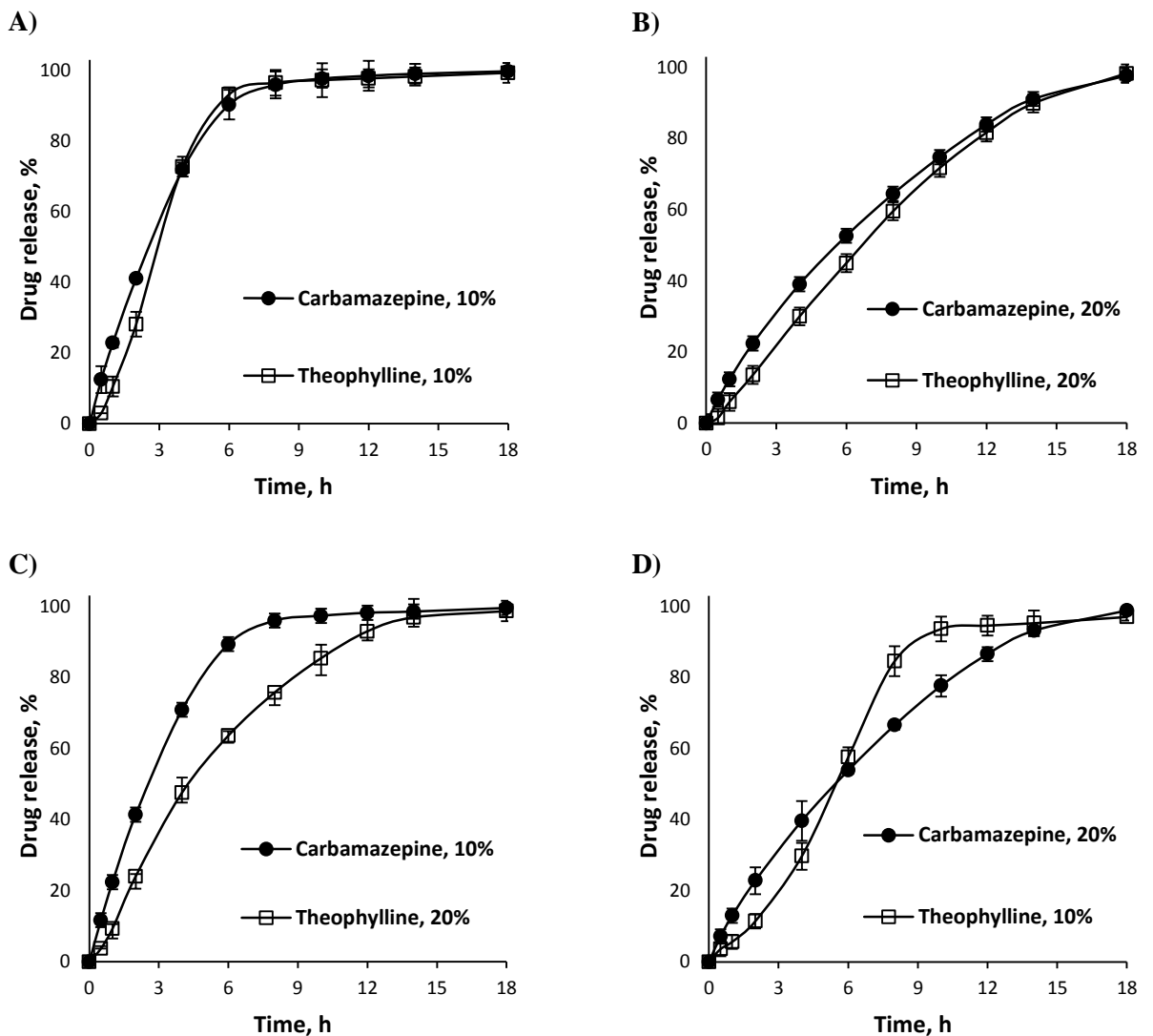
Fig. 55: Effect of drug loading in each layer on the release of both drugs, first layer theophylline:EC 1:0.6, top layer carbamazepine:EC:HPC 1:0.2:0.05.

Similarly, increasing amount of ethylcellulose layered with theophylline, led to a decrease in its release only without affecting the release of carbamazepine (Fig. 56 A, B and C). While, increasing amount of ethylcellulose layered with carbamazepine (top drug), led to a decrease in the release of both drugs (Fig. 56 A vs. D). The delayed release of the first drug can be improved by optimizing the ratio of the pore-former in the top layer.
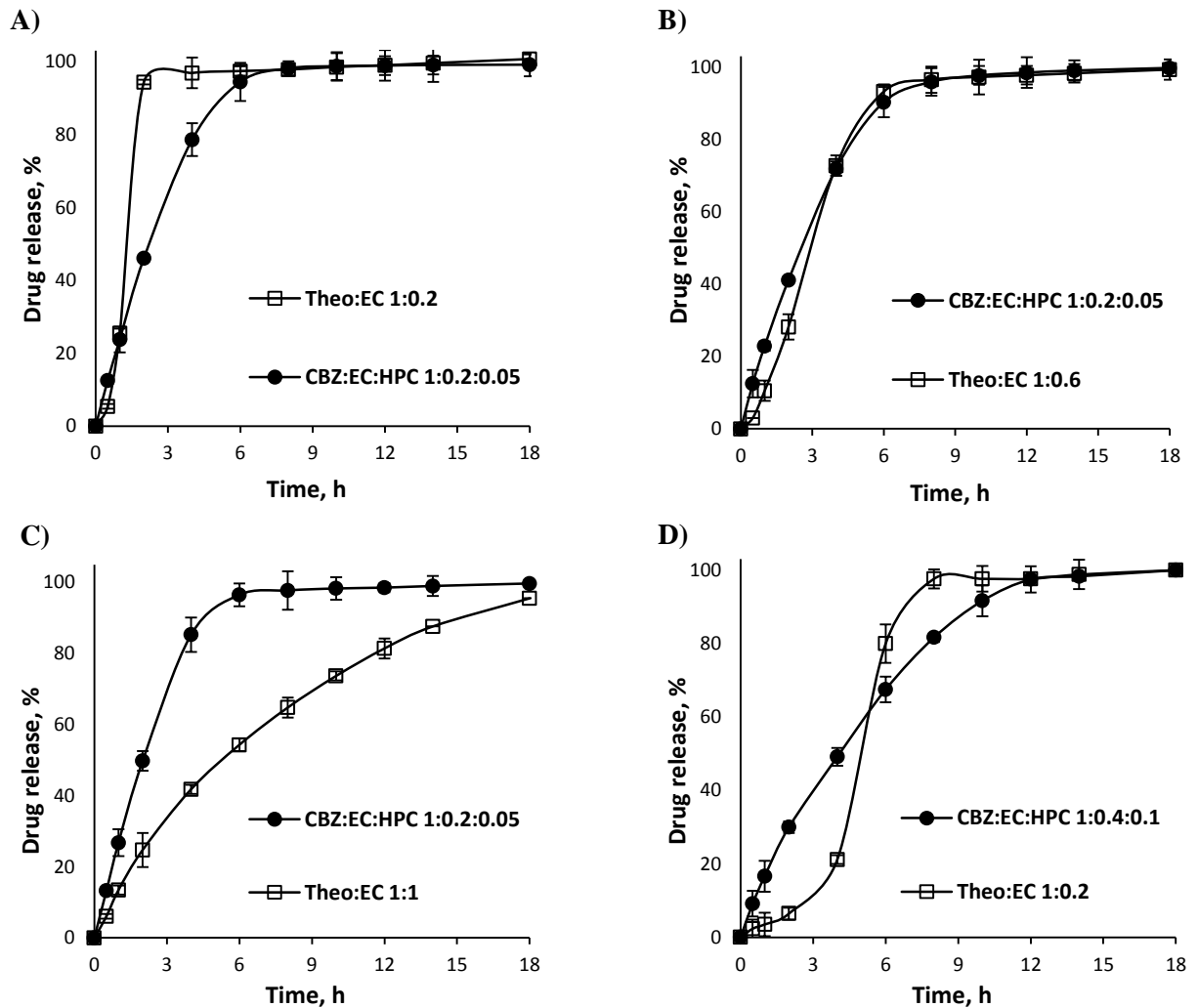
Fig. 56: Effect of ethylcellulose amount in each drug layer on release of both drugs (theophylline (Theo), carbamazepine (CBZ) loading 10% w/w).

Similar findings were obtained with the second drug combination, where propranolol HCl was layered first onto the cores, then, carbamazepine was layered on top. Increasing amount of ethylcellulose layered with propranolol HCl, led to a decrease in its release only without affecting the release of carbamazepine (Fig. 57 A vs. B). While, increasing amount of ethylcellulose layered with carbamazepine (top drug), led to a decrease in the release of both drugs (Fig. 57 C vs. B).

A)

B)

C)
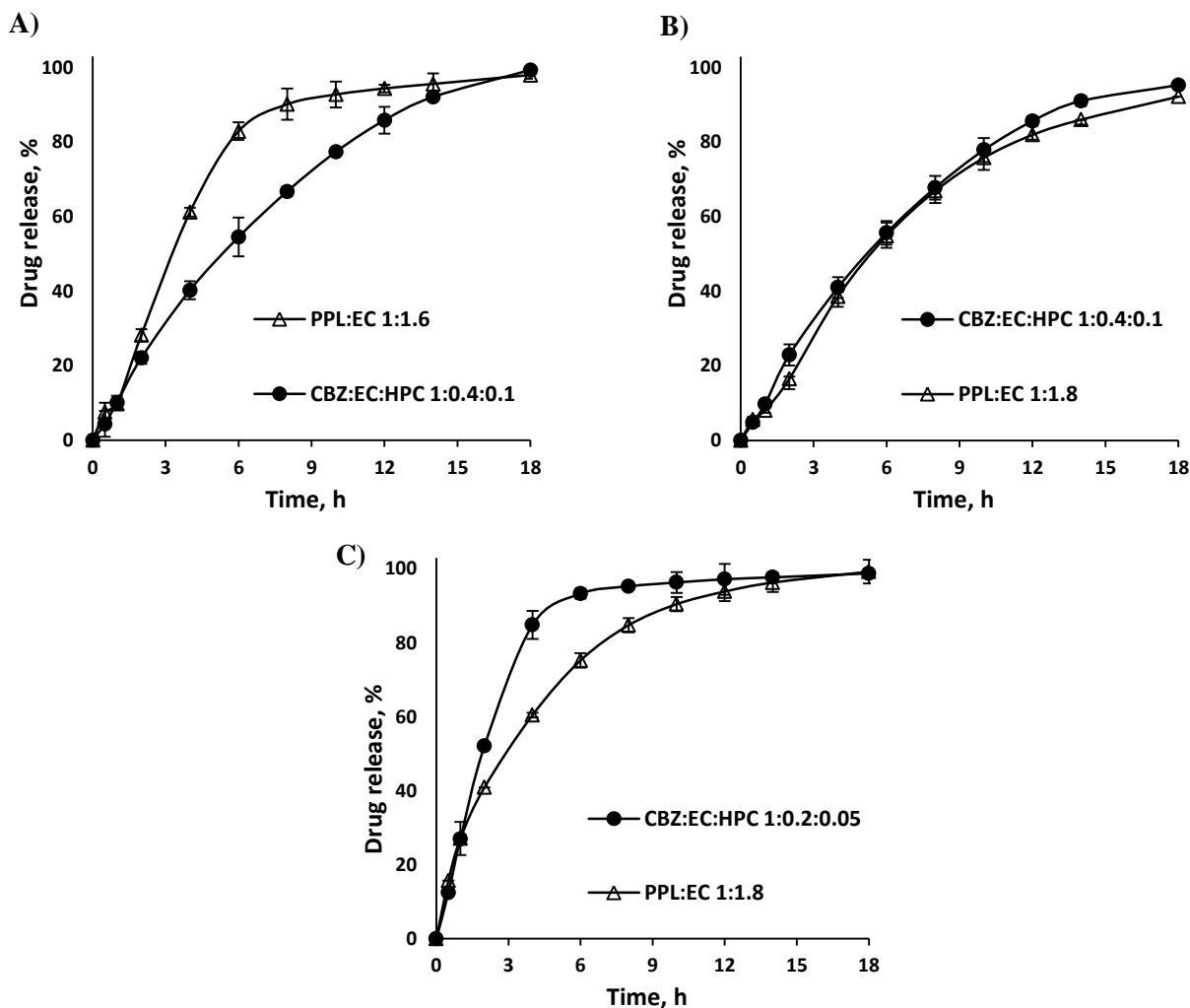
Fig. 57: Effect of ethylcellulose amount in each drug layer on the release of both drugs (propranolol HCl (PPL), carbamazepine (CBZ) loading 10% w/w).

In spite of the obvious retardation effect of the top drug layer on the release of the first drug, it still required a high amount of ethylcellulose to control the release of the first drug. This is because of the low amount of ethylcellulose, which was required to control the release of carbamazepine (layered on top). When carbamazepine starts to dissolve and release, the top layer becomes highly porous, thus, will not able to protect the first drug effectively.

In the third combination, the more soluble drug propranolol HCl was layered first onto the cores, then, the less soluble theophylline was layered on top. The amount of ethylcellulose, which was required to control the release of theophylline was relatively high (Theo:EC 1:0.8, 1:1). Therefore, the release of propranolol HCl was delayed and slower than theophylline (Fig. 58 A-D), although it was layered with very low amount of ethylcellulose (PPL:EC 1:0.2) relative to its solubility. Addition of the pore-former HPC (25% w/w based on ethylcellulose amount) to theophylline layer, led to an increase in the release of both drugs

significantly (Fig. 58 C, D vs. E, F), however, in higher extent for propranolol HCl, that it matched theophylline release.

Fig. 58: Effect of drug loading, amount of ethylcellulose in each drug layer and the pore former on release of both drugs (PPL: propranolol HCl, Theo: theophylline).

3.4   Matrix layering with aqueous polymer dispersions for controlled release pellets

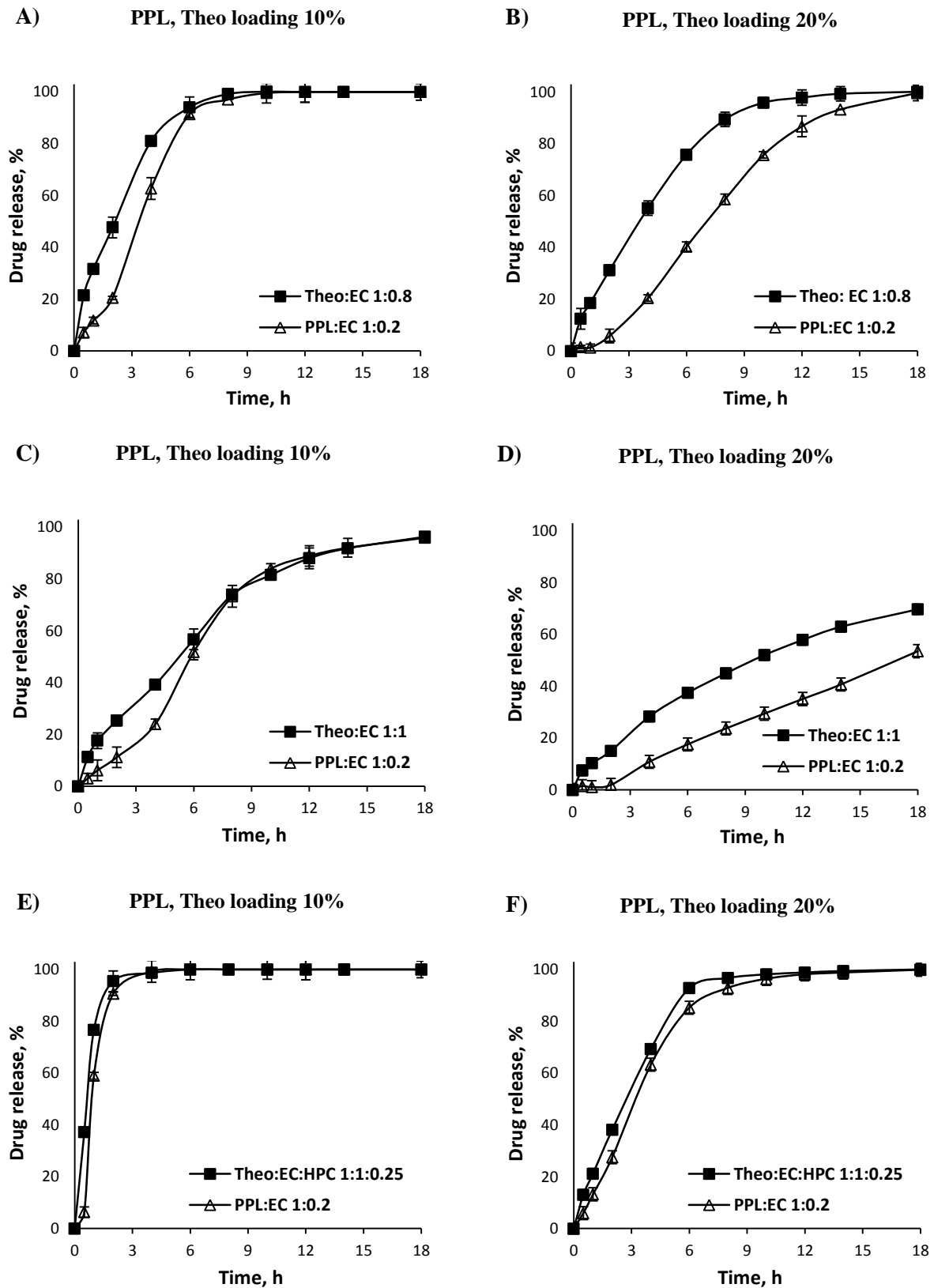As discussed in the previous part, drug layering with water-insoluble polymers, applied from organic solution, was an effective formulation tool to control the drug release, without or with a very thin additional coating layer. Aqueous polymer dispersions have several advantages over organic polymer solutions, such as higher solids loading thus shorter process time, and low toxicity and flammability therefore environmentally friendly process (McGinity and Felton, 2008). However, they may require addition of plasticizers and /or a further curing step under elevated temperature and humidity to facilitate and ensure the film formation (McGinity and Felton, 2008; Williams and Liu, 2000; Hamed and Sakr, 2003). The objective of this part of the study was to investigate the applicability of aqueous polymer dispersions as a carrier for pellets drug layering, and to study the factors which may affect the drug release. Same groups of polymers which were used in the previous part in the form of organic solution, have been used in this study in the form of aqueous dispersion including ethylcellulose (Aquacoat$^®$ ECD), Acrylic polymers (Eudragit$^®$ RS 30 D, Eudragit$^®$ NE 30 D, Eudragit$^®$ L 30 D, Eudragit$^®$ FS 30 D), polyvinyl acetate (Kollicoat$^®$ SR 30 D). Drugs with different aqueous solubilities were dissolved or dissolved/dispersed in the aqueous polymer dispersion, and layered onto sugar or microcrystalline cellulose-based cores to achieve 50% w/w weight increase (based on the original core weight).

3.4.1 Effect of polymer type

All tested aqueous dispersions were applicable as binder for drug layering with layering efficiency of 88-94%. They were able to control carbamazepine release over 18 hours, in concentration of 20% w/w (based on the drug) in comparison to an immediate release from pellets layered with the commonly used water-soluble binder HPMC (Fig. 59). Carbamazepine release retardation from uncured pellets was in the order: Eudragit® NE 30 D > Kollicoat® SR 30 D ≈ Eudragit® RS 30 D > Aquacoat® ECD. Aquacoat® ECD-layered pellets released the drug faster because of insufficient film formation (lack of coalescence) at the layering temperature (30-35 °C). The release from pellets prepared using Kollicoat® SR 30 D and Eudragit® RS 30 D was faster because of leaching of the water-soluble components PVP and quaternary ammonium groups (HCl salt) respectively, providing a pore forming effect.
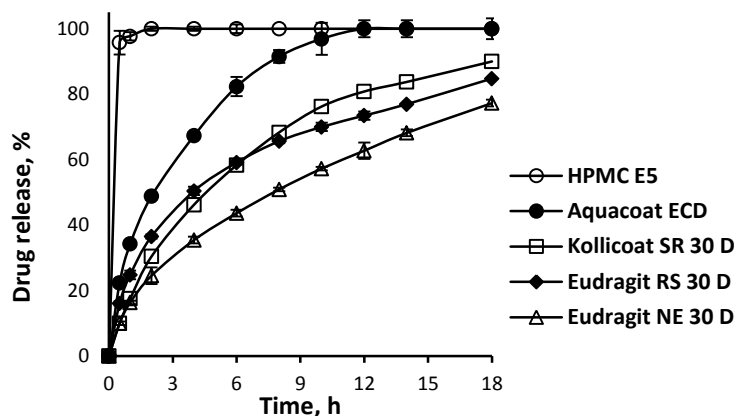
Fig. 59: Effect of polymer type on carbamazepine release from uncured pellets (drug:polymer 1:0.2).

3.4.2 Effect of drug:polymer ratio and drug solubility

Controlled drug release was achieved with all tested drugs using different ratios of drug:Kollicoat® SR 30 D, depending on aqueous solubility of the drug (Fig. 60). With the poorly soluble drug carbamazepine, controlled release was achieved with small amounts of Kollicoat® SR 30 D (10-20% w/w based on the drug) (Fig. 60 A). The more soluble drugs theophylline and metoprolol tartrate required more Kollicoat® SR 30 D to control the release. The release profile can be characterized by an initial release phase, which represents the release of uncovered/incompletely covered drug at the pellets surface, followed by a typical sigmoidal release phase, which tends to be zero order release at higher portions of Kollicoat® SR 30 D (Fig. 60 B, C). The high initial release phase (20%) of metoprolol tartrate was decreased by applying a top coating of (2% w/w) drug-free Kollicoat® SR 30 D (Fig. 60 C).

A) **Carbamazepine**

B) **Theophylline**

C) **Metoprolol tartrate**
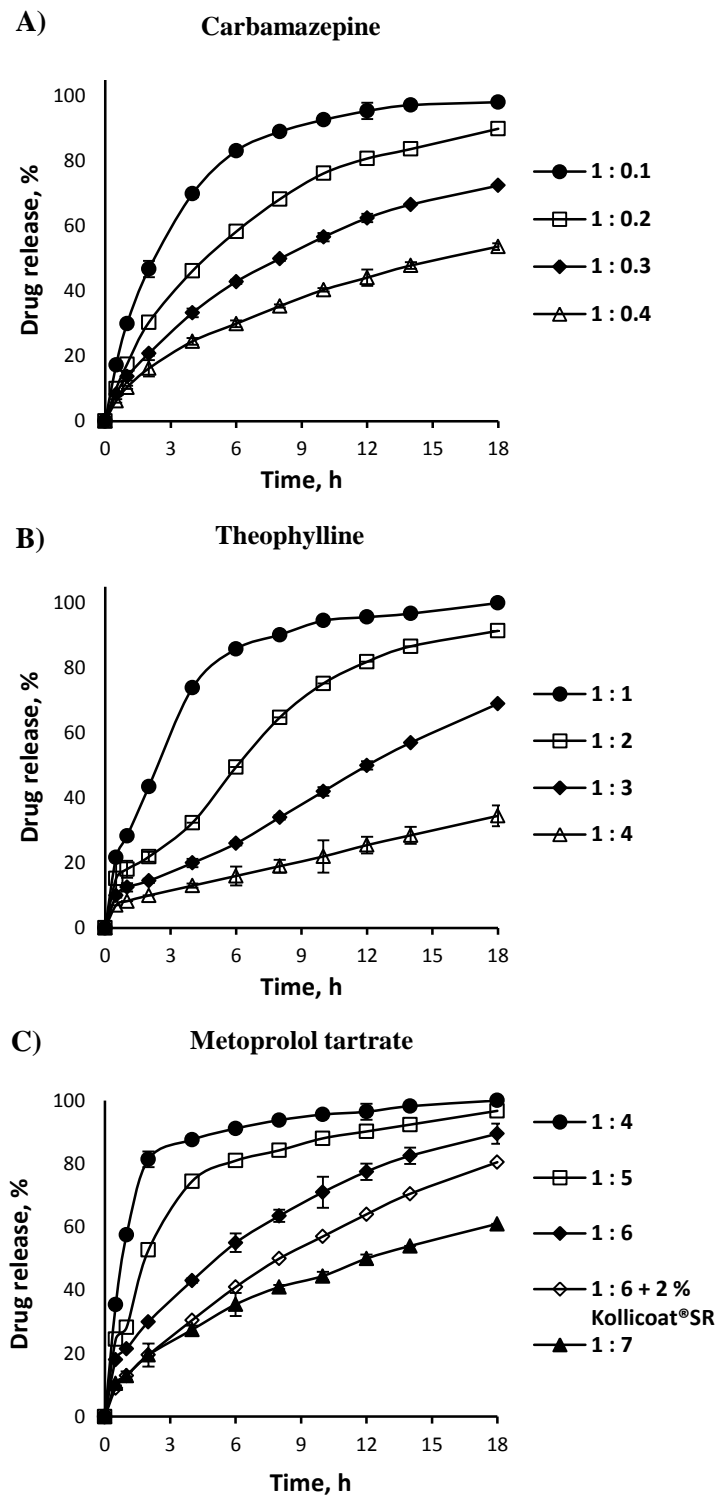
Fig. 60: Effect of drug:Kollicoat® SR 30 D ratio on drug release.

3.4.3 Effect of drug loading

The drug release decreased with increased drug loading (Fig. 61), this is due to decreased surface area/dose ratio, and increased diffusion path length.

A) **Theophylline : Kollicoat SR 30 D 1 : 2**

B) **Metoprolol tartrate : Kollicaot SR 30 D 1 : 6**
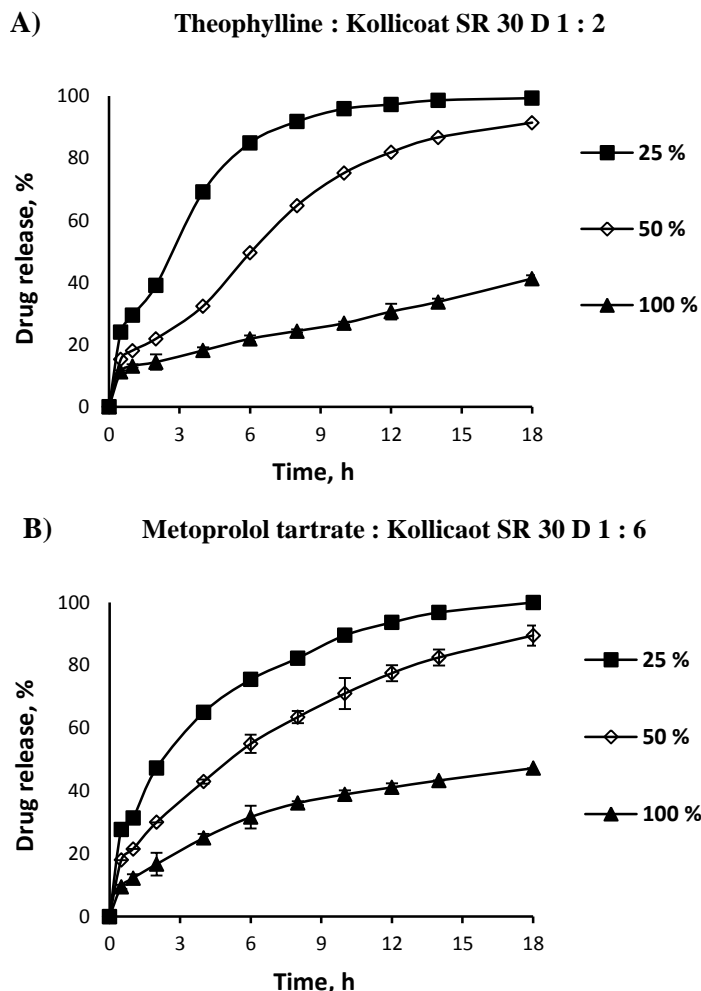
Fig. 61: Effect of drug loading (weight gain, w/w based on starter cores) on drug release.

3.4.4 Effect of starter core type

The release of carbamazepine was significantly higher from MCC-based cores vs. sugar-based cores, when layered with the brittle Aquacoat® ECD (Fig. 62 A). This is because of swelling of the MCC cores upon exposure to release medium. This has created a high pressure on the drug/Aquacoat® ECD layer leading to crack formation, thus, a faster drug release. However, with flexible polymers such as Eudragit® NE 30 D, Kollicoat® SR 30 D and Eudragit® RS 30 D, drug release was almost not affected by the starter core (Fig. 62 B, C, and D). With the more soluble drugs theophylline and metoprolol tartrate at higher content of Kollicoat® SR 30 D, the drug was released by diffusion through the polymeric matrix and

pores, the release profiles therefore changed when osmotically active sugar cores vs. osmotically inactive MCC cores were used (Fig. 62 E, F).
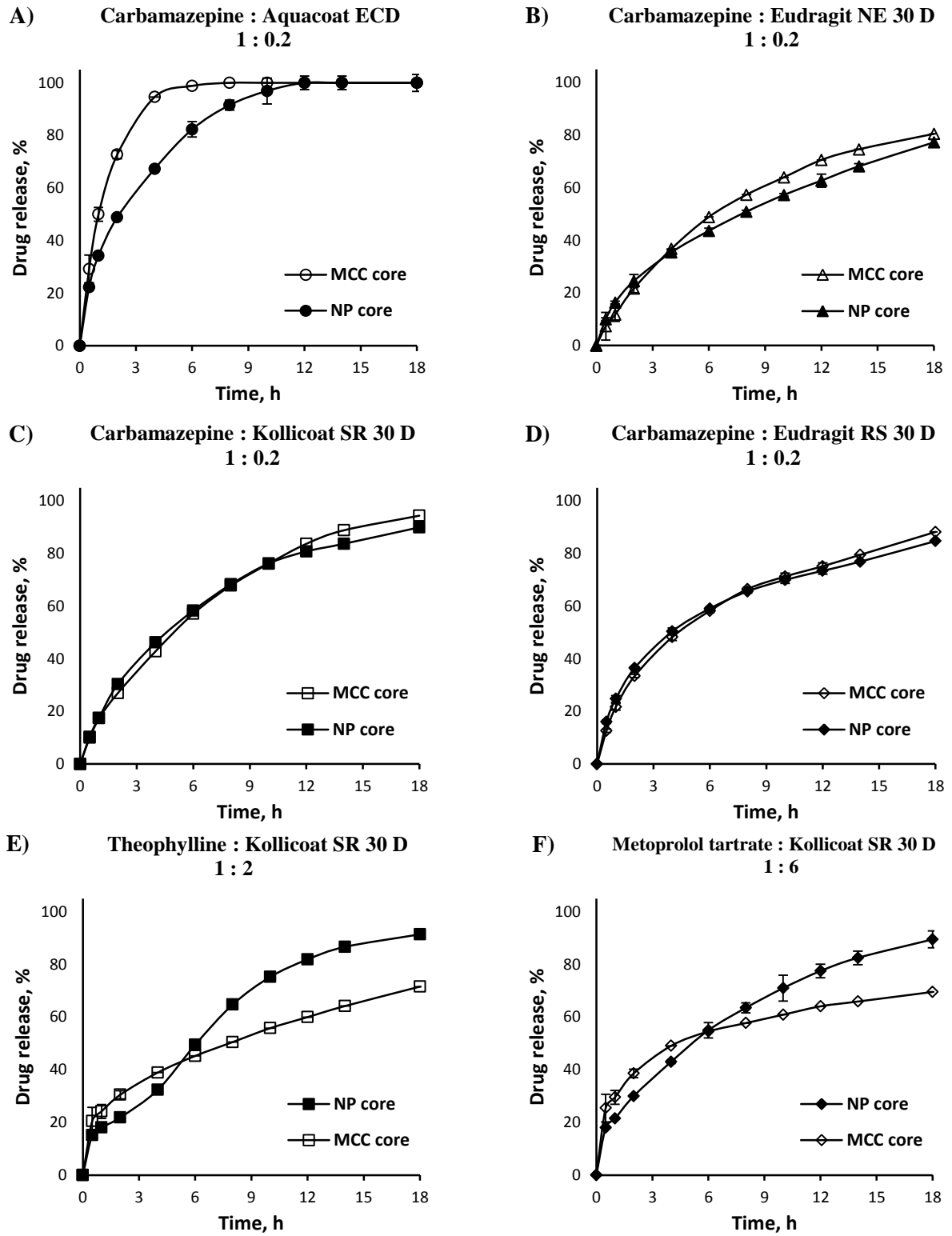
Fig. 62: Effect of starter core type on drug release.

3.4.5 Effect of plasticizer

Kollicoat® SR 30 D is one of the new and commonly used aqueous polymer dispersions for controlled release coatings. Because of its low minimum film formation temperature (MFT = 18 °C), plasticizer addition is not necessary (Dashevskiy et al., 2005). In this study, where the drug is dispersed or dissolved/dispersed in Kollicoat® SR 30 D, the necessity of the plasticizer was dependent on the aqueous solubility of the drug. Release of the slightly soluble theophylline from Kollicoat® SR 30 D-layered pellets was not affected with the plasticizer (Fig. 63 A). However, for the highly soluble metoprolol tartrate, pellets layered with plasticized Kollicoat® SR 30 D released the drug significantly slower than those prepared with unplasticized polymer (Fig. 63 B). Also, a stronger swelling of the pellets prepared with plasticized vs. unplasticized Kollicoat® SR 30 D (Fig. 64) and a higher medium uptake (145% vs. 53% respectively) were observed, indicating a more flexible matrix and less cracking by presence of the plasticizer.
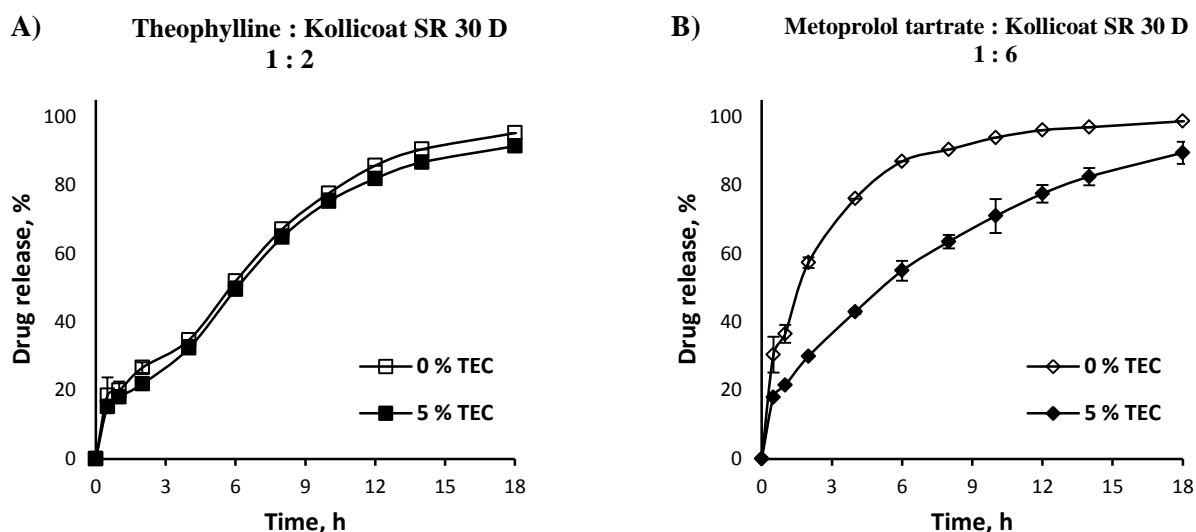
Fig. 63: Effect of plasticizer ratio on drug release.
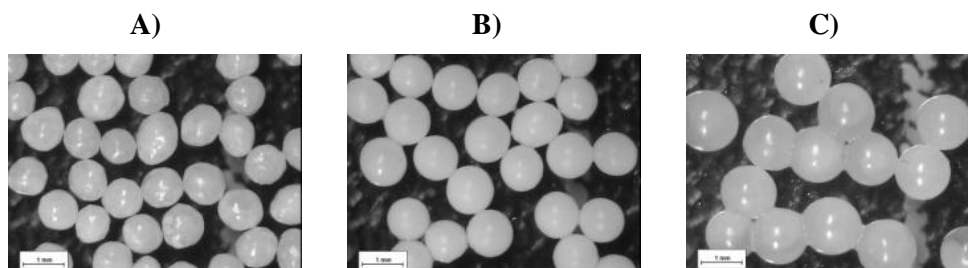
Fig. 64: Macroscopic pictures of metoprolol tartrate: Kollicoat® SR 30 D 1:6 pellets, A) before drug release B) after drug release, <u>unplasticized</u> C) after drug release, <u>plasticized</u>.

3.4.6   Effect of anti-tacking agent

Kollicoat® SR 30 D usually has a high tackiness during coating, especially in presence of the plasticizers, because of its low glass transition temperature. On the other hand, drug addition to the aqueous dispersion may have negative or positive effect on the tackiness during coating, depending on the aqueous solubility of the drug. The poorly and slightly soluble drugs carbamazepine and theophylline were layered easily with Kollicoat® SR 30 D without agglomeration or tackiness during the process, as they were mostly dispersed (not dissolved) in Kollicoat® SR 30 D. They played a positive role as an anti-tacking agent. However, for the highly soluble metoprolol tartrate, addition of ant tacking agent was required, as the drug was completely dissolved in the aqueous phase of Kollicoat® SR 30 D, resulting in a sticky dispersion. Addition of talc (20% w/w based on dry polymer weight), led to an increase the release of metoprolol tartrate (Fig. 65). Probably, the talc has affected the coalescence of polymer particles and decreased flexibility of the polymer.
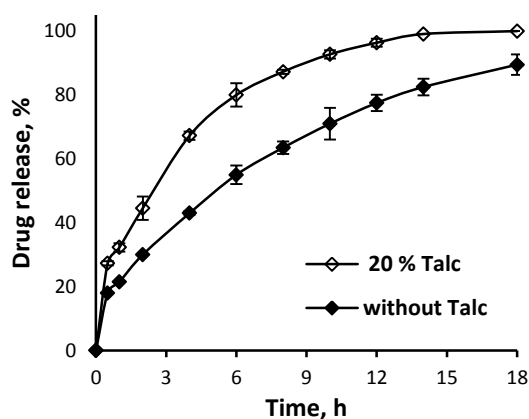
Fig. 65: Effect of talc on drug release (Metoprolol tartrate:Kollicoat® SR 30 D 1:6).

3.4.7   Effect of drug:polymer mixing time

As mentioned before, drug was mixed with the aqueous polymer dispersion for 2 hours before layering on the starter cores. In this part of the study, effect of mixing time on drug release from layered pellets was investigated. No remarkable effect of mixing time on theophylline release from Kollicoat® SR 30 D layered pellets (Fig. 66).
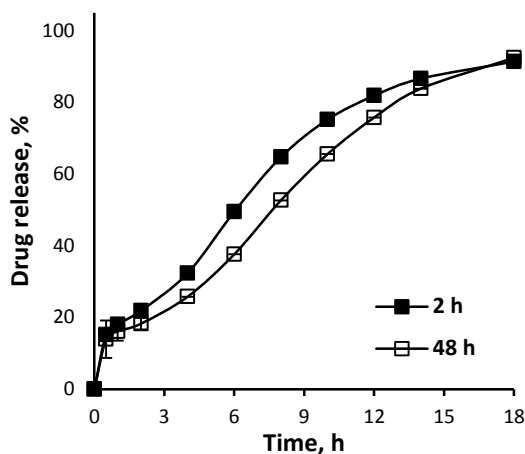
Fig. 66: Effect of drug mixing time in the aqueous dispersion before layering, on drug release (Theophylline:Kollicoat® SR 30 D 1:2).

3.4.8   Effect of curing

Curing of pellets coated with aqueous polymer dispersions at elevated temperature and humidity can enhance the coalescence of polymer particles. This leads to more integrated coating layer, which further retards the drug release (Bodmeier and Paeraktakul, 1994). In case of matrix layered-pellets, where the drug is dispersed between polymer particles, pellets curing can potentially facilitate fusion of the polymer particles into a more homogeneous matrix (Bodmeier and Wang, 1993). Plasticizers also decrease MFT of the aqueous dispersions, which enables of a complete film formation during the process (Lippold et al., 1990; Bodmeier and Paeratakul, 1992) and might at certain concentration obviate the need for curing (Bodmeier and Paeraktakul, 1994; Wesseling and Bodmeier, 2001). Based on the recommendation of polymers manufacturers and different research articles, Eudragit® NE 30D was used without plasticizer, Kollicoat® SR 30 D was plasticized with triethyl citrate TEC (5% w/w based on dry polymer weight), Aquacoat® ECD was plasticized with tributyl citrate TBC (20% w/w based on dry polymer weight), Eudragit® RS 30 D was plasticized with TBC (0, 10, 20% w/w based on dry polymer weight).

No curing effect was observed on carbamazepine release from pellets layered with the low MFT aqueous dispersions Eudragit® NE 30 D and Kollicoat® SR 30 D (5 °C and 8 °C respectively) (Evonik, 2007; Dashevskiy et al., 2005), which suggests a complete film formation during layering process (Fig. 67 A, B). High curing effect was seen with Aquacoat® ECD-layered pellets (Fig. 67 C), because of its high MFT (≈ 40 °C), which was not reached during layering process (at 30-35 °C). Therefore, further particles coalescence upon thermal treatment resulted in a slower drug release.
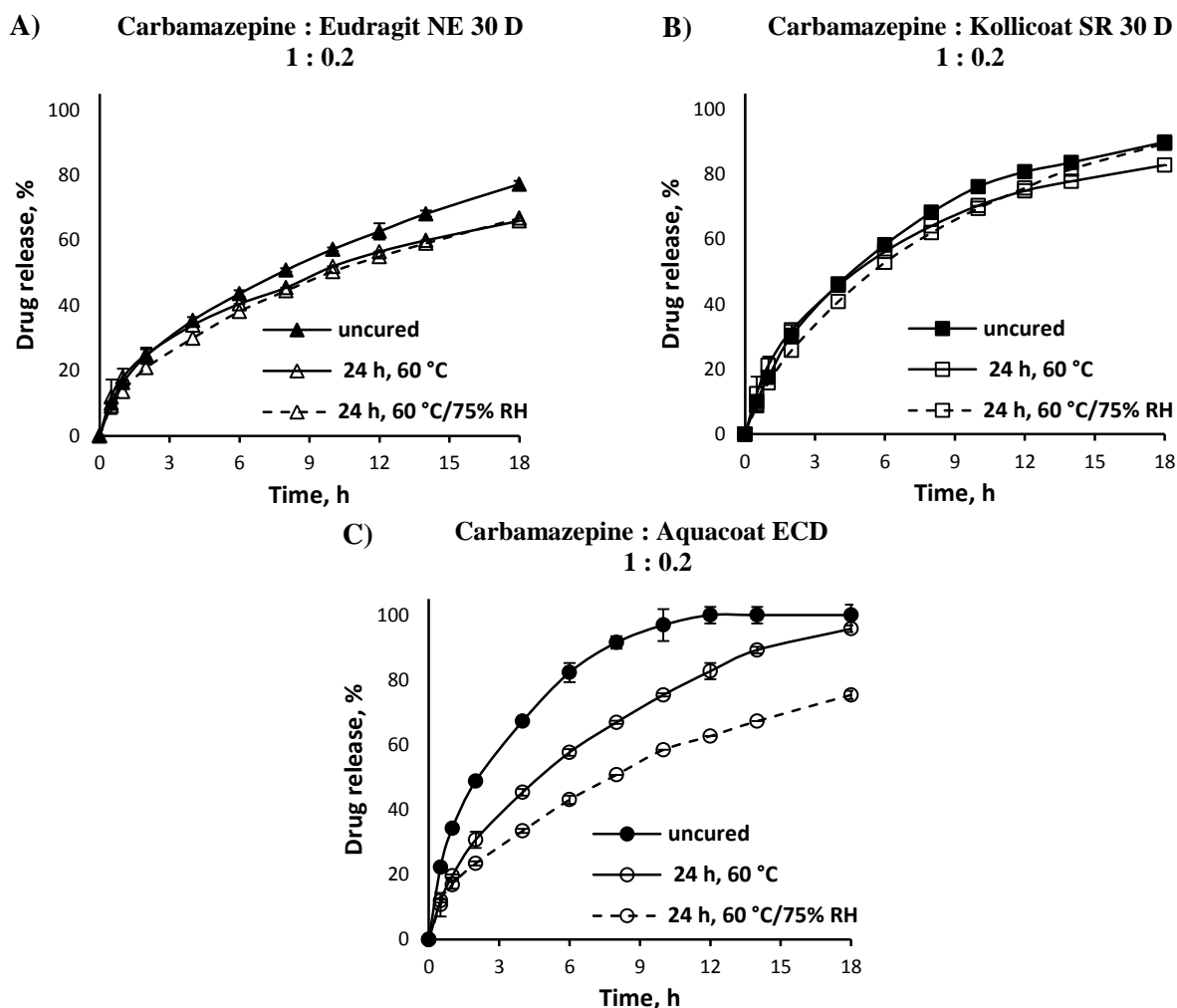
Fig. 67: Effect of curing on drug release.

Fig. 68 shows the effect of curing condition and plasticizer content on the carbamazepine release from Eudragit® RS 30 D layered pellets. Carbamazepine release from un-plasticized polymer was decreased when the pellets were cured at 60 ºC (Fig. 68 A). This is due to polymer particles coalescence at elevated temperature. In addition, the drug release was further decreased when pellets were cured at similar temperature with 75% relative humidity, because of the plasticization effect of the water. At high plasticizer amount (20% w/w based on dry polymer weight), curing has increased the drug release (Fig. 68 C). This could be due to the plasticizer evaporation at elevated temperature and humidity as function of curing time, which increased permeability of the polymer. At intermediate plasticizer amount (10% w/w based on dry polymer weight), no curing effect on drug release was seen (Fig. 68 B). Probably, at this plasticizer amount, a balance between plasticizer evaporation and polymer particles coalescence upon curing was achieved.

A)   **Unplasticized**   **B)**   **10% Tributyl citrate**

C)   **20% Tributyl citrate**
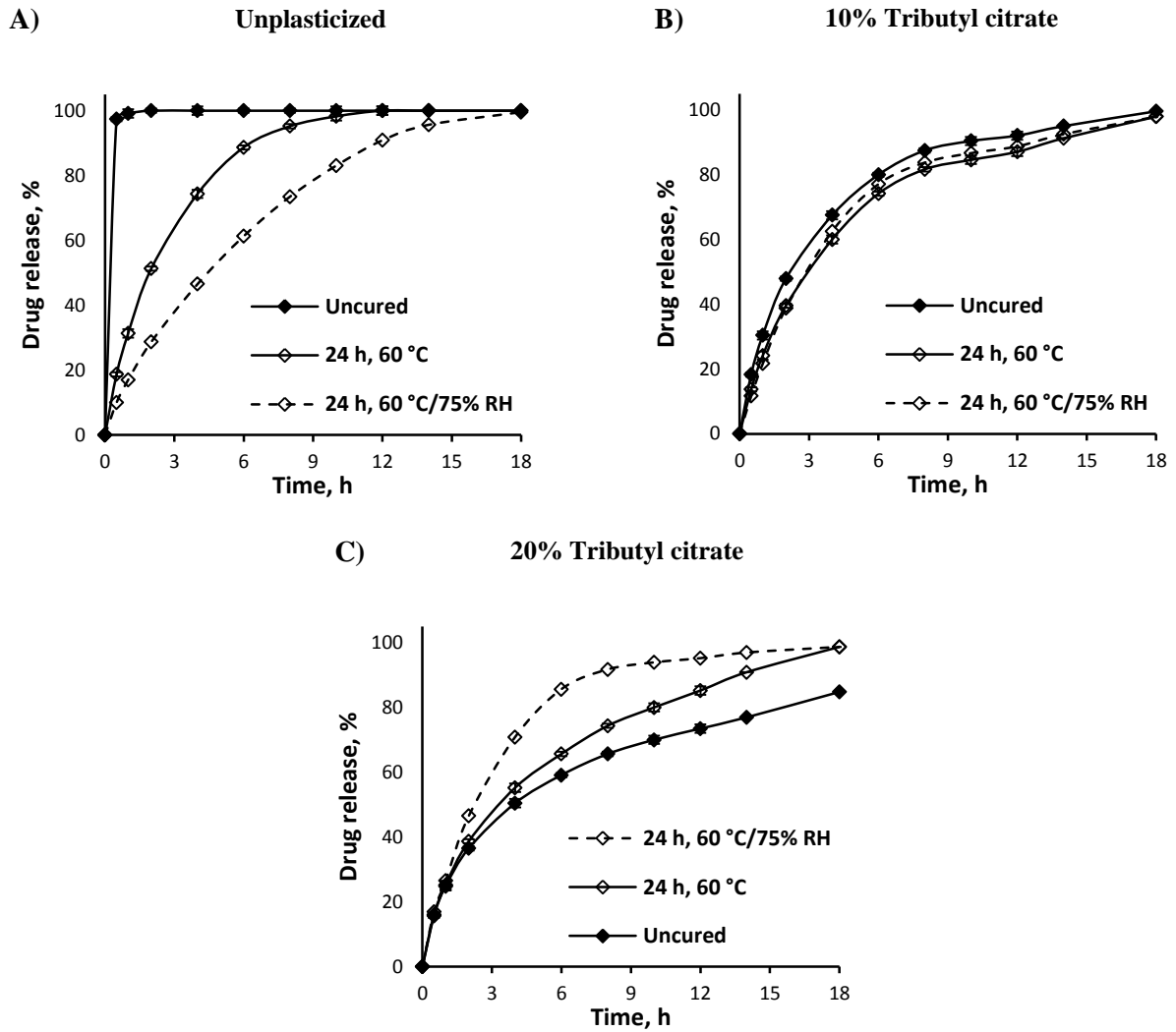
Fig. 68: Effect of curing in presence of different amounts of plasticizer on carbamazepine release from Eudragit® RS 30 D layered pellets (drug:polymer 1:0.2).

To find the reason behind increased drug release with increased plasticizer content, effect of curing period on the drug release from plasticized (20%) pellets was investigated (Fig. 69). Curing at 60 °C, decreased the drug release in the first 6 hours, which indicates a further polymer coalescence, however, after 6 hours, the drug release started to increase, which represents the beginning of plasticizer evaporation (Fig. 69 A). Curing at more stressful conditions 60 °C/75% RH increased the drug release from the first 2 hours of the curing (Fig. 69 B).
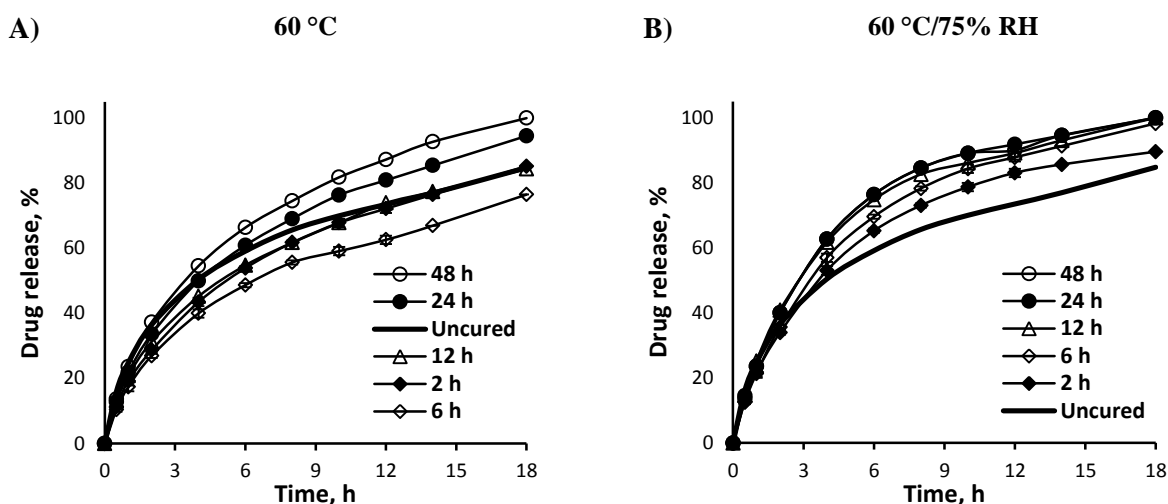
Fig. 69: Effect of curing period on carbamazepine release from Eudragit® RS 30 D layered pellets (drug:polymer 1:0.2, 20% tributyl citrate).

For theophylline pellets layered with Kollicoat® SR 30 D, curing at elevated temperature 60 °C, did not affect the drug release (Fig. 70), because of its low MFT. At elevated temperature and humidity 60 °C/75% RH the pellets fused together, because Kollicoat® SR 30 D has low T_g and was used in much higher amount than with carbamazepine pellets.
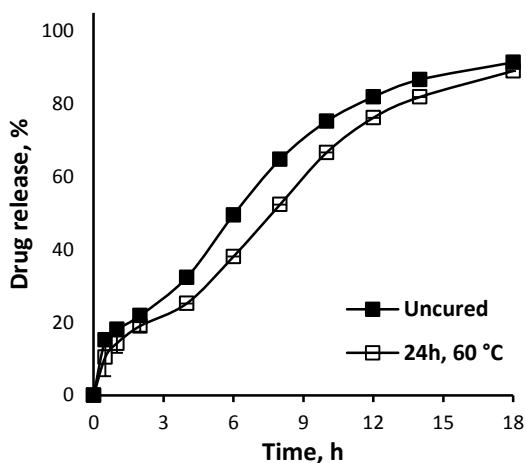
Fig. 70: Effect of curing on theophylline release (Theophylline:Kollicoat® SR 30 D 1:2).

For the highly soluble metoprolol tartrate, a significant curing effect on drug release was seen from the pellets layered with Kollicoat® SR 30 D without/with plasticizer and with talc (Fig. 71 A, B, C). Also a stronger swelling and a higher water uptake from cured vs. uncured pellets were observed (Table 13), indicating a more flexible polymer and less cracking upon curing. This improvement in flexibility upon curing was observable only with the highly

soluble metoprolol tartrate, because of its high osmotic activity, which represents a challenge to differentiate between flexible and brittle polymers.

A) **Unplasticized**

B) **5% Triethyl citrate**

C) **5% Triethyl citrate + 20% Talc**
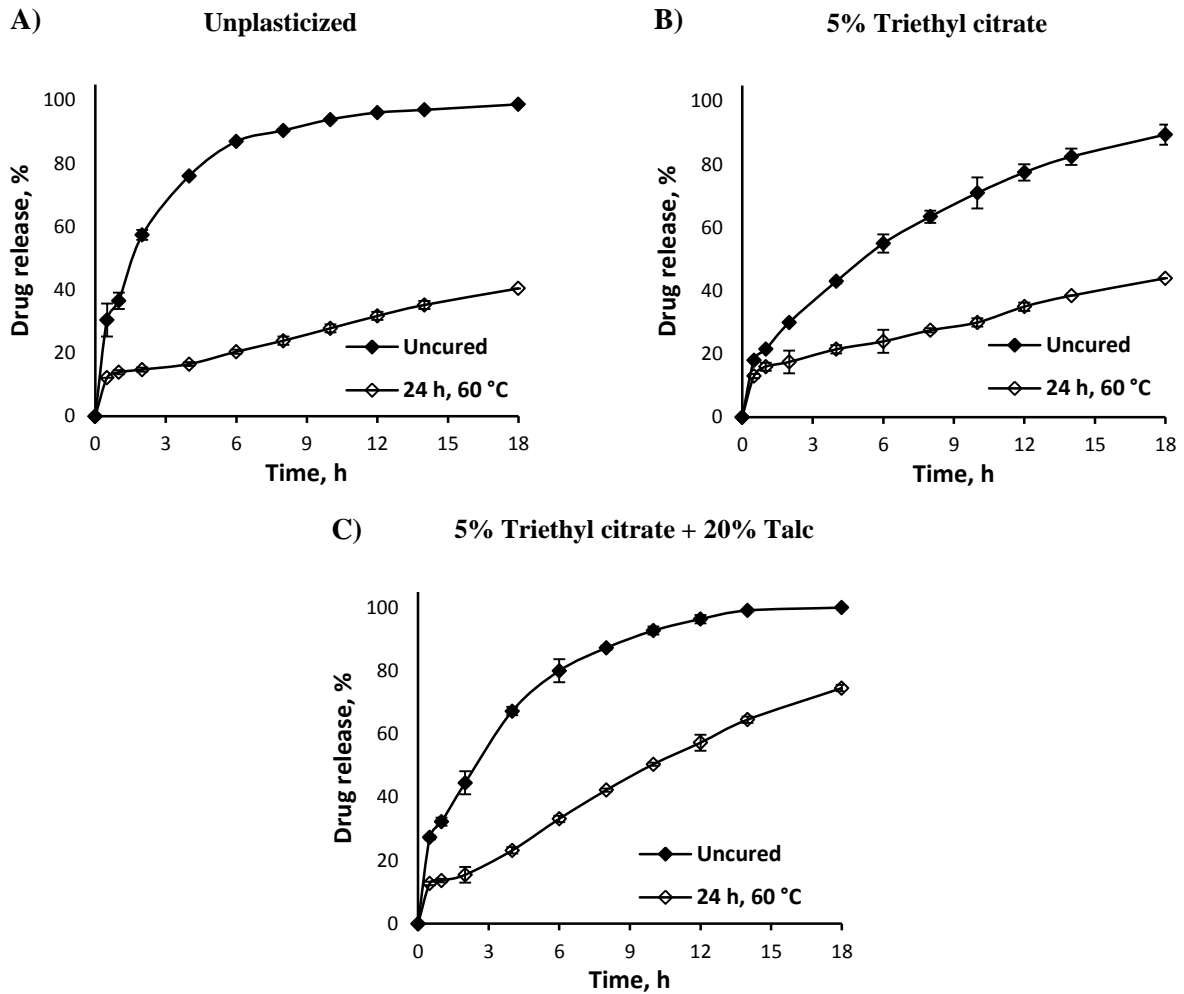
Fig. 71: Effect of curing on metoprolol tartrate release (Metoprolol tartrate:Kollicoat® SR 30 D 1:6).

Table 13: Water uptake (%) after drug release test (after 18 h) of metoprolol tartrate pellets layered with Kollicoat® SR 30 D

	Metoprolol tartrate : Kollicoat® SR 30 D 1 : 6					
	Unplasticized		**5% Triethyl citrate**		**5% Triethyl citrate + 20% Talc**	
	Uncured	**24 h, 60 °C**	**Uncured**	**24 h, 60 °C**	**Uncured**	**24 h, 60 °C**
Water uptake, %	53 ± 3	325 ± 8	145 ± 5	358 ± 10	120 ± 8	360 ± 10

3.4.9   Solid state characterization

To characterize the solid state of the drug in the polymeric matrix, casted films of the layering suspension (drug + aqueous dispersion) were prepared and tested with DSC. In addition, physical mixtures of the drug powder and the polymer were tested in parallel.

In contrast to physical mixture, no melting peak of the drug was observed in the casted film at two ratios (metoprolol tartrate: Kollicoat® SR 30 D 1:3, 1:6) (Fig. 72). Here, two scenarios are possible: either the drug was dissolved in the polymer, or the drug turned into amorphous form. As the clarity of the casted film (drug + polymer) was not as of drug-free casted film, the second scenario is more suggested.
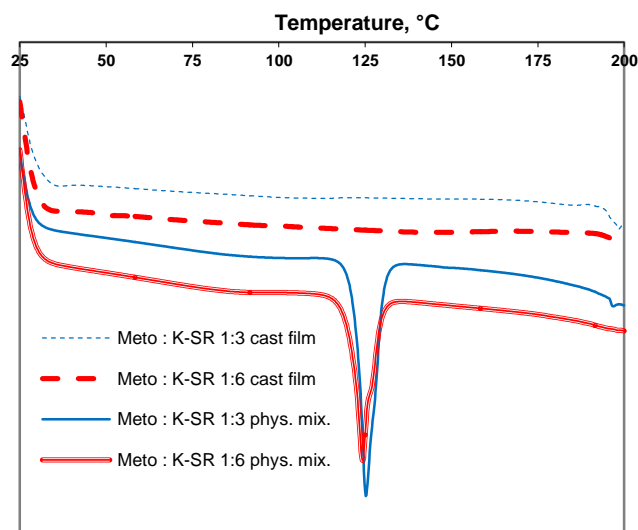
Fig. 72: DSC curves of physical mixtures and casted films of metoprolol tartrate (Meto) and Kollicoat® SR 30 D (K-SR).

For the slightly and very slightly soluble theophylline and carbamazepine, no DSC test was performed. Because of the low solubility of these drugs in the aqueous phase of the aqueous dispersion, the majority of the drug is dispersed and not dissolved in the polymeric dispersion.

3.4.10 Drug layering with enteric aqueous dispersions

Two enteric dispersions were used in this study, Eudragit® L 30 D-55 plasticized with tributyl citrate (20% w/w based on dry polymer weight) which dissolves at pH 5.5 (Evonik, 2007), and Eudragit® FS 30 D plasticized with triethyl citrate (5% w/w based on dry polymer weight) which dissolves at pH 7 (Evonik, 2007). As mentioned before, enteric dosage forms should not release more than 10% of the labelled amount of the drug in acid stage (2 h in 0.1 N HCl). This is considered as a challenge for matrix system, because of the uncovered or incompletely covered drug at matrix surface, which cause a high initial drug release (Huang and Brazel, 2001). Carbamazepine release from Eudragit® L 30 D-55 layered-pellets in acidic medium decreased significantly upon curing only at elevated temperature and humidity (60 °C/75% RH) (Fig. 73). This is because of the hydration/plasticization effect induced by the moisture (Rujivipat and Bodmeier, 2012), resulting in more integrated matrix and slower drug release. Furthermore, the drug release was dependent on polymer content and drug loading (Fig. 73). With increased polymer content from 20% to 40% (w/w based on the drug), or increased drug loading (weight gain) from 50% to 100% w/w, the release decreased to less than 10% within 2 h in acidic medium (Fig. 73 A vs. B vs. C).
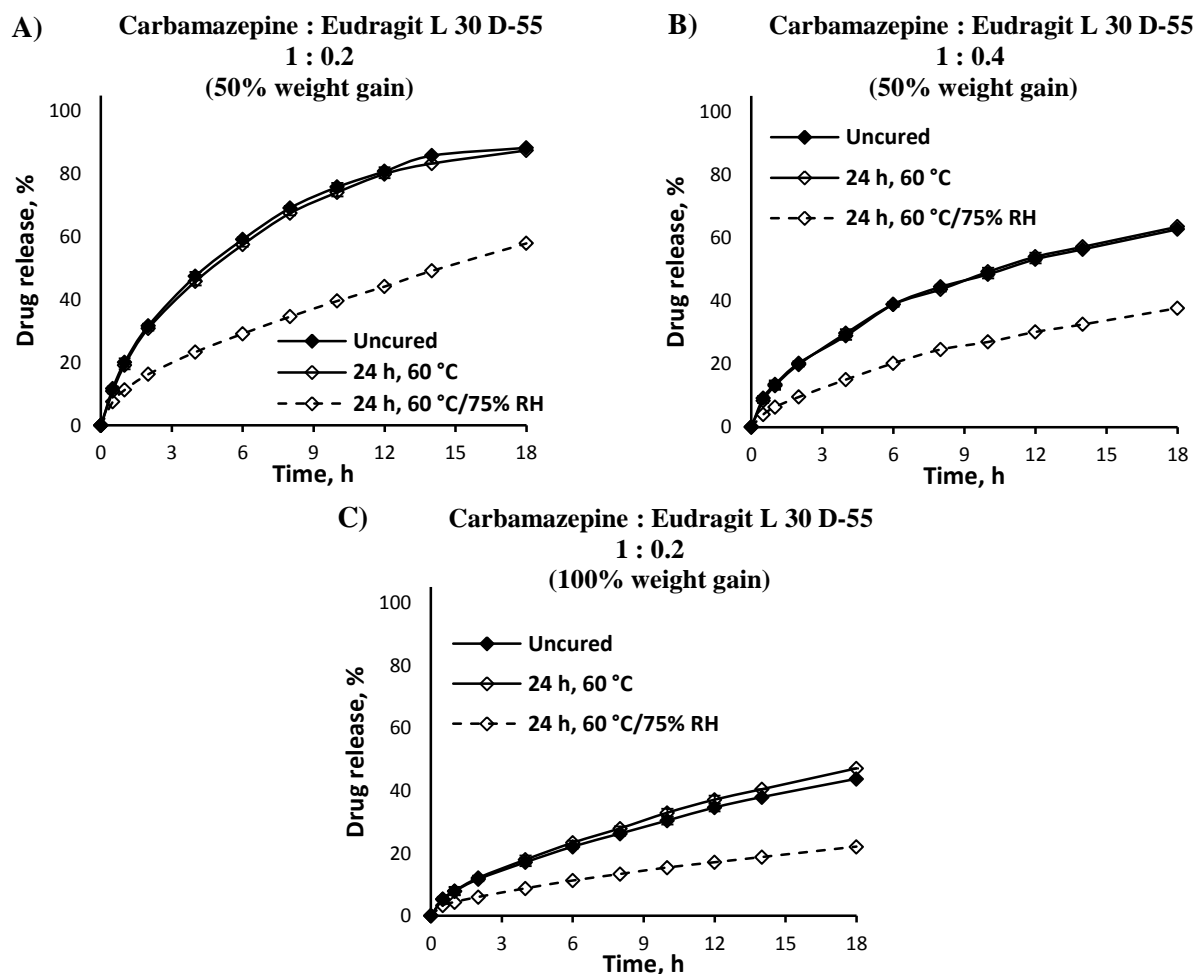
Fig. 73: Drug release from Eudragit® L 30 D-55 layered pellets in 0.1 N HCl.

In pH 6.8 phosphate buffer, the drug released immediately, due to polymer dissolution (Fig. 74).

Carbamazepine : Eudragit L 30 D-55, weight gain
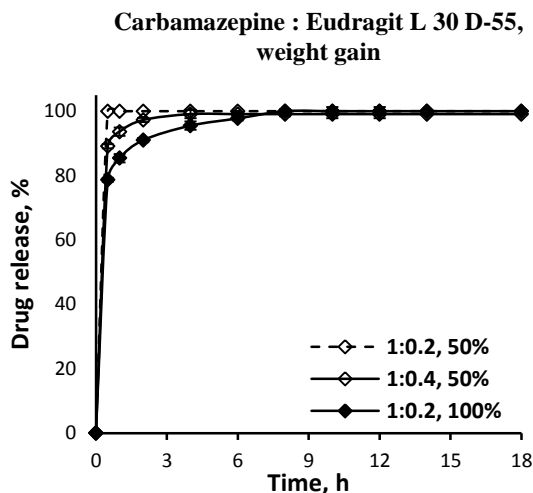
Fig. 74: Drug release from Eudragit® L 30 D-55 layered pellets in PBS pH 6.8 (cured pellets 24 h, 60 °C/75% RH).

Carbamazepine release from Eudragit® FS 30 D layered pellets in 0.1 N HCl was comparable with Eudragit® L 30 D-55 layered pellets (Fig. 75 A vs. Fig. 73 B), however, was not affected with curing. In pH 6.8, the polymer is insoluble, and the release was controlled over 18 hours, however decreased upon curing (Fig. 75 B) resulting in a release rate comparable to the release in 0.1 N HCl. Obviously, higher amount of polymer is required to achieve an enteric or colonic release profile.

A) **0.1 N HCl**   B) **PBS pH 6.8**
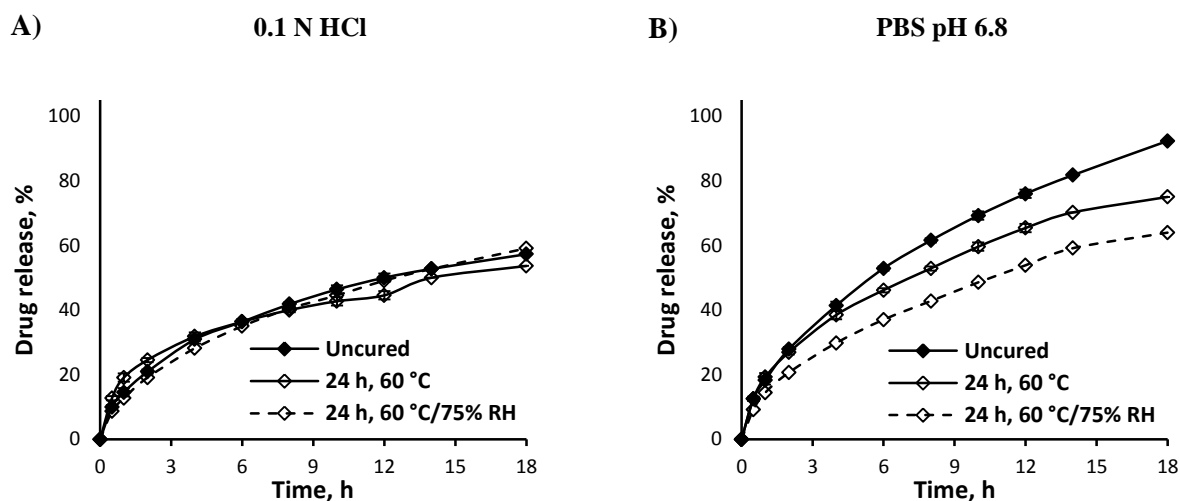
Fig. 75: Carbamazepine release from Eudragit® FS 30 D layered pellets (drug:polymer 1:0.4).

3.4.11 Crushing force of single pellets

Crushing force was studied to evaluate the robustness of pellets against mechanical stress, which might be faced during production and packaging processes, furthermore, to predict primarily performance of the pellets upon compression into tablets. The crushing force of carbamazepine pellets layered with different aqueous dispersions was similar (Table 14). As the pellets differ from each other only with the type of dispersion used, which represents only (5% w/w of total pellet weight). Aquacoat® ECD layered pellets showed relatively lower crushing force because of brittleness of this polymer. Similarly, the crushing force of uncured-unplasticized Eudragit® RS 30 D layered pellets was low, because of incomplete film formation and lack of polymer solid bridges. Therefore, after curing or addition of plasticizer, crushing force was increased. Interestingly, curing of pellets layered with Eudragit® RS 30 D (plasticized with 20% w/w TBC), led to a slight decrease in the crushing force, probably because of evaporation of the plasticizer upon curing leaving a more brittle polymer (as discussed before).

Table 14: Crushing force of carbamazepine single pellet layered with different aqueous dispersions

	Aqueous dispersion		Crushing force, N (n = 20)		
			Mean ± SD	Max.	Min.
Carbamazepine : polymer 1 : 0.2	Kollicoat® SR 30 D (5% TEC)	Uncured	11.0 ± 1.6	14.6	8.8
	Eudragit® NE 30 D (unplasticized)	Uncured	10.9 ± 2.3	15.0	7.4
	Aquacoat® ECD (20% TBC)	Cured, 24 h 60 °C/75% RH	7.2 ± 1.8	10.2	4.1
	Eudragit® RS 30 D (unplasticized)	Uncured	8.3 ± 1.8	11.7	4.9
		Cured, 24 h 60 °C/75% RH	10.3 ± 2.1	13.6	6.1
	Eudragit® RS 30 D (10% TBC)	Uncured	12.5 ± 1.5	14.9	9.6
	Eudragit® RS 30 D (20% TBC)	Uncured	11.8 ± 1.8	15.3	9.2
		Cured, 24 h 60 °C/75% RH	10.4 ± 2.2	15.0	6.2

Carbamazepine pellets layered with different aqueous dispersions showed two profiles of stress-strain curves (Fig. 76). Pellets layered with aqueous dispersions that have low MFT such as Eudragit® NE 30 D, Kollicoat® SR 30 D and plasticized Eudragit® RS 30 D showed a linear ascending phase, which represents the densification phase of the pellet, followed by a descending phase after pellet rupture. However, pellets layered with high MFT aqueous dispersions such as Aquacoat® ECD and unplasticized Eudragit® RS 30 D showed an additional peak in the densification phase in all tested pellets (n = 20), uncured and cured pellets. That peak represents probably the rupture of the drug layer, followed by rupture of the starting core. This could be explained by weak attachment of drug layer to the starter core, due to incomplete polymer coalescence and absence of solid bridges.
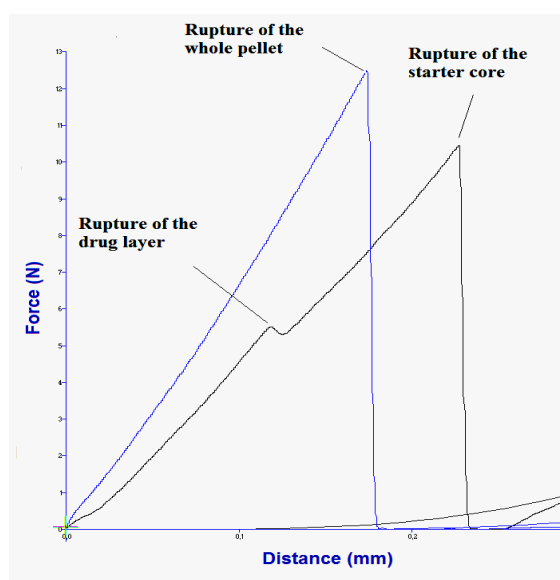
Fig. 76: Stress-strain profiles of carbamazepine pellets (drug:polymer 1:0.2).

Metoprolol tartrate pellets layered with plasticized Kollicoat® SR 30 D, showed a higher plastic deformation (longer distance before rupture) and crushing force, however without clear crushing peak, in comparison with unplasticized polymer (Fig. 77). On the other hand, curing of the pellets has increased crushing force (Table 15), which indicates a higher cohesive force and more homogeneous matrix upon curing.
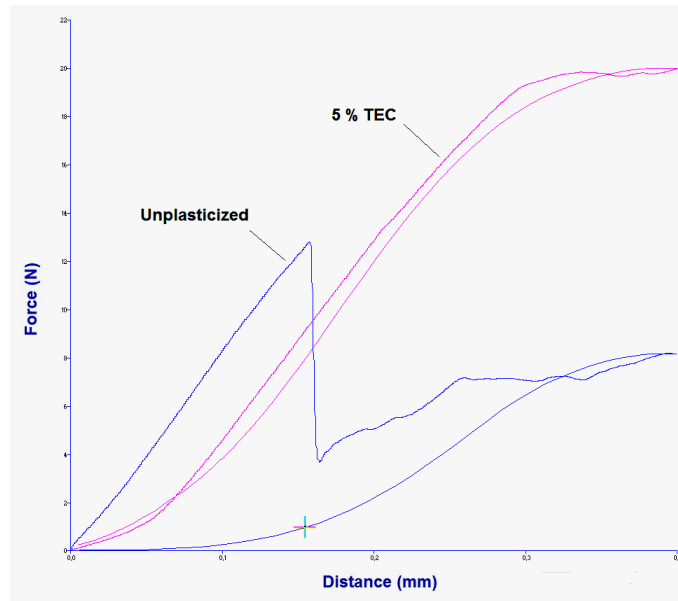
Fig. 77: Effect of plasticizer on mechanical properties of the pellets (Metoprolol tartrate: Kollicoat$^®$ SR 30 D 1:6).

Table 15: Crushing force of metoprolol tartrate pellets layered with Kollicoat$^®$ SR 30 D

		Metoprolol tartrate : Kollicoat$^®$ SR 30 D 1 : 6		
		Crushing force, N (n = 20)		
		Mean ± SD	Max.	Min.
Unplasticized polymer	Uncured	9.5 ± 1.5	11.8	6.9
	Cured, 24 h 60 °C	13.2 ± 1.5	16.1	11.1
5% TEC	Uncured and cured	No clear crushing peak		

3.4.12 Pellets performance upon compression

Drug release from Eudragit® NE and Kollicoat® SR layered pellets was not affected (F2 > 50) by compression up to a compression force of 20 KN irrespective of the starter core, due to the good flexibility of these polymers (Fig. 78).
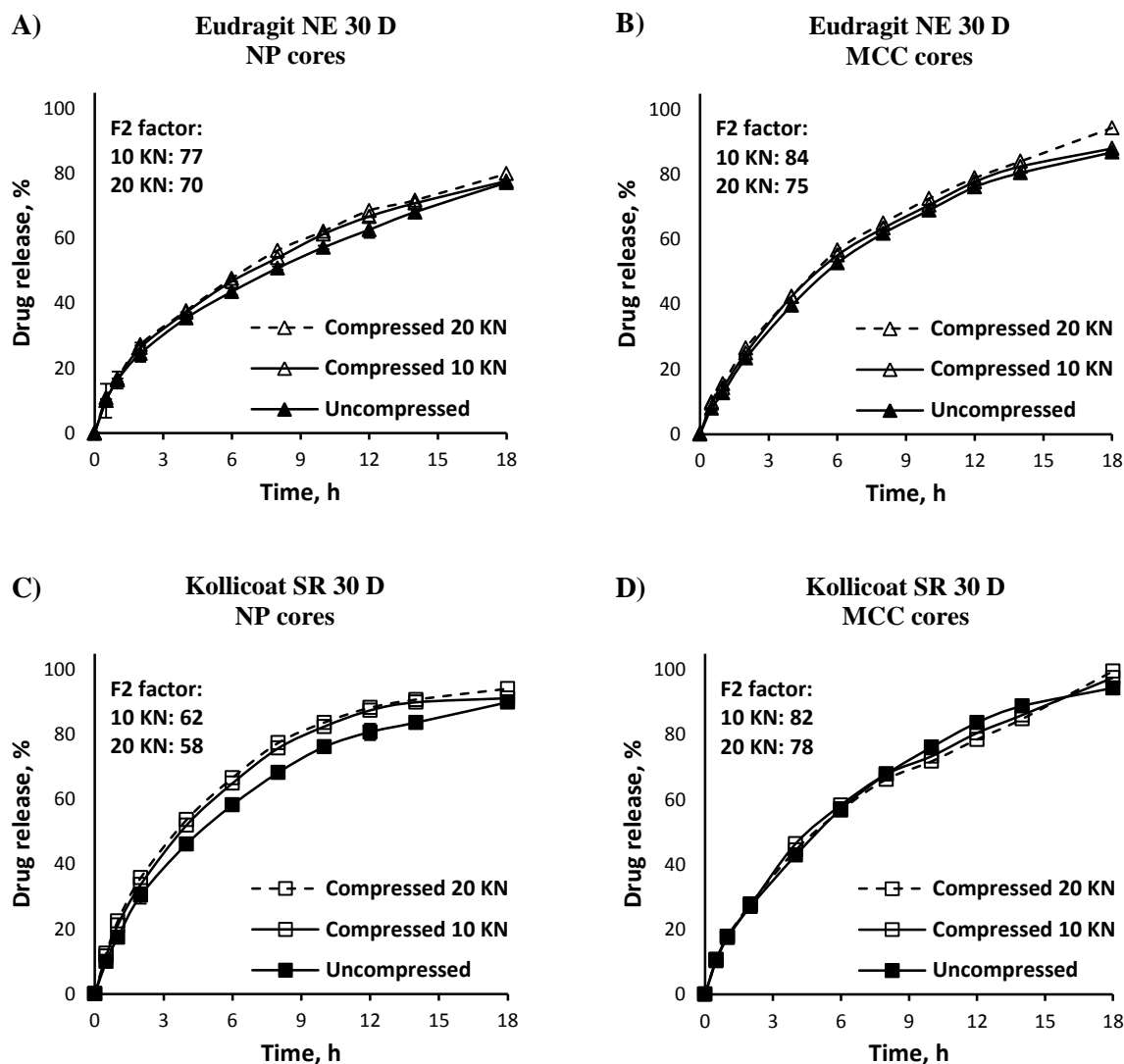
Fig. 78: Effect of pellets compression on drug release (Carbamazepine:polymer 1:0.2, pellet content 50% w/w).

Drug release from uncured Aquacoat® ECD layered pellets was also unchanged after compression (Fig. 79 A, B), as the polymer solid bridges have not formed yet to be damaged by compression. While, compression of cured Aquacoat® ECD layered pellets led to an increase in the drug release significantly (Fig. 79 C), due to brittleness of this polymer. However, this increase in drug release was less pronounced with MCC cores (Fig. 79 D). This is due to plasticity of these cores; furthermore the polymer rupture occurred in both

uncompressed (during dissolution test upon swelling of MCC cores) and compressed pellets (during compression).
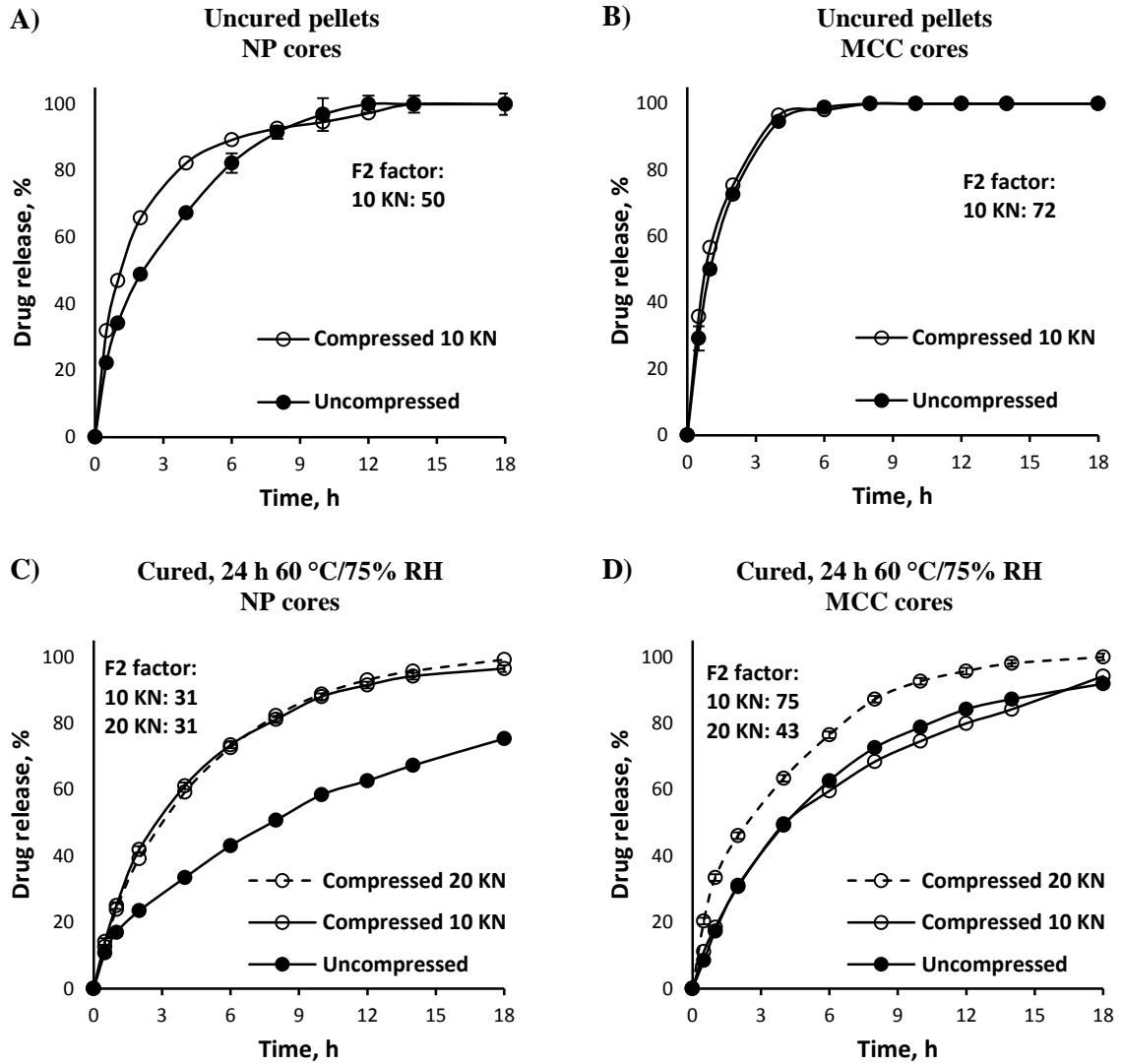
Fig. 79: Effect of pellets compression on drug release (Carbamazepine:Aquacoat® ECD 1:0.2, pellet content 50% w/w).

Drug release from Eudragit® RS 30 D layered pellets was not affected by compression (F2 > 50) irrespective of curing or plasticizer content (Fig. 80).
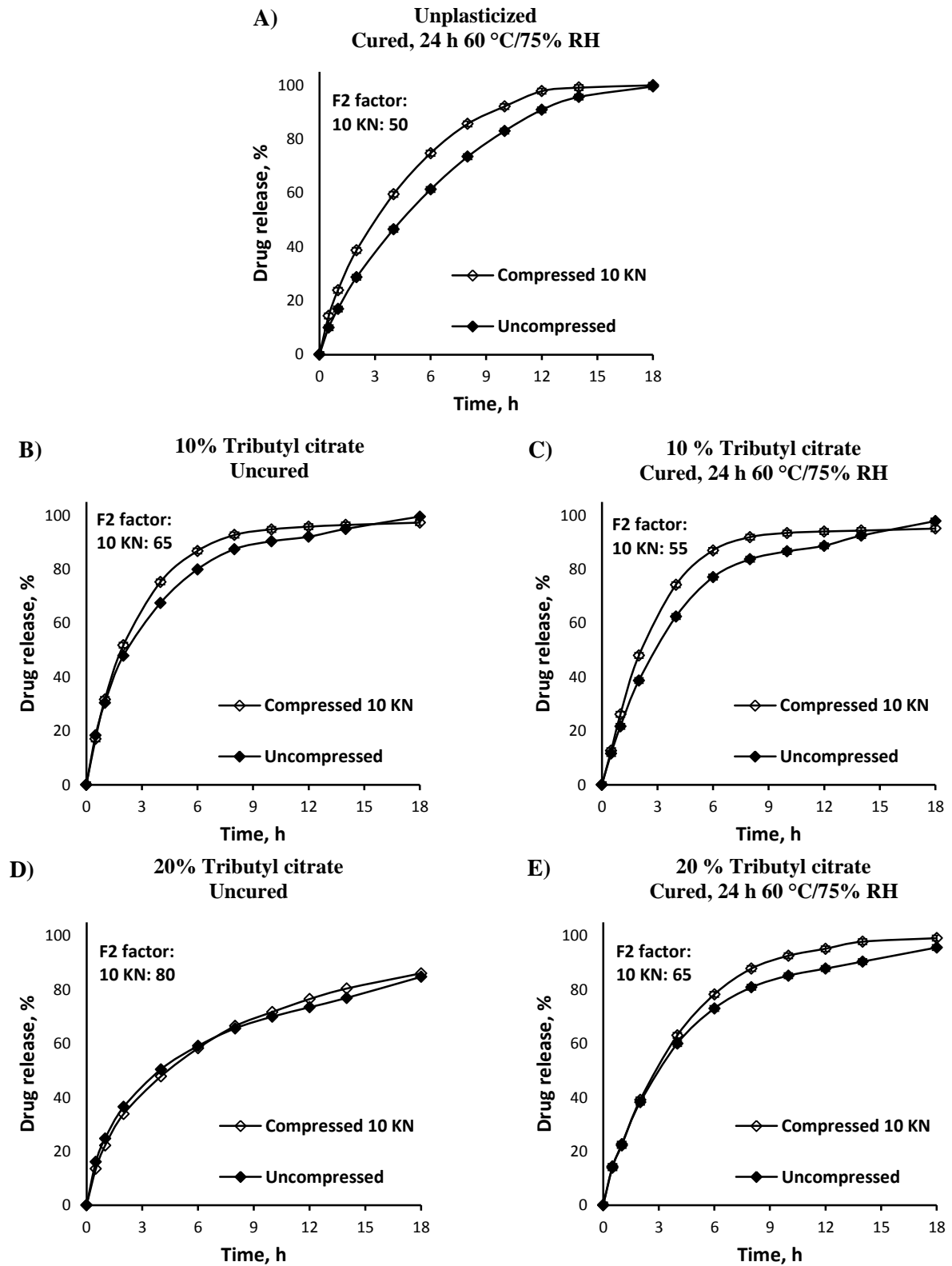
Fig. 80: Effect of pellets compression on drug release (Carbamazepine:Eudragit® RS 30 D 1:0.2, pellet content 50% w/w).

3.4.13 Effect of dissolution test conditions

The same conditions, which were used in paragraph (3.2.10) (for pellets layered using organic solution of the polymers), were used here. The results were evaluated using F2 similarity factor (Table 16). Carbamazepine release was independent of agitation speed or pH of the release medium (F2 > 50). In medium with high osmolality (NaCl was added into the release medium), the drug release decreased only from Eudragit® RS 30 D layered pellets, because of the common ion effect which reduced permeability of the polymer. Drug release from pellets layered with Kollicoat® SR 30 D, Eudragit® NE 30 D and Aquacoat® ECD was not affected with addition of Tween® 80 into the release media (F2 > 50). In these formulations, sodium lauryl sulfate (SLS) was added additionally (5% w/w based on the drug) to stabilize the high solid content dispersion before layering. Therefore, presence of surfactant in the pellets structure could normalize the effect of surfactant in the release media. However, in case of Eudragit® RS 30 D layered pellets (which contain PVP K30 as stabilizer instead of SLS), drug release increased in Tween® 80 media. Addition of SLS to the release media, led to an increase in drug release from all formulations significantly (Table 16), because of the significant increase of carbamazepine solubility in presence of SLS in the release media (Table 10).

Table 16: Effect of dissolution test conditions on carbamazepine release from pellets layered with different aqueous dispersion (drug:polymer 1:0.2), represented by F2 similarity factor

Aqueous dispersion	F2 similarity factor				
	pH	Osmolality, mosmol/kg	Surfactants PBS pH 6.8 with vs. without		Agitation rate, rpm
	1 vs. 6.8	600 vs. 100	0.25% w/v Tween® 80	0.25% w/v SLS	150 vs. 50
Kollicoat® SR 30 D	88	64	85	(+) **22**	71
Eudragit® NE 30 D	91	83	80	51	90
Aquacoat® ECD	84	75	53	(+) **33**	65
Eudragit® RS 30 D	55	(-) **34**	(+) **45**	(+) **33**	84

(+) the drug release increased, (-) the drug release decreased.

3.4.14 Storage stability

Carbamazepine release from pellets layered with different aqueous dispersions was stable (F2 > 50) over 24 months storage at room temperature (Table 17). Similarly, theophylline release from pellets layered with Kollicoat® SR 30 D was also unchanged by storage (Table 18). Metoprolol tartrate uncured pellets layered with Kollicoat® SR 30 D showed a significant decrease in drug release during storage (Fig. 81 A, C, E), however, the release from cured pellets was stable over the time (Fig. 81 B, D, F).

Table 17: Effect of storage on carbamazepine release from pellets layered with different aqueous dispersion (drug:polymer 1:0.2), represented by F2 similarity factor

	F2 similarity factor (1 day vs. 24 months)	
	Uncured pellets	**Cured pellets 24 h 60 °C/75% RH**
Kollicoat® SR 30 D (5% TEC)	73	76
Eudragit® NE 30 D (unplasticized)	66	69
Aquacoat® ECD (20% TBC)	53	72
Eudragit® RS 30 D (unplasticized)	84	79
Eudragit® RS 30 D (10% TBC)	69	75
Eudragit® RS 30 D (20% TBC)	72	68

Table 18: Effect of storage on theophylline release from pellets layered with Kollicoat® SR 30 D (drug:polymer 1:2), represented by F2 similarity factor

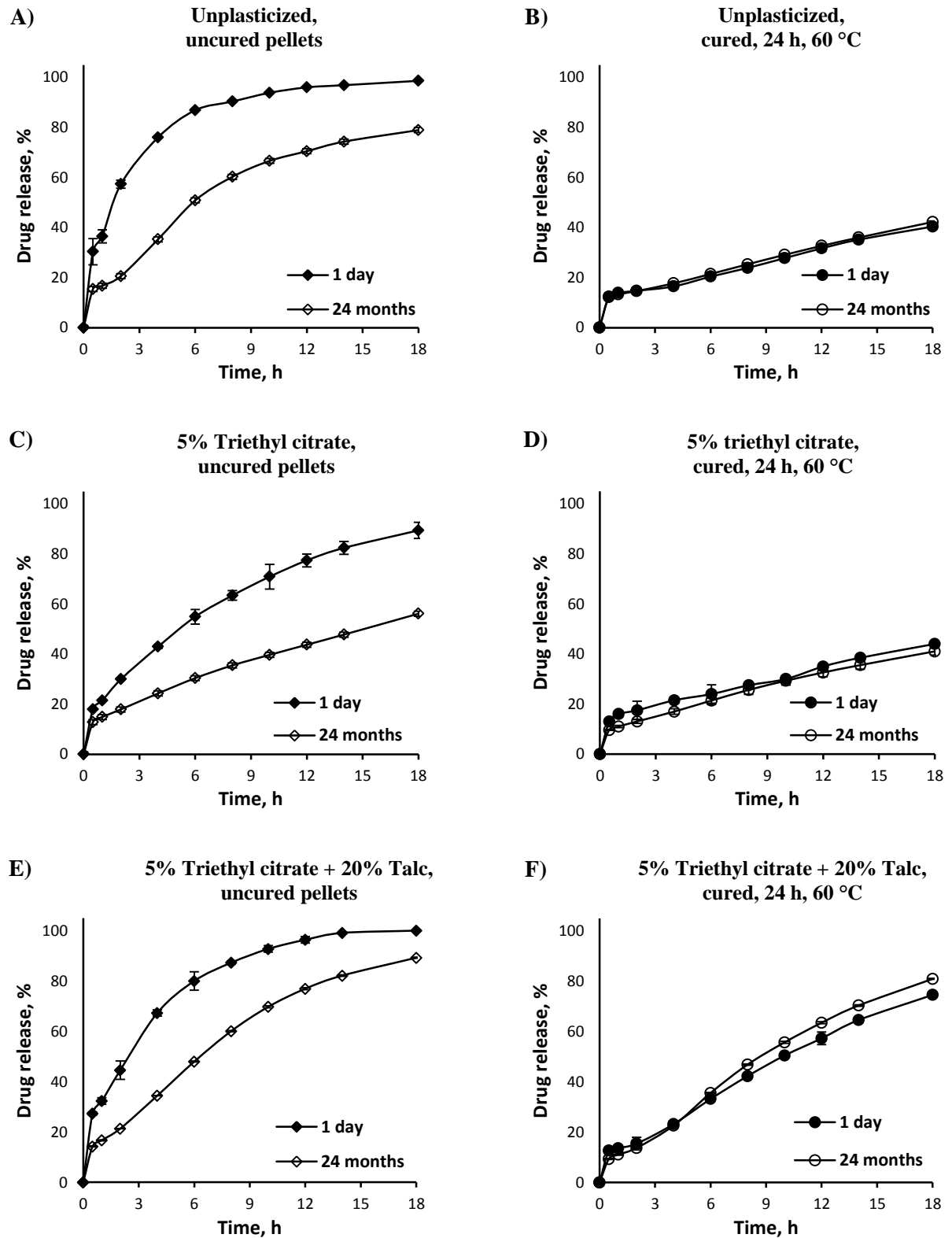|	F2 similarity factor (1 day vs. 24 months)	
	Uncured pellets	**Cured pellets 24 h 60 °C**
0% TEC	63	81
5% TEC	55	64

Fig. 81: Effect of storage on metoprolol tartrate release from pellets layered with Kollicoat® SR 30 D (drug:polymer 1:6).

Chapter 4. Summary

4.   Summary

The typical manufacturing process of controlled release pellets includes preparation of drug cores using water-soluble binders, followed by coating with release-controlling polymers. The main objective of this work was to investigate the applicability of water-insoluble polymers, usually used for coating, as binders for pellets preparation as an alternative formulation tool to control the drug release. Water-insoluble polymers were applied as binders in the form of organic solution or aqueous dispersion, using two different pelletization techniques: extrusion/spheronization and solution/suspension drug layering onto starter cores. The pellets were characterized with regard to different properties including drug release, and were compared to those prepared with water-soluble polymers.

For pellets prepared by extrusion/spheronization, remarkable differences were observed between pellets prepared with the water-insoluble ethylcellulose (EC) using isopropanol:water as granulation fluid, and those prepared with the water-soluble hydroxypropyl methylcellulose (HPMC) and water. Pellets prepared with ethylcellulose/isopropanol:water had a lower density (higher porosity) and crushing force than those prepared with HPMC/water. The higher porosity of these pellets resulted in reduced swellability (size increase) upon contact with the release medium. Drug release from pellets prepared with ethylcellulose as binder was slower than from those prepared with HPMC for all tested drugs. With the poorly soluble drug carbamazepine, the release from ethylcellulose pellets was much slower than from HPMC pellets prepared with the same granulation fluid isopropanol:water. However, the less porous HPMC pellets prepared with water had the same release rate as ethylcellulose pellets prepared with isopropanol:water. With the higher solubility drugs paracetamol, propranolol HCl and metoprolol tartrate, the release from coated pellets was much slower with the water-insoluble binder ethylcellulose. The difference in drug release between pellets prepared with ethylcellulose and HPMC (t_{80} EC $-$ t_{80} HPMC) increased with increasing binder content and coating thickness, however, it decreased with increasing drug loading.

For pellets prepared by solution/ suspension layering, the use of water-insoluble polymers as binders (20-40% based on the drug) was also an effective tool to control the drug release. With the poorly soluble drugs carbamazepine and ibuprofen, controlled and enteric release profiles were achieved without a further coating step. This was in contrast to an immediate

release from pellets layered with the most commonly used water-soluble binder HPMC. Comparing different water-insoluble binders, the release retardation efficiency was in the order of ethylcellulose > Eudragit® RS 100 > Kollidon® SR. A combination of controlled and enteric polymers as a binder prevented the release in pH 1 and retarded it in pH 6.8. Upon compression, the release from ethylcellulose- or Eudragit® RS-layered pellets increased significantly. However, pellets prepared with higher molecular weight of ethylcellulose or higher binder content were less affected. The release from pellets prepared with the more flexible Kollidon® SR was not affected by compression. A combination of ethylcellulose and Kollidon® SR resulted in a better drug release retardation than Kollidon® SR and was more resistant to compression than ethylcellulose. For higher soluble drugs, theophylline and propranolol HCl, a much lower coating level was required to achieve the same release rate, when ethylcellulose was used as binder instead of HPMC. Neither the drug layering method (suspension vs. solution), nor the molecular weight of ethylcellulose had an influence on drug release. Pellets layered with both binders released the drug faster with the swellable MCC starter cores when compared to nonpareils, however, the ethylcellulose-layered pellets were more affected than those layered with HPMC. The difference in drug release between pellets prepared with ethylcellulose and HPMC increased with increasing drug loading, binder content or coating level.

Because of the several advantages of matrix systems, the higher soluble drugs were additionally formulated into controlled release matrix-layered pellets by layering with high amounts of ethylcellulose (80-200% based on the drug). The required amount of ethylcellulose was highly dependent on drug solubility. The higher the drug solubility, the more ethylcellulose was required to control the release, except for the surface-active propranolol HCl, which required a higher amount of ethylcellulose than was expected based on its solubility. Drug release decreased by increasing the drug loading (layering thickness) because of a decreased surface area/dose ratio and increased diffusion path length.

Regarding the release adjustment of drug combinations from multilayer matrix-pellets, factors like layering order, drug solubility, drug:polymer ratio, drug loading and ratio of the pore-former in the top drug layer had to be considered. The drugs with higher solubility were layered first onto the cores and the less soluble ones were layered on top. Amounts of ethylcellulose in each drug layer were similar to those of single-drug matrix pellets. The release of higher soluble drug (first drug) was delayed and slower compared to the less

soluble drug (second drug). This is due to the additional diffusion barrier presented by the second drug layer. By addition of a pore-former to the second drug layer, the release of both drugs increased, with a higher extent for the first drug. Decreasing the ethylcellulose amount in the first layer resulted in an increase in the release of the first drug, without affecting the release of the second drug. However, decreasing the amount of ethylcellulose in the second layer, the release of both drugs increased. Similar release of both drugs could be achieved by an appropriate selection of the amount of ethylcellulose in each drug layer and the ratio of the pore-former in the second drug layer.

Same polymers which were used in the form of organic solution as carrier for drug layering, were also applied in the form of aqueous dispersions including ethylcellulose (Aquacoat® ECD), acrylic polymers (Eudragit® RS 30 D, Eudragit® NE 30 D) and polyvinyl acetate-based polymer (Kollicoat® SR 30 D). All tested aqueous dispersions were applicable as carrier (binder) for drug layering with layering efficiencies of 88-94%. Controlled drug release without a further coating step was achieved with all tested drugs using different ratios of drug:polymer. With the poorly soluble drug carbamazepine, the release was already controlled with small amounts of polymer (10-20% w/w based on the drug). The release retardation from uncured pellets was in the order of Eudragit® NE 30 D > Kollicoat® SR 30 D ≈ Eudragit® RS 30 D > Aquacoat® ECD. A curing effect was seen only with Eudragit® RS 30 D and Aquacoat® ECD and was dependent on plasticizer concentration and curing time. Pellets layered with high MFT aqueous dispersions such as Aquacoat® ECD, showed a weak attachment of the drug/polymer layer to the starter core, as it ruptured separately from the core under compression. This was reflected by the dual peaks profile of the stress-strain curve, which represent the rupture of the drug/polymer layer, followed by rupturing of the starter core. However, pellets layered with low MFT aqueous dispersions such as Eudragit® NE 30 D, Kollicoat® SR 30 D and plasticized Eudragit® RS 30 D, showed a one-peak stress-strain curve, which represents rupturing of the whole pellet. For this reason, upon pellet tableting, an increase in drug release was seen only with Aquacoat® ECD-layered pellets, while with the other polymers, the release was unchanged.

The higher soluble drugs, theophylline and metoprolol tartrate required higher amounts of Kollicoat® SR 30 D to control their release. Release of the slightly soluble theophylline from Kollicoat® SR 30 D-layered pellets was independent of plasticizer content, and not affected by curing. However, in the case of the highly soluble metoprolol tartrate, the release was

significantly slower from plasticized vs. unplasticized, and from cured vs. uncured Kollicoat® SR 30 D- layered pellets. Compared to drugs with a lower solubility, a stronger swelling and a higher water uptake were observed additionally. Therefore, plasticizer addition and curing were required to increase the polymer flexibility and reduce cracking. The drug release from pellets layered with different aqueous dispersions was stable over 24 months storage at room temperature, except for metoprolol tartrate uncured pellets layered with Kollicoat® SR 30 D, which showed a significant decrease in drug release during storage. However, the release from cured pellets was stable over the time.

Kapital 5. Zusammenfassung

5.   Zusammenfassung

Der typische Herstellungsprozess von Pellets mit kontrollierter Wirkstofffreisetzung besteht aus der Herstellung von wirkstoffhaltigen Pellets mithilfe von wasserlöslichen Bindemitteln und anschließendem Überziehen mit retardierenden Polymeren.

Das Hauptziel dieser Arbeit war es zu untersuchen, ob sich wasserunlösliche Polymere, die normalerweise für das Überziehen verwendet werden, als Bindemittel bei der Herstellung von Pellets eignen und inwieweit dies als alternative Formulierungsmethode zur Veränderung der Wirkstofffreisetzung genutzt werden kann. Die Pellets wurden mit zwei verschiedenen Verfahren hergestellt: Extrusion/Sphäronisation und Beschichtung von Starter-Kernen mit einer Wirkstofflösung oder –suspension. Die wasserunlöslichen Polymere wurden dabei entweder als wässrige Dispersionen oder gelöst in organischen Lösungsmitteln als Bindemittel verwendet. Verschiedene Eigenschaften der Pellets, einschließlich der Wirkstofffreisetzung, wurden untersucht und verglichen mit denjenigen von Pellets, die mit wasserlöslichen Polymeren hergestellt wurden.

Durch Extrusion/Sphäronisation hergestellte Pellets zeigten beachtliche Unterschiede zwischen den Pellets, die mit wasserunlöslicher Ethylcellulose (EC) und Isopropanol:Wasser als Granulierflüssigkeit hergestellt wurden und denjenigen, für die wasserlösliche Hydroxypropylmethylcellulose (HPMC) und Wasser verwendet wurden. Pellets, die mit Ethylcellulose/Isopropanol:Wasser verarbeitet wurden, hatten eine geringere Dichte (höhere Porosität) und Bruchfestigkeit als die, die mit HPMC:Wasser hergestellt wurden. Die höhere Porosität dieser Pellets führte zu einem geringeren Aufquellen (Zunahme der Größe) bei Kontakt mit dem Freisetzungsmedium. Die Freisetzung aus Pellets, die Ethylcellulose als Bindemittel enthielten, war für alle getesteten Wirkstoffe langsamer, als wenn HPMC verwendet wurde. Mit dem schwer löslichen Wirkstoff Carbamazepin war die Freisetzung viel langsamer aus den Ethylcellulose-Pellets als aus den HPMC-Pellets, wenn die gleiche Granulierflüssigkeit (Isopropanol:Wasser) verwendet wurde. Hingegen hatten die weniger porösen HPMC-Pellets, die mit Wasser hergestellt wurden, die gleiche Freisetzungsgeschwindigkeit wie die mit Isopropanol:Wasser hergestellten Ethylcellulose-Pellets. Für die besser löslichen Wirkstoffe Paracetamol, Propranolol HCl und Metoprolol Tartrat, war die Freisetzung aus überzogenen Pellets viel langsamer mit dem wasserunlöslichen Bindemittel Ethylcellulose. Der Unterschied in der Wirkstofffreisetzung von Pellets hergestellt mit Ethylcellulose oder HPMC (t_{80} EC – t_{80} HPMC) nahm bei höherem

Bindemittelgehalt oder höherer Überzugsmenge zu. Mit zunehmender Wirkstoffbeladung nahm der Unterschied hingegen ab.

Auch für Pellets, die durch Beschichtung mit Wirkstofflösung oder -suspension in der Wirbelschicht hergestellt wurden, war die Verwendung von wasserunlöslichen Polymeren (20-40% bezogen auf den Wirkstoff) als Bindemittel eine effektive Methode um die Freisetzung zu kontrollieren. Für die schwer löslichen Wirkstoffe Carbamazepin und Ibuprofen konnten ohne zusätzliches Überziehen retardiere oder magensaftresistente Freisetzungsprofile erzielt werden. Im Gegensatz dazu führte die Verwendung des gängigsten, wasserlöslichen Bindemittels HPMC zu einer sofortigen Arzneistofffreisetzung. Der Vergleich verschiedener wasserunlöslicher Bindemittel ergab für ihre Retardierungseffizienz folgende Rangordnung: Ethylcellulose > Eudragit® RS 100 > Kollidon® SR. Die Kombination von retardierenden und magensaftresistenten Polymeren als Bindemittel verhinderte die Freisetzung in pH 1 und verlangsamte diese in pH 6.8. Durch das Verpressen erhöhte sich die Freisetzung aus den mithilfe von Ethylcellulose oder Eudragit RS beschichteten Pellets signifikant. Wenn Ethylcellulose mit einem höheren Molekulargewicht verwendet wurde, oder bei höherem Bindemittelanteil, war die Auswirkung des Verpressens geringer. Wenn das flexiblere Kollidon® SR für die Herstellung verwendet wurde, beeinflusste das Verpressen die Freisetzung nicht. Das Kombinieren von Ethylcellulose und Kollidon® SR führte zu einer stärkeren Retardierung der Wirkstofffreisetzung als Kollidon® SR alleine und die Pellets waren widerstandsfähiger gegenüber dem Verpressen als nur mit Ethylcellulose. Für Wirkstoffe mit einer höheren Löslichkeit, wie Theophyllin und Propranolol HCl, wurde eine viel geringere Überzugsmenge für das Erreichen der gleichen Freisetzungsrate benötigt, wenn Ethylcellulose anstelle von HPMC als Bindemittel eingesetzt wurde. Weder die Methode der Wirkstoffbeschichtung (Lösung versus Suspension), noch das Molekulargewicht der Ethylcellulose, hatten einen Einfluss auf die Wirkstofffreisetzung. Die Freisetzung nahm mit beiden Bindemittel zu, wenn die aufquellenden MCC-Kerne verwendet wurden im Vergleich zu den Nonpareil-Kernen. Jedoch war der Effekt größer bei Pellets, die mithilfe von Ethylcellulose beschichtet wurden, als bei diejenigen mit HPMC. Der Unterschied zwischen den Freisetzungsprofilen der mit Ethylcellulose oder HPMC hergestellten Pellets wurde größer bei einer Erhöhung der Wirkstoffbeladung, des Bindemittelanteils oder der Überzugsmenge.

Aufgrund der verschiedenen Vorteile von Matrix-Systemen, wurden die Wirkstoffe mit höherer Löslichkeit ebenfalls als matrix-beschichtete Pellets formuliert, wobei hohe Anteile von Ethylcellulose (80-200% bezogen auf den Wirkstoff) verwendet wurden. Die notwendige Menge Ethylcellulose hing stark von der Löslichkeit des Wirkstoffs ab. Je höher die Löslichkeit, desto mehr Ethylcellulose war notwendig um die Freisetzung zu kontrollieren. Das oberflächenaktive Propranolol HCl stellte eine Ausnahme dar, da es eine größere Menge Ethylcellulose benötigte, als aufgrund der Löslichkeit erwartet wurde. Die Freisetzungsgeschwindigkeit nahm mit zunehmender Wirkstoffbeladung (dickere Wirkstoffschicht) ab, aufgrund des reduzierten Oberfläche/Dosis-Verhältnisses und der längeren Diffusionswege.

Um die Freisetzung von Wirkstoffkombinationen aus mehrschichtigen Matrixpellets zu kontrollieren, mussten Faktoren wie die Reihenfolge der Wirkstoffschichten, die Löslichkeit der Wirkstoffe, das Verhältnis von Wirkstoff:Polymer, die Wirkstoffbeladung und der Anteil an Porenbildner in der äußeren Wirkstoffschicht berücksichtigt werden. Die Wirkstoffe mit höherer Löslichkeit wurden zuerst auf die Kerne aufgetragen und darüber die Wirkstoffe mit geringerer Löslichkeit. Die verwendeten Mengen an Ethylcellulose in jeder Wirkstoffschicht waren ähnlich wie bei den entsprechenden Matrix-Pellets mit nur einem Wirkstoff. Die Freisetzung des besser löslichen Arzneistoffs (erster Arzneistoff) war verzögert und langsamer als diejenige des schlechter löslichen Arzneistoffes (zweiter Arzneistoff), da die äußere Wirkstoffschicht eine zusätzliche Diffusionsbarriere darstellt. Die Zugabe eines Porenbildners zu der äußeren Schicht beschleunigte die Freisetzung beider Wirkstoffe, jedoch diejenige des inneren Wirkstoffs in höherem Ausmaß. Ein geringerer Ethylcellulose-Anteil in der ersten Schicht erhöhte die Freisetzungsgeschwindigkeit des ersten Wirkstoffs und hatte keinen Einfluss auf die Freisetzung des zweiten Arzneistoffs. Im Gegensatz dazu führte ein erniedrigter Ethylcellulose-Anteil in der äußeren Schicht zu einer schnelleren Freisetzung für beide Wirkstoffe. Eine ähnliche Freisetzungsrate für beide Wirkstoffe konnte erzielt werden durch die Wahl einer geeigneten Menge Ethylcellulose in jeder Schicht und einem geeigneten Anteil Porenbildner in der zweiten Wirkstoffschicht.

Die gleichen Polymere, die als organische Lösungen verwendet worden waren, wurden auch in Form von wässrigen Dispersionen als Bindemittel für die Wirkstoffbeschichtung benutzt. Zu den verwendeten Polymeren zählen Ethylcellulose (Aquacoat® ECD), acrylische Polymere (Eudragit® RS 30 D, Eudragit® NE 30 D) und ein polyvinylacetat-basiertes

Polymer (Kollicoat® SR 30 D). Alle getesteten wässrigen Dispersionen waren mit einer Sprüheffizienz von 88-94% als Bindemittel für die Wirkstoffbeschichtung geeignet. Eine kontrollierte Wirkstofffreisetzung konnte für alle getesteten Wirkstoffe ohne einen zusätzlichen Überzug erreicht werden, indem verschiedene Wirkstoff:Polymer-Verhältnisse eingesetzt wurden. Für den schwer löslichen Arzneistoff Carbamazepin war die Freisetzung schon mit kleinen Polymermengen (10-20% bezogen auf den Wirkstoff) retardiert. Das Ausmaß der Retardierung von nicht getemperten Pellets hatte folgende Rangfolge: Eudragit® NE 30 D > Kollicoat® SR 30 D ≈ Eudragit® RS 30 D > Aquacoat® ECD. Ein Effekt durch das Tempern wurde nur für Eudragit® RS 30 D und Aquacoat® ECD beobachtet und war abhängig von der Weichmacherkonzentration und der Temperungszeit. Bei Pellets, die mithilfe eines Bindemittels mit hoher MFT beschichtet wurden (Aquacoat® ECD), haftete die Wirkstoff/Polymer-Schicht nur schwach am Starter-Kern, wie das separate Zerreißen dieser Schicht unter Kompression zeigte. Die Spannungs-Verformungs-Diagramme wiesen ein Zwei-Peak-Profil auf, wobei der erste Peak durch das Reißen der Wirkstoff/Polymer-Schicht und der zweite Peak durch das Brechen des Starter-Kerns entsteht. Wurden die Pellets mithilfe von wässrigen Dispersionen mit einer niedrigen MFT beschichtet, wie Eudragit® NE 30 D, Kollicoat® SR 30 D und mit Weichmacher versetztes Eudragit® RS 30 D, so wiesen die Spannungs-Verformungs-Diagramme nur einen Peak auf, welcher den Bruch des gesamten Pellets repräsentiert. Daher veränderte sich nach dem Tablettieren der Pellets nur die Freisetzung der Aquacoat® ECD-Pellets, während die Freisetzung aus den Pellets mit den anderen Polymeren gleich blieb.

Die Wirkstoffe mit einer höheren Löslichkeit, Theophyllin und Metoprolol Tartrat, benötigten größere Mengen an Kollicoat® SR 30 D um die Freisetzung zu kontrollieren. Die Freisetzung des wenig löslichen Theophyllins aus Pellets mit Kollicoat® SR 30 D war unabhängig vom Weichmachergehalt und nicht beeinflusst durch das Tempern. Im Gegensatz dazu war die Freisetzung des sehr leicht löslichen Metoprolol Tartrates aus Pellets mit Kollicoat® SR 30 D signifikant langsamer, wenn Weichmacher zugesetzt wurde und wenn die Pellets getempert wurden. Im Vergleich zu Wirkstoffen mit einer niedrigeren Löslichkeit wurde außerdem ein stärkeres Aufquellen und eine höhere Wasseraufnahme beobachtet. Daher waren die Zugabe eines Weichmachers und Temperung erforderlich um die Flexibilität des Polymers zu erhöhen und Rissbildung zu vermeiden. Die Wirkstofffreisetzung der Pellets, die mithilfe der verschiedenen wässrigen Dispersionen beschichtet wurden, war nach 24 Monaten Lagerung bei Raumtemperatur unverändert. Eine

Ausnahme waren die nicht getemperten Metoprolol-Tartrat-Pellets mit Kollicoat® SR 30 D, bei welchen die Freisetzung mit der Zeit signifikant langsamer wurde. Bei den getemperten Pellets hingegen war die Freisetzung stabil während der Lagerungszeit.

Chapter 6. References

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Chapter 7. Publications and presentations

7.   Publications and presentations

Research publications:

1- **M. G. Zoubari,** R. Bodmeier, Comparison of water-soluble and -insoluble polymers used as binders for controlled release pellets. (In preparation).

2- **M. G. Zoubari,** R. Bodmeier, Water-insoluble polymers as binders for pellets drug layering, influence on drug release and performance upon compression. (In preparation).

3- **M. G. Zoubari,** R. Bodmeier, Matrix layering with ethylcellulose for controlled release pellets of single drug and drug combination. (In preparation).

4- **M. G. Zoubari,** R. Bodmeier, Matrix layering with the aqueous polymer dispersion Kollicoat$^®$ SR 30 D for controlled release pellets. (In preparation).

Poster presentations:

1- **M. G. Zoubari,** A. Dashevskiy, R. Bodmeier, Comparison of water-soluble and -insoluble polymers used as binders in drug-layered extended release pellets. AAPS Annual Meeting and Exposition, November 2013, San Antonio, USA, poster T2097.

2- **M. G. Zoubari,** A. Dashevskiy, R. Bodmeier, Drug layering with aqueous polymer dispersions for extended release pellets. PBP world meeting, April 2014, Lisbon, Portugal, poster 89.

3- **M. G. Zoubari,** R. Bodmeier, Aqueous polymer dispersions used as binder drug layering; Influence on drug release and performance upon compression. Tag der Pharmazie, July 2014, FU Berlin, Berlin, Germany, poster 57.

4- **M. G. Zoubari,** A. Dashevskiy, R. Bodmeier, Drug layering with the aqueous polymer dispersion Kollicoat$^®$ SR 30 D for controlled release pellets. CRS, Annual Meeting and Exposition, July 2014, Chicago, USA, poster 10516.

5- **M. G. Zoubari,** A. Dashevskiy, R. Bodmeier, Water insoluble polymers used as binders in drug layering to prepare matrix-type pellets: Influence on drug release and performance upon compression. AAPS Annual Meeting and Exposition, November 2014, San Diego, USA, poster W4028.

6- **M. G. Zoubari,** A. Dashevskiy, R. Bodmeier, Matrix pellet layering with drug-ethylcellulose solutions for controlled release of single drug and drug combinations. AAPS Annual Meeting and Exposition, October 2015, Orlando, USA, poster T3128.

Chapter 8. Curriculum vitae

8.   Curriculum vitae

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