Hot melt extrusion for the production of controlled drug delivery systems

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vorgelegt von
Nutsawadee Apichatwatana
aus Phitsanulok, Thailand

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แสงสว่างเสมอด้วยปัญญาไม่มี

Intellect outshines the brilliance of all stones

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1. Introduction

1.1. Oral extended-drug release system

Oral administration is the most common and preferable route for drug delivery. This is attributed to patient's acceptance, ease of administration without any training, accurate dose, cost-effectiveness of preparation, long time stability (Tiwari and Rajabi-Siahboomi, 2008). Extended release dosage forms which release the drug over extended periods of time are developed in order to improve the pharmacotherapy. The advantages of extended release dosage forms are: maintenance of a steady drug plasma level over prolonged time thus reduce the fluctuation of drug plasma level, maintenance the therapeutic drug level hence stabilize the medical treatment and reduce the side effect of drug, and reduction in a frequency of drug administration and totally dose leading to improve patient's compliance and consequence therapeutic efficacy (Perrie and Rades, 2010; Tiwari and Rajabi-Siahboomi, 2008; Well and Rubinstein, 2005). Various physical and chemical approaches have been successfully applied to produce the controlled delivery systems that extend drug release into the gastrointestinal tract with the desired release profile. Today, most proprietary and nonproprietary extended-release technologies are based on polymeric systems. The fundamental design principles, theoretical considerations, and applications of these systems have been extensively addressed and reviewed (Qiu and Zhang, 2000; Robinson and Lee, 1987; Wen and Park, 2010). Common oral extended-release system from a survey of commercial products indicates that every system falls into one of three broad categories: (i) matrix system, (ii) reservoir (or membrane controlled) system and (iii) osmotic systems **(Table 1)** (Qiu, 2009; Wen and Park, 2010).

Drug release from these extended release systems is generally based on one or a combination of the following mechanisms: drug diffusion (through pores of a barrier, through tortuous channels, or through a viscous gel layer between polymer chains), system swelling (followed by diffusion and/or erosion and dissolution), or osmotic pressure induced release (drug solution, suspension or wet mass forced out of the system). Each type of system has its advantages and shortcomings with respect to the performance, applicability, manufacture, control, development time, cost, etc. **(Table 2)** (Qiu, 2009). The guideline for preparing of suitably extended release system, concerning dose and drug solubility, is suggested in **Table 3** (Qiu, 2009).

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From the aspects of simplicity, production cost, process variability and robustness of controlled release, matrix system seems to be the most favorable method for the extended release preparation.

Table 1   **Oral extended-release systems commonly utilized in commercial products**

	Matrix	Reservoir	Osmotic
System	Hydrophilic matrix ; - Erosion/diffusionControlled - Swelling/Erosion controlled Hydrophobic matrix; - Homogenous (dissolved drugs) - Heterogeneous (dispersed drugs)	Membrane controlled; - Constant activity - Non-constant activity Membrane matrix Combination	Elementary osmotic pump Microporous osmotic pump Layered osmotic pump (e.g., Push-Pull®, Push-Stick®)
Common dosage forms	Monolithic tablet Multi-unit minitablets Layered tablet Compression coated tablet	Multi-unit coated beads Multi-unit coated minitablets Monolithic coated tablet	Coated monolithic tablet Coated layered tablet

Table 2   Comparison of commonly used oral extended-release technologies

System	Advantage	Disadvantage
Hydrophilic matrix	Suitable for compounds with a wide range of properties and low to high drug loading Generally robust formulation and process when rationally designed Use of conventional manufacturing equipment and process Cost effective: shorter development time and lower cost Release kinetics and profiles can be tailored with modification Multi-units possible	Drug release often sensitive to test conditions Less flexibility for adjusting dose strengths for single-unit system Increased formulation/process complexity for tailored drug release (layered or compression coated system)
Hydrophobic matrix	Suitable for soluble compounds and low to high drug loading Use of conventional manufacturing equipment and process Release kinetics and profiles can be tailored with modification Multi-units possible	Not applicable to compounds with low solubility Non-zero-order release Propensity for incomplete drug release Drug release often sensitive to processing and test conditions Less flexibility for adjusting dose strengths for single-unit system Increased formulation/process complexity for tailored drug release (layered or compression coated system)

Table 2   Comparison of commonly used oral extended-release technologies (cont.)

System	Advantage	Disadvantage
Multi-unit reservoir	Readily tailored release kinetics and profiles (e.g., zero-order, pulsatile, biphasic, colonic)	Drug release often sensitive to test conditions
	Minimized risk of dose dumping and local irritation	Limited drug loading
	Lower *in vivo* variability (favorable transit property)	Many process parameters are considered
	More consistent *in vivo* performance	
	Easy dose adjustment: single formulation amenable to multiple strengths	
	Suitable for pediatric/geriatric use	
	Use of conventional manufacturing equipment and process	
Osmotic pump	Applicable to compounds with a relatively wide range of properties	Limited drug loading
	Drug release generally independent of drug properties and test conditions	Ghost tablets
		Delayed onset (1–2 hrs) and/or incomplete drug release
	Zero-order release	Solvent-based process
		Lengthy, complex, and inefficient manufacturing processes and control (e.g., layered tablet)
		Specialized equipment and facility
		Highest development and manufacturing cost and time

Table 3   Guideline for MR system selection on the basis of dose and solubility

System	HS/HD	HS/MD	HS/LD	MS/HD	MS/MD	MS/LD	LS/HD	LS/MD	LS/LD
Hydrophilic matrix tablet	0	+	+	+	+	+	+	+	+
Hydrophobic matrix tablet	+	+	+	-	0	+	-	-	-
Hydrophobic matrix pellets	-	-	-	-	+	+	-	+	+
Coated matrix tablet	+	+	+	-	0	+	-	-	-
Coated pellets	-	+	+	-	+	+	-	-	-
Osmotic pump	-	0	0	-	+	+	-	+	+

Note: (1) HS = high solubility; MS = medium solubility; LS = low solubility; HD = high dose; MD = medium dose; LD = low dose

(2) "+" = suitable; "-" = unsuitable; "0" = borderline (may be suitable via system modification)

1.2. Matrix Systems

In a matrix system, drug is homogeneously mixed (dissolved or dispersed form) into the rate-controlling material(s) and other inactive ingredients as a crystalline, amorphous or, in rare cases, molecular dispersion. The matrix system has been most widely utilized to provide extended delivery of drug substances because of its effectiveness and the capability of accommodating both low- and high-loading of drugs with a wide range of physical and chemical properties. From a product development point of view, it is cost-effective and easy to scale-up and manufacture. In addition, this type of system is usually manufactured using conventional processes and equipment. However, the release characteristics of a matrix (e.g., kinetics and pH-dependency) are usually determined by the property of the drug substance. To alter release profiles or to achieve unique release patterns (e.g., biphasic or delayed ER), a more complex design and process, such as a layered or compression coated tablet, is sometimes required. Furthermore, a matrix system typically lacks flexibility in offering the multiple strengths that are usually required for clinical studies in developing a new chemical entity, because compositionally proportional dosage forms of different strengths usually do not have the same release rate. Thus, additional resources and time are often required for new dosage strengths (Liu et al., 2006; Qiu et al., 1998). Drug release from matrix occurs either by drug diffusion and /or erosion of the matrix system. Based on the characteristics of the rate-controlling material, the matrix system can be divided into: (i) hydrophilic; and (ii) hydrophobic systems. For practical purposes, the former refers to a matrix system in which the rate-controlling materials are water-soluble and /or swellable, while the latter consists of a water-insoluble inert matrix with minimum swelling.

1.2.1. Hydrophilic Matrix Systems

Hydrophilic matrix system is polymer-based drug delivery system in which two competing mechanisms are involved in the drug release: Fickian diffusional release, and relaxational release. The primary rate-controlling materials are polymers that hydrate and swell rapidly in an aqueous medium, and form a gel layer on the surface of the system. Diffusion across the viscous gel layer is not the only drug release pathway, as erosion of the matrix following polymer relaxation also contributes to the overall release. The relative contribution of each component to total release is primarily dependent upon the

properties of a given drug and matrix composition. For instance, the release of a sparingly soluble drug from hydrophilic matrices involves the simultaneous ingress of water and desorption of drug via a swelling-controlled diffusion mechanism. As water penetrates into a glassy matrix and lowers the polymer glass transition temperature, the polymer swells, slowly disentangles, and eventually dissolves, releasing the undissolved drug. At the same time, the dissolved drug diffuses through this swollen rubbery region into the external releasing medium. This type of diffusion, with concurrent swelling and erosion, generally does not follow a Fickian diffusion mechanism. The continuously changing variables that affect drug release (e.g., diffusion path length, viscosity, system dimension, etc.) make obtaining a mechanistic equation or model describing the release profile impossible. Over the past three decades, various models have been explored and developed to achieve a fundamental understanding of drug release from hydrophilic matrices. Commonly available hydrophilic polymers are hydroxypropylmethylcellulose (HPMC) (Colombo et al., 1999; Colombo et al., 1996; Hardy et al., 2007), hydroxypropyl cellulose (HPC) (Alvarez-Lorenzo et al., 2000; Dürig and Fassihi, 1997; Tajiri et al., 2010), sodium carboxymethylcellulose (NaCMC) (Nokhodchi et al., 2008; Vatsaraj et al., 2002), polyethylene oxide (Choi et al., 2003; Kojima et al., 2008), xantham gum (Fukuda et al., 2006b; Vendruscolo et al., 2005), alginate (Mandal et al., 2009; Moroni et al., 2011), copolymers of acrylic acid chemically cross-linked with polyalkenyl alcohols (Carbopol®) (Fayed et al., ; Tapia-Albarran and Villafuerte-Robles, 2004; Tatavarti et al., 2004).

1.2.2. Hydrophobic Matrix Systems

In a hydrophobic inert matrix system, the drug is dispersed throughout a matrix. The primary rate controlling components of a hydrophobic matrix are water insoluble properties of materials. The presence of water insoluble in the formulation involves essentially negligible increase of the device surface or change in dimension of a matrix during drug release. Therefore, the release of the active drugs is controlled by diffusion through a network of channels in a matrix and the release behavior can be described by the Higuchi equation. Generally, hydrophobic matrix systems are not appropriate for poorly soluble drugs since the concentration gradient is too low to provide adequate drug release. To moderate drug release incorporation of soluble substances may be necessary to include in the formulation (Liu et al., 2006; Martini et al., 2000). The suitability of

hydrophobic matrix systems for extended release of highly soluble drug has been reported (Martini et al., 2000; Sudha et al., 2010). Hydrophobic polymers provide some advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications (Tiwari et al., 2003). The hydrophobic materials can be used as matrix carrier such as ethycellulose (Quinten et al., 2009a; Quinten et al., 2009b; Verhoeven et al., 2009b), cellulose acetate (Makhija and Vavia, 2002; Papadokostaki and Petropoulos, 1998), acrylic polymer (Eudragit® RL, RS, NE) (Bodmeier and Paeratakul, 1989; Boyapally et al., 2009; Ubrich et al., 2005), polyamide (Frutos et al., 2001), and waxes (Agata et al., ; Cheboyina and Wyandt, 2008)

1.3. Enteric drug delivery system

Enteric drug delivery system is developed to avoid drug release in gastric region thus preventing problems such as degradation, or pharmacological effects including gastric irritation and nausea. Moreover, it can be used to deliver drugs intended for local treatment in the intestine or drugs which are absorbed in the small intestine or colon (Wang and Shmeis, 2006). The underlying principle of this approach is the employment of polymers that are able to withstand the lower pH values of the stomach, but disintegrates/dissolves and release the drug as the pH in the small bowel increases.

The conventional coating of enteric polymers (**Table 4**) is typically used to obtain enteric delivery system. However, the coating process contains many parameters, which could affect the quality of coating and also the properties of the system. To simplify the manufacture of enteric dosage forms, a homogenous matrix system with enteric properties without the need for an enteric coating step would be considered in term of processing time and cost. Sustained release characteristics of enteric matrix are beneficial for delivering drug targeted at the entire part of lower GI tract; for instance ulcerative colitis, inflammation is observed in all region of the colon (Hua et al., 1999).

Enteric polymers; Eudragit L100-55, cellulose acetate phthalate and hydroxyl-propylmethyl cellulose phthalate, have been used as a part of matrix forming material for the production of phenylbutazone microspheres by extrusion-spheronization (Varshosaz et al., 1997). Eudragit L100-55 has shown the superior gastric protection to cellulose acetate phthalate (CAP) and hydroxypropylmethyl cellulose phthalate (HPMCP) due to the harder and less porous microspheres. Phenylbutazone release from Eudragit L100-55 matrix microspheres was closer to the coated microspheres than the formulations containing the other polymers.

Recently, hot-melt extrusion (Wang and Shmeis); a process pharmaceutically approved thermoplastic carrier systems, has been introduced and studied for the preparation of enteric matrix containing high density and uniformity (Andrews et al., 2008).

The combination of reservoir and monolithic system with enteric polymers for multiparticulates targeted to lower gastrointestinal tract was investigated (Marvola et al., 1999).

Table 4   Enteric polymers have been commercially used in pharmaceutical dosage forms (Mukherji and Wilson, 2003)

Polymer	Threshold pH	Brand name	Manufacturer
Phthalate-Based Enteric Polymers			
Cellulose acetate phthalate	6.0–6.4	C-A-P	Eastman
		Aquacoat® CPD	FMC
Hydroxypropyl methylcellulose phthalate 50	4.8	H.P.M.C.P. 50	Eastman
		HP-50	Shin-Etsu
Hydroxypropyl methylcellulose phthalate 55	5.2	H.P.M.C.P. 55	Eastman
		HP-55	Shin-Etsu
Polyvinylacetate phthalate	5.0	Sureteric®	Colorcon
Methacrylic Acid–Based Copolymers			
Methacrylic acid- methyl methacrylate copolymer (1:1)	6.0	Eudragit® L 100/L 12.5	Evonik Industries AG
Methacrylic acid– methyl methacrylate copolymer (2:1)	6.5–7.5	Eudragit® S 100/S 12.5	Evonik Industries AG
Methacrylic acid–ethyl acrylate copolymer (2:1)	5.5	Eudragit® L 100-55/	Evonik Industries AG
		Eudragit® L 30 D-55	Colorcon
		Acryl-EZE®	Eastman
		Eastacryl™ 30D	
Miscellaneous Enteric Polymers			
Shellac	7.0	-	Zinsser
			Pangaea Sciences
Hydroxypropyl methylcellu lose acetate succinate (HPMCAS)	7.0	Aqoat® AS-HF	Shinetsu
Poly (methyl vinyl ether/ maleic acid) monoethyl ester	4.5–5.0	Gantrez® ES-225	ISP
Poly (methyl vinyl ether/ maleic acid) *n*-butyl ester	5.4	Gantrez® ES-425	ISP

1.4. Manufacturing method for matrix drug delivery system

Typically, the preparation for matrix drug delivery system can be classified into four methods; (i) direct compression, (ii) dry granulation by compaction, (iii) wet granulation and (iv) hot melt extrusion

1.4.1. Direct compression

This method has been employed since 1950. The drug and the excipients are mixed homogeneously and compressed into tablets. The advantages of this method are the process simplicity, less energy and equipment needed leading to faster process compared to other methods. Furthermore, the formulations with moisture and temperature stability problems can be prepared due to the absence of used liquid especially water. As the process required less equipment and processing step, this can reduce the process and equipment validation and other related documentation. Although this method provides many advantages, there are some limitations of the process. The compressibility and flow properties of materials are required in this method. The difference in particle size of powder components of the formulation can affect a segregation of the powder mixture (Cooper and Rees, 1972), resulting in the high variation of tablet properties (weight variation, hardness and friability) and the homogeneity of the mixture for low drug content formulation. This is one factor which can directly affect drug release from tablets (Velasco et al., 1999).

1.4.2. Dry granulation by compaction

In this method, the powder mixture is compacted and then milled. The compaction can be processed with (i) an eccentric compression machine to make a greater than 20 mm tablet (slugging) or (ii) a roller compactors. The process is characterized by lower energy, cost requirement and shorter processing time compared to wet granulation. This method is used for drugs and excipients that are sensitive to humidity and heat. However, the granule preparation by compaction, and afterwards compression would increase the disintegration time due to multiple compactions. Moreover, the high percentage of fines could be occurred during granulation. In case the percentage exceeds 10-15%, a repetition of compaction is necessary (Patel et al., 2006).

1.4.3. Wet granulation

This method is the most widely used even it requires higher cost and energy consumption. Many processing steps; (i) powder mixing, (ii) granulation, (iii) drying and (iv) granule screening are required. Drug and excipients become an agglomeration as solid matrix (through wet mass formation) by using a binder liquid. The flowability of the mixed powder is improved. The particle size and the size distribution of granules could be controlled, leading to increase in homogeneity of mixture and avoiding segregation. It is recommended that the liquid added to powder mixture will not exceed 30% of the powder for the traditional kneading granulation, although higher binder is possibly incorporated. This is time consuming and makes the process more complicated (Ritschel and Bauer-Brandl, 2002).

Binder used in wet granulation can be either cellulose derivatives, starches, polysaccharides or synthetic polymers. Binder in wet granulation can be incorporated once or several steps. The drying step can take place in either a drying oven, fluid bed vacuum, or microwaves devices (Giry et al., 2006).

The benefit-limitation of each method used for matrices preparation; direct compression, dry granulation and wet granulation, were summarized **(Table 5)**. Recently, the attempted use of matrix system as a carrier in other drug delivery systems such as gastroretentive DDS (Chavanpatil et al., 2006; Fukuda et al., 2006a; Senyigit et al., 2011; Singh and Pathak, 2011; Tadros, 2010) and colonic DDS (Krogars et al., 2000) has been intensively investigated.

Table 5   Benefits and limitation of typical tablet manufacturing processes

Manufacturing process	Advantage	Disadvantage
Direct compression	Simplified process, retains compactibility of materials	Segregation flow
Dry granulation	Overcomes poor physical properties of API (particle size, shapes)	Longer processing time, may compromise compactibility
Wet granulation	Improving uniformity, flow and compactaility	Physical and chemical stability, residual solvents (non-aqueous granulation)
Hot melt extrusion	Single and continuous process, solventless, homogeneous API distribution, poor compactibility can be formed	Heat and pressure induce degradation

1.4.4. Hot melt extrusion

Hot melt extrusion is one of the most widely used processes in plastic and food industry since 1930s (Rauwendaal, 1986a). More than half of the plastic products including plastic bags, sheets, and pipes (Kaufman and Falcetta, 1977) and many food products such as pastas, cereals, ready-to-eat snacks or pet food (Harper and Clark, 1979) are produced by this technique. Hot melt extrusion is a process of turning raw materials into a uniform shape and density by forcing it through a die under elevated temperature (Breitenbach, 2002; Crowley et al., 2007). The interest in hot melt extrusion for pharmaceutical applications is growing rapidly with over 100 scientific publications over the last decade (Crowley et al., 2007). Hot melt extrusion was used to prepare pharmaceutical drug delivery systems including granules (Albers et al., 2009), pellets

(Young et al., 2005b), sustained release tablets (Brabander et al., 2003; Özgüney et al., 2009; Verhoeven et al., 2006), sustained release capsules (Mehuys et al., 2005; Mehuys et al., 2004a; Mehuys et al., 2004b), floating gastroretentive (Fukuda et al., 2006a), enteric tablets (Andrews et al., 2008; Yang et al., 2008), colonic delivery system (Bruce et al., 2005), transdermal (Repka and McGinity, 2001a, 2001b) and implants (Ghalanbor et al., 2010; Gosau and Müller, 2010a). Moreover, hot melt extrusion improved the bioavailability of poorly soluble drug by formation of solid dispersions / solid solution (Hülsmann et al., 2000; Rambali et al., 2003).

1.4.4.1. Advantages and disadvantages

Hot melt extrusion offers several benefits over the conventional methods. The process is continuous which can be processed as a single unit operation. Extruders can be functioned for mixing, melting and extruding or reacting of materials (Mollan, 2003). It is an anhydrous and solventless process, which circumvents the hydrolysis of the materials being used. The energy saving and toxicity reduction are obtained by avoiding the solvent elimination step. The poorly compactable materials can be formed as tablets by cutting the extrudates.

Hot melt extrusion utilizes the heat and pressure for production; therefore, the degradation of materials should be optimized before used.

The advantages and disadvantages of hot melt extrusion comparing to the other methods are shown in **Table 5**

1.4.4.2. Hot melt extrusion equipment

Hot melt extrusion is classified into two categories: (i) ram extrusion and (ii) screw extrusion. Ram extrusion is simple in design and discontinuity in the mode of operation. It operates with the positive displacement ram which generates high pressure to push materials through the die (**Fig1**). Materials are heated in the cylinder until soften materials are obtained thus extruding through a desired shape die is pushed by a ram (Perdikoulias and Dobbie, 2003). The drawback of ram extrusion is the limited melting capacity and poor temperature uniformity thus leading to the poor temperature uniformity (Rauwendaal, 2001). In addition the extruded products have poor homogeneity than the products from screw extrusion (Crowley et al., 2007).
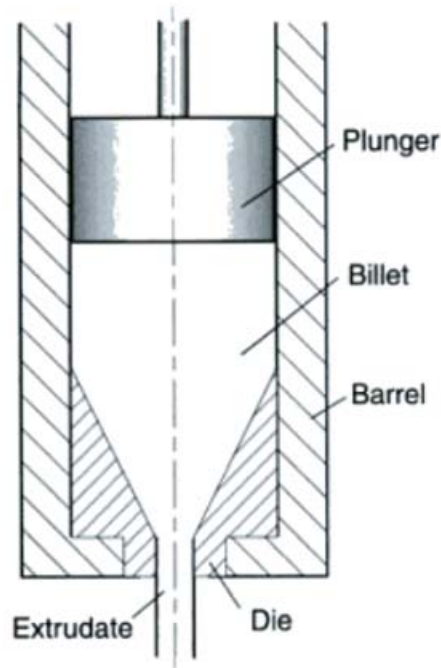
Fig 1 Ram extruder (Rauwendaal, 2001)

A screw extruder provides higher shear stress and intense mixing. Screw extruder consists of at least three parts: (i) a conveying system for material transport and mixing, (ii) a die for forming, and (iii) equipment for cooling, cutting and collecting. The components in the extruder are a feed hopper, a barrel with heating system, a rotating screw and die (Griff, 1968). Screw extruder is classified into two categories; (i) single screw extruder and (ii) twin screw extruder.

Single screw extruder is the most widely used extruder. A screw inside the barrel is used for feeding, melting, devolatilizing and pumping. It is continuous, high-pressure pumps for viscous materials that can generate thousands of pounds of pressure while melting and mixing. The screw is driven from the hopper end by a variable-speed motor. The motor drives a transmission that increases the torque and decreases the screw speed. Pressure, generated by the viscous melt being pumped through a die, commonly pushes against the tip of the screw. This exerts a backward force that is absorbed by thrust bearings. The barrel usually has three or more heating zones to raise the barrel and screw to the required process temperature. Once the polymer is melted and mixed, it flows through a breaker plate with filter and shaping die, and thereafter is cooled into solid form (Luker, 2003) (**Fig 2**).
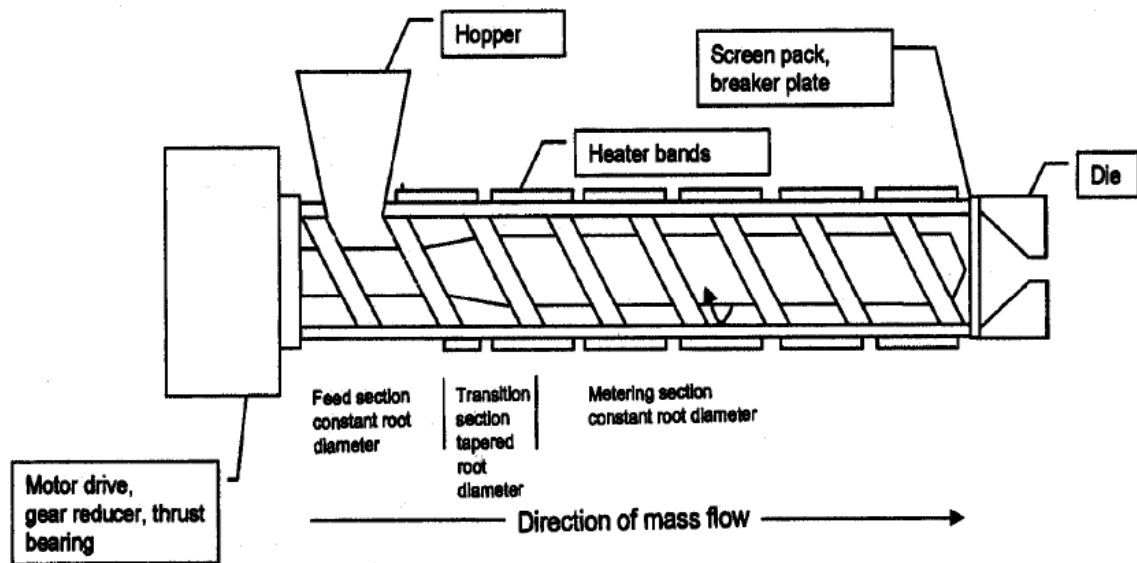
Fig 2 single screw extruder (Chokshi and Zia, 2004)

The differences between single screw extruder and twin screw extruder is the transport mechanism and in their mixing abilities (Rauwendaal, 1981). The transport mechanism in a single-screw extruder is based on frictional forces in the solid conveying zone and viscous forces in the melt conveying zone. The single screw exhibits poorly mixing than the twin screw extruder. The rationale behind these results is because the mixing in a twin screw extruder occurs both at the macroscopical level, where the material is exchanged from one screw to another, as well as at the microscopical level, where the mixing occurs at the high-shear regions of screw elements interactions (Ferns, 1974). The advantages of single screw extruder over twin screw extruder are mechanical simplicity and less expensive. The advantages of twin screw extruder over single screw extruder are the shorter residence times in the extruder, the stability of the melting process, and the smaller equipment size required to achieve an equivalent output (Mollan, 2003). The comparison of single screw extruder and twin screw extruder are presented in **Table 6**.

Table 6   Comparison between twin screw and single screw extruder (Rauwendaal, 1986b)

Single screw extruder	Twin screw extruder
Used in simple profile extrusion and co-extrusion	Used in compounding profile and reactive extrusion
Modular design of screw and barrel is rarely used, less flexibility	Often used with modular design of screw and barrel, great flexibility
Prediction of extruder performance less difficult than for TSE	Prediction of extruder performance is often difficult
Fair feeding, slippery additives tend to cause problems	Good feeding, can handle pellets, powder, liquids
Fair melting, continuous solid melting mechanism	Good melting, dispersed solids melting mechanism
Good distributive mixing with effective mixing elements	Good distributive mixing with effective mixing elements
Good dispersive mixing with effective mixing elements	Good dispersive mixing with effect mixing elements
Fair degassing	Good degassing
Not self-wiping, barrel is wiped but screw root and flight flanks are not	Intermeshing can have completely self-wiping characteristics
Relatively inexpensive	Modular is very expensive
Usually run between 10-150 rpm; high screw speeds possible but not often used	Co-rotating can run at very high screw speed, up to 1400 rpm

Twin screw extruder uses two screws arranged side by side. The use of two screws allows a number of different configurations to be obtained. The two screws can either rotate in the same direction (co-rotation), or the screws can rotate in opposite directions (counter-rotation) (**Fig 3**). Co-rotational screws can rotate either clockwise or counterclockwise, and both directions are equivalent from a processing standpoint. If the two screws rotate in different directions (either rotate toward the center, or rotate away from the center), they are known as counter-rotating extruders (Mollan, 2003). Co-rotation extruder is further classified into (i) fully intermeshing co-rotation extruder and

(ii) non-intermeshing co-rotation extruder. The fully intermeshing extrude is self-wiping where it minimizes the non-motion and prevents localized overheating of materials in the extruder. The extruder operates by first in/ first out principle since the materials does not rotate along with the screw. The non-intermeshing extruder are often used for processing when large amounts of volatiles need to be removed from a material due to the large vent opening that can be accommodated as the screws are positioned apart from each other. They are also used when processing highly viscous materials, where the intermeshing extruder can cause problematical torque buildups (Mollan, 2003).
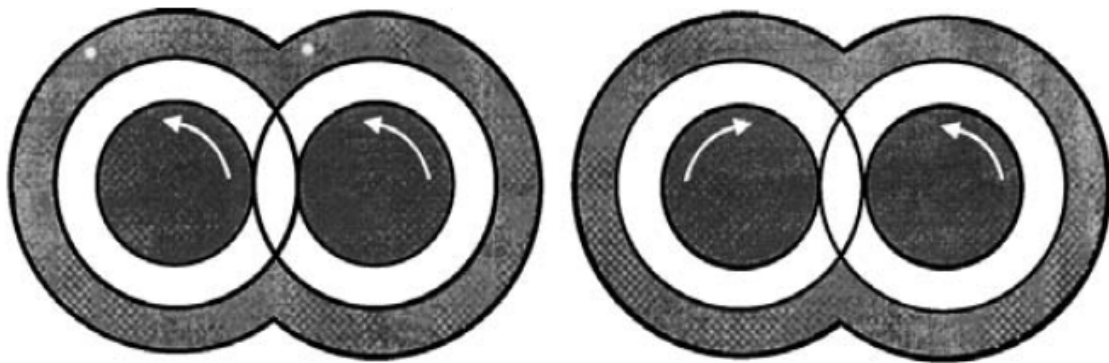

Fig 3 co-rotating (left) and counter-rotating (right) (Mollan, 2003)

The hot melt extrusion process is divided the process into four sections: (i) feeding of the extruder, (ii) conveying of mass (mixing and reduction of particle size), (iii) flowing through the die and (iv) exiting from the die and down-stream processing.

The screw is divided into three sections along the length of the barrel: (i) feeding, (ii) melting or compression, and (iii) metering as shown in **Fig 2**. Feeding section is to transfer the materials from the hopper to the barrel. The polymer typically begins to soften and melt in the compression zone mainly by the heat generated from the frictional force between materials and screws and also the heated barrel. The melt moves circularly in a helical path by means of transverse flow, drag flow, pressure flow, and leakage. Thermoplastic polymers primarily exist in a molten state when entering the metering section. Metering zone reduces the pulsating flow and ensures a uniform delivery rate through the die (Crowley et al., 2007).

1.4.4.3. Materials for hot melt extrusion

Active drug substances

The properties of the active drug substance always limit the formulation and processing choices available in the dosage forms development e.g. incompatible ingredient and processing temperature. Depending on the properties of the drug substance and the other materials, the drug may be presented as solid dispersion, a solid solution, or a combination in the final dosage form (Crowley et al., 2007). The active drug substance may function like other components in the formulation e.g. plasticizer (Wu and McGinity, 1999).

Carriers

In hot melt extrude dosage form, the active drug is embedded in the carrier which must be able to deform easily and remains stable during processing. The molten carriers functioned as thermal binder and drug release retardants. The choice of the carrier selection is based on the processability and thermal stability as well as drug-polymer compatibility, drug release kinetics and route of administration. (Chokshi and Zia, 2004; Crowley et al., 2007; Yucun, 2002). The carrier could be a polymer or the low melting point wax. Typical carrier materials include vinyl polymer, polyethylene oxide, acrylates, polyethylene glycol, and cellulose derivatives (Andrews et al., 2009).

Plasticizer

Plasticizer is used to reduce the glass transition temperature and thus melt viscosity of a polymer leading to facilitate the hot melt extrusion process (Repka et al., 1999). Moreover, it improves the physical and mechanism properties of final products. Plasticizer can reduce the glass transition temperature by increasing the free volume between polymer chains thus the mobility of polymer chains increase (Aharoni, 1998). Plasticizers could alter the matrices permeability, depending on the type of plasticizer. For instance, hydrophilic plasticizers are low barriers to moisture and tend to have a more pronounced effect on increasing water permeability (Zhu et al., 2006). This would result in the loss of controlled release of matrices. The common plasticizers used in

pharmaceutical products such as: triethyl citrate, acetyl tributyl citrate, triacetin, dibutyl sebacate, polyethylene glycol. In addition, several substances were reported to function as plasticizer e.g. active drug substances e.g. ibuprofen and chlorphemiramine maleate, pressurized carbondioxide, preservative e.g. methylparaben (Aitken-Nichol et al., 1996; Özgüney et al., 2009; Repka et al., 1999; Wu and McGinity, 2003b; Zhu et al., 2002).

Thermal lubricant

Thermal lubricant is defined as materials which are added into the formulation to improve its processability (Nielsen, 1977). Thermal lubricants decrease the melt viscosity of the molten materials and reduce the friction of molten materials in the extruder during processing. Unlike plasticizers thermal lubricants have just little effect on the solid state properties. Thermal lubricant is also affecting the final product properties. Glycerol monostearate, wax material, are two examples of the thermal lubricant (Yucun, 2002).

Antioxidants

The degradation of materials may occur under the thermal process. Incorporation of antioxidants can prevent the thermal oxidation thus improve the stability of materials. Some substances used for prevention of oxidation are ascorbic acid and citric acid (Crowley et al., 2007; Yucun, 2002).

1.4.4.4. Oral controlled drug release applications of hot melt extrusion

Hot melt extrusion gains much attention in the pharmaceutical research. It has been demonstrated as an efficient process for a production of oral controlled drug release in several dosage forms e.g. pellets granules and tablets.

To produce pellets or granules, the particle size has to be reduced. After hot melt extrusion, extrudates are cut and spheronized to be a spheroid pellet or grinded as fine particles for granules.

Rippie studied the dissolution rate based upon the pellet geometry of pellets containing cellulose acetate phthalate prepared by ram extruder (Rippie and Johnson, 1969). A number of thermoplastic polymers used in extrusion to produce sustained release pellets were reported (Mank et al., 1989, , 1990).

Hot melt extrusion technique was use to produce sustained-release pellets (Follonier et al., 1994). Diltiazem hydrochloride, a stable and freely soluble drug was included into the polymer-based pellets. Pellets were then filled in capsules. Polymers used to optimize the drug-release profiles were ethylcellulose, cellulose acetate butyrate, poly (ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) (Eudragit$^®$ RSPM), and polyethylene-co-vinyl acetate. Triacetin and diethyl phthalate were selected as plasticizer. The pellets showed a smooth surface and low porosity. The slowest release of diltiazem was obtained from cellulose acetate butyrate and polyethylene-co-vinyl acetate pellets. The type and amount of plasticizer used, drying time of the polymers, extrusion temperatures, and plasticization times also varied with each formulation. The polymer to drug ratio caused a varying of drug release profile. Additives such as pore former and hydrophilic polymers were used to increase the drug-release rate by increasing the porosity of the pellet during dissolution. Viscosity inducing agents were included in the polymer matrix to limit the burst release which is often seen with matrix systems. The incorporation of swelling agents such as croscarmellose sodium (Ac-Di-Sol$^®$) and sodium starch glycolate (Explotab$^®$) influenced drug release as well. Incorporation of enteric polymers: cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit$^®$ S, resulted in increase the dissolution rate of diltiazem hydrochloride in dissolution media (pH 7.0) due to leaching of enteric polymer (Follonie et al., 1995).

Young et al. (2002) successfully prepared controlled release pellets containing anhydrous theophylline, Eudragit$^®$ 4135 F, microcrystalline cellulose, and polyethylene glycol 8000. The hot-melt extruded pellets were prepared by first cutting an extrudate into symmetrical pellets. The pellets were then spheronized at elevated temperatures. The surface morphology of the pellets was dependent on the spheronization parameters. The melt-extruded matrix pellets exhibited diffusion-controlled drug release. Drug release was influenced by the pH of the release medium due to the solubility of Eudragit$^®$ 4135 F is pH dependent.

The use of wax is advantageous because wax is inert to most pharmaceutical active compounds. Miyagawa et al. (1996) and Sato et al. (1997) studied the controlled release properties of hot melt extruded using diclofenac sodium as model drug and canauba wax as matrix carrier. The additives: hydroxypropylcellulose, Eudragit$^®$ L100 and sodium chloride were investigated as the rate controlling substances. Miyagawa et al. (1996) showed that a wax matrix with high mechanical strength could be produced even

at temperatures below the melting point of the wax. Dissolution of diclofenac from the wax matrix granules was strongly influenced by the formulation. Drug release profiles of diclofenac sodium from the canauba wax matrix granules were influenced by the additive in the granules. Increasing the content of hydroxypropylcellulose or Eudragit® L100 in the wax matrix granules caused an increasing release rate. Drug release from hydroxypropylcellulose/wax matrices was less pH dependent than the system containing wax/Eudragit® L100 because of the insoluble properties of Eudragit® L100 in the pH below 6.0. Sato et al. (1997) concluded that the physicochemical properties of additive such as solubility and swelling characteristics had a significant impact on the properties of wax matrix granules prepared by hot melt extrusion process.

Liu et al. (2001) compared the properties of wax based granules and tablets prepared by hot-melt extrusion to those prepared by high shear melt granulation. The extrudates contained phenylpropranolamine hydrochloride, Precirol®, Sterotex® K, and various excipients: microcrystalline cellulose, lactose, and Emcompress®. The extrudates were passed through a 14-mesh screen to form granules. Hot melt extruded granules were observed to be less spherical than high shear melted granules and had lower densities. Less variability in content uniformity was observed with hot melt extruded granules. Drug release from tablets decreased in the order of using microcrystalline cellulose, lactose, and Emcompress® as the additives. The differences in the dissolution properties of the tablets were attributed to the differences in the solubility, swellability, and density of the filler excipients.

Effervescent granules have been prepared by hot melt extrusion (Lindberg et al., 1988a; Lindberg et al., 1988b; Lindberg et al., 1987; McGinity and Robinson, 2001; Robinson and McGinity, 2000; Robinson et al., 2001). The couple of acid and base that can react and effervesce upon taking up liquid was incorporated in the hot melt extrudable binders such as polyethylene oxide, methyl cellulose, poloxamers and waxs. The rate of effervescence could be controlled by varying the amount of the components in the formulation. Increasing the binder caused less friable granule. Generally, forming a eutectic mixture between the acidic agent and the hot melt extrudable binder before hot melt extruding with the base agent yielded the harder and slower dissolving granules.

Zhang and McGinity (2000) investigated the influence of granule size and drug loading level on the drug release properties of polyvinylacetate matrices by using theophylline as model drug. After hot melt extrusion, extrudates were ground into granules using cryogenic grinder. Increasing granules size caused a decrease in

theophylline release rate. Since the drug was released from the matrix by a diffusion mechanism, the decrease in the drug release rate from the tablets containing larger granules was concluded to be a result of a longer diffusion pathway. The drug loading as high as 50% was able to include in hot melt extruded polyvinylacetate matrices. Polyvinylacetate was not susceptible to degradation by either thermal or shearing stress under the processing conditions.

Hot melt extrusion tablets are easily prepared by cutting the extrudates into a desired size or weight.

Crowley et al. (2004) studied the properties of matrix tablets prepared by direct compression or hot-melt extrusion of binary mixtures of guaifenesin and either fine or coarse particle size ethylcellulose. The slower guaifenesin release was observed with the tablet containing fine particle size ethylcellulose. Hot melt extruded tablets exhibited better sustained drug release than direct compressed tablets. This attributed to the less porosity and more tortuosity of the hot melt extruded tablets.

The properties of polyethylene oxide as a matrices carrier and release properties of chlopheniramine from matrix tablets were investigated (Zhang and McGinity, 1999). The stability of polyethylene oxide was reported as a function of polymer type, temperature and residence time in the extruder. Additional mixing of the components occurred in the barrel of the extruder, because the content uniformity of the extruded tablets was within 99 % to 101 % of the theoretical content. The drug release properties were influenced by molecular weight of polyethylene oxide, drug loading, and polyethylene glycol which was used as a processing aid plasticizer. Drug release from the matrix tablet was controlled by the erosion of polyethylene oxide matrix and the diffusion of the drug through the swollen gel layer at the surface of the tablets. With low drug loading, chlopheniramine was dispersed at the molecular level in the polyethylene oxide matrix and recrystallized at high drug loading levels. Increasing polyethylene glycol increased the release rate of chlopheniramine. Polyethylene glycol hydrated and dissolved faster than polyethylene oxide. The hydration and dissolution rate of the entire matrix system were thus accelerated because of the presence of polyethylene glycol. The presence of the polyethylene glycol also decreased the viscosity of the hydrated gel layer, which facilitated the diffusion of the chlopheniramine from the swollen gel layer surrounding the tablets. Drug release rate did not change with increasing drug loading from 6% to 12%. There was only a slight increase when the drug loading reached 20%. Drug release was significantly reduced when the polyethylene oxide (7 m) was presented in the

polymeric matrix. Thermal stability of polyethylene oxide in hot melt extruded tablets was investigated by Crowley et al. (2002). The stability of polyethylene oxide was dependent on the storage and processing temperature and also the molecular weight of the polymer. Storage of polyethylene oxide above the melting point caused polymer degradation and the degradation process was accelerated as the molecular weight was reduced. The extent of polyethylene oxide degradation was influenced by the processing temperature and the transit time through the extruder. At low screw speed, the thermal degradation was more dominant than the mechanical degradation. On the contrary at high screw speed, the degradation at high screw speed was due to both thermal degradation and mechanical degradation. Stability of polyethylene oxide was improved by incorporating of vitamin E, vitamin E succinate or vitamin E TPGS in the formulations.

Zhu et al. (2004) prepared the hot melt extruded chlopheniramine tablets containing Eudragit® RS, triethylcitrate and glyceryl monostearate. Triethylcitatre and glyceryl monostearate was used as plasticizer and thermal lubricant, respectively, to facilitate the hot melt extrusion process. While triethylcitrate lowered both the Tg and melt viscosity of the molten polymer, glyceryl monostearate had no effect on Tg but decreased only melt viscosity of the molten polymer. Increasing glyceryl monostearate resulted in an increasing drug release rate.

Fukuda et al. (2006b) also prepared the hot melt extruded tablets containing chlopheniramine, chitosan and xanthan gum. Drug release from tablets containing either chitosan or xanthan gum was pH and buffer species dependent and the release mechanism were controlled by the solubility and ionic properties of the polymers. The tablets contained both chitosan and xanthan gum exhibit pH and buffer species independent sustained release. In 0.1N HCl, the tablets formed a hydrogel that retards drug release in subsequent pH 6.8 and 7.4 phosphate buffers even when media contained high ionic strength. As the tablets without chitosan did not form a hydrogel structure, thus loss of drug releases retardation.

Hot melt extruded mini-matrix containing ibuprofen or theophylline and Kollidon® SR was investigated by Özgüney et al. (2009). Ibuprofen exhibited the plasticizing effect for Kollidon® SR by reducing the Tg and maximum processing torque, whereas theophylline did not have the plasticization effect. Ibuprofen was dissolved in polymer up to 35% drug loading, while theophylline was just dispersed in the polymer matrix. Increasing drug loading and inclusion of Klucel® LF resulted in an increase drug release.

Brabander et al. (2004) compared the bioavailability of ibuprofen from hot-melt extruded mini-matrices based on ethyl cellulose and a hydrophilic excipient, xanthum gum compared with a commercially available sustained release product (Ibuslow®). The sustained release behavior was obtained from the formulation consisted of 30% ibuprofen, 35% ethyl cellulose, and 35% hydroxypropyl methylcellulose and the formulation contained 60% ibuprofen, 20% ethyl cellulose, and 20% xanthum gum. Although the experimental formulations demonstrated significantly lower C_{max}, T_{max}, and $AUC_{0—24\ h}$ values than values of commercial formulation, the relative bioavailability of both experimental formulations was about 80%.

Verhoeven et al. (2009a) used hot melt extrusion to prepare mini-matrices with sustained release properties of metoprolol tartrate. Ethylcellulose was used as a matrix carrier and polyethylene glycol or polyethylene oxide was included to increase drug release. Increasing these hydrophilic polymer increased drug release. The influence of hydrophilic polymer molecular weight on drug release depended on the polymer amount. The limited sustained release and relatives bioavailabilities of 66.2% and 148.2% were obtained for 5% and 20% polyethylene oxide hot melt extruded mini-matrices, respectively.

Almeida et al. (2011a) characterized the different grades of ethylene vinyl acetate on the hot melt extrusion processing. Polymer crystallinity, polymer flexibility, Tg and Tm were influenced by the vinyl acetate content. Matrices containing 50% metoprolol tartrate resulted in smooth surface extrudate, whereas at 60% drug loading severe surface defects were observed. Increasing drug release with increase processing temperature was reported and explained by changing the crystalline drug into amorphous drug. Therefore, drug release mechanism was a complex combination of drug and polymer crystallinity, drug loading which was responsible for the matrix porosity and extrusion temperature which affected the ratio of amorphous and crystalline drug. The total matrix porosity was decreased after dissolution due to the elastic rearrangement of the polymer. Ethylene vinyl acetate was not modified during GI transit nor affected the GI ecosystem following oral administration.

Using enteric polymer as matrix carrier, the enteric matrices can be produced. The advantage of hot melt extruded enteric matrices over the matrices prepared by conventional method is less burst drug release. This is attributed to the dense structure of hot melt extruded enteric matrices.

The physicochemical properties of melt extruded rods, tablets and pellets containing Acryl-EZE® were studied by Young et al. (2005a). The influence of gelling agent, hydroxypropylmethylcellulose and carbomer on drug release was also investigated. The pH-dependent release profiles were observed due to the insolubility of polymer in acidic medium and the solubility in higher pH. The kinetic of drug release was changed with including gelling agent. Rapid release from hot melt extruded pellets than the tablets was achieved and attributed to increasing in surface area to volume ratio.

Yang et al. (2008) used hot melt extrusion technique to prepare the enteric and sustained release tablets containing ketoprofen and Eudragit® L100. Diethyl phthalate was used as a plasticizer to reduce the processing temperature. Ketoprofen was homogeneously dispersed in the matrix in a non-crystalline state. Drug release was below 3% in 0.1N HCl and sustained release for 6-12 h in pH 6.8 buffer was obtained with the direct cutting of the extrudates and by compressing the pulverized extrudates. The difference in their porosity resulted in difference drug release mechanism. Drug release from the cut tablets was controlled by erosion while the drug was released from compressed extrudate tablets by erosion and diffusion mechanism.

Bruce et al. (2005) prepared the colonic dosage form by using Eudragit® S100 as matrix carrier for delivery of 5-aminosalicylic acid. Attributed to the high Tg of polymer, plasticizer (triethylcitrate) was needed to reduce the Tg thus polymer extrusion at lower processing temperature was possibly done. The amount of plasticizer also had an influence on the drug release rate due to the leaching during drug release. Citric acid monohydrate was also used to plasticize Eudragit® S100. Additionally, drug release retardation was found and due to a decrease in the micro-environmental pH thus suppresses polymer ionization and dissolution. The influence of plasticizer on the properties of Eudragit® S100 hot melt extruded matrix pellets was also studied by Schilling et al. (2010a). The effect of three plasticizers: triethylcitrate, methylparaben, and polyethylene glycol 8000 at 10% and 20% on the properties of hot melt extruded Eudragit® S100 properties were investigated. All plasticizers produced similar reduction in polymer melt viscosity and presented in amorphous state. The drug release in pH 1.2 was influenced by the aqueous solubility of plasticizer. Drug release in pH 7.4 was due to the dissolution and was not influenced by the low levels of plasticizer, but increase with increasing plasticizer level. The tensile strength of the hot melt extruded pellets decreased with the present of plasticizers.

Schilling et al. (2010b) successfully prepared enteric matrix pellets with a diameter below 1 mm containing 30% theophylline by hot-melt extrusion when Eudragit® S100 plasticized with either triethyl citrate or methylparaben. Enteric polymer: Eudragit® L100-55, L100, S100, Aqoat® LF, and HF were investigated as matrix former in this study. Eudragit® S100 exhibited superior gastric protection and acceptable processability. Efficient plasticization of Eudragit® S100 was necessary for facilitating the hot melt extrusion process. The use of water soluble plasticizer caused a loss of gastric protection. The release rate of theophylline in pH 7.4 buffer was faster for pellets that were prepared with efficient plasticizer. Pellets prepared with efficient plasticizers had less porosity and homogeneously drug dispersion in original polymorphic form whereas the one plasticized with less efficient plasticizer were processed at elevated temperature and resulted in physical instabilities in the form of recrystallization at room temperature.

Mehuys et al. (2005) developed an alternative technique for enteric coating consisting of the hot melt extruded coating polymer. Pre-plasticized polymer, polyvinyl acetate and hydroxypropylmethylcellulose acetate succinate was extruded into hollow cylinders. The hollow pipes were filled with a model drug, hydralazine before sealing both open ends by using the hot pincers. The capsules showed excellent gastro-resistant, since no drug release in 0.1N HCl was observed. Previously, this technique was also used to prepare the sustained release system consisting of a hot melt extruded ethylcellulose pipe surrounding a drug-containing hydroxypropylmethylcellulose-Gelucire® 44/14 core. During the dissolution the hydroxypropylmethylcellulose-Gelucire® 44/14 core forms a gel plug which released the drug through the open ends of the pipe by erosion (Mehuys et al., 2004b). Modifying the dimension of the pipe and the core formulation caused a change of drug release. Drug release profile and mechanism was independent on drug solubility. Increasing drug loading slightly increased drug release rate but did not alter the release mechanism (Mehuys et al., 2004a). An ideal sustained release profile with constant plasma level maintained over 24 h was studied in dogs. This system increased 4 fold bioavailability when comparing with a commercial sustained release formulation (Mehuys et al., 2004a).

A novel application of hot melt extrusion for the preparation of monolithic matrices containing enteric-coated particles was investigated by Schilling and McGinity (2010). The particles coated with Eudragit® L30D-55 were incorporated into a water-soluble matrix using hot melt extrusion. Poloxamer and polyethylene oxides were studied as the matrices carrier. The delay-release properties of the incorporated particles were

independent of the particle tensile strength, but influenced by the carrier polymer. The miscibility between the polymer carrier and the coating polymer associated with the increase of film permeability and drug release in acidic medium. Poloxamer 407 exhibited lower miscibility with Eudragit® L30D-55 and the matrices containing up to 40% enteric pellets were compliant with the USP requirements.

A floating sustained release dosage form was reported to be prepared by hot melt extrusion. Nakamichi et al. (2001) prepared a floating sustained release tablet containing nicardipine HCl and hydroxypropyl methylcellulose acetate succinate. By adjusting the position of the high-pressure screw elements near the die outlet and the barrel temperature the puffed extrudate with small and uniform pores was obtained. The puffed tablets had excellent floating ability and mechanical strength in acid release medium. In pH 6.8 rapid dissolution of drug and loss of buoyancy were observed.

Fukuda et al. (2006a) investigated the influence of sodium bicarbonate on the physicochemical properties of controlled release hot melt extruded tablet. The tablets composed of Eudragit® RS PO and sodium bicarbonate showed sustained release properties and floated for 24 h. The floating properties were due to the porous structure since carbondioxide was generated due to the thermal decomposition of sodium bicarbonate during processing.

In conclusion, hot melt extrusion is a potential technique for oral controlled drug release dosage form production. Solventless and continuous process makes it superior to the conventional techniques. The mixing in an extruder during processing resulted in homogeneous drug distribution. Since the process involves the use of heat and high pressure therefore the materials must be stable at the processing condition. Recently increasing number of publications and patents reveals the growing interest in using hot melt extrusion for pharmaceutical manufacturing and ascertains the hot melt extrusion as the promising process of choices for the development of oral controlled release dosage forms.

1.5. Research Objectives

The purposes of this work were:

1. to compare the controlled release properties of matrices prepared by hot melt extrusion, wet granulation and direct compression and to investigate the influence of polymer type, drug solubility, drug loading and tablet size on drug release. In addition, an applicability-map was created in order to be a guideline of suitable preparation technique for controlled release matrices.

2. to investigate the feasibility of hot melt extrusion to produce mini-matrices with both enteric and controlled release properties and the potential of hot melt extruded mini-matrices for colonic drug delivery.

3. to study the effect of propranolol HCl on the gastric resistant failure of Eudragit L100-55 coated propranolol HCl pellets and to investigate the reason of the failure by studying the interactions between propranolol HCl and Eudragit L100-55.

2. Materials and Methods

2.1. MATERIALS

2.1.1. Model drugs

Metoprolol tartrate (MOEHS IBÉRICA S.L., Barcelona, Spain), diltiazem HCl (PCAS Division Seloc France, Limay, France), propranolol HCl (K.-W.Pfannenschmidt GmbH, Hamburg, Germany), caffeine anhydrous (BASF AG, Ludwigshafen, Germany), diprophylline (BASF AG, Ludwigshafen, Germany), theophylline anhydrous (BASF AG, Ludwigshafen, Germany), carbamazepine (Fabrica Italiana Simetici, Italy), 5-aminosalicylic acid (5-ASA, Pharmazell GmbH, Raubling, Germany)

2.1.2. Polymers

Ammonio methacrylate copolymer (RS, Eudragit®RS PO, Evonik Industries AG, Darmstadt, Germany), methacrylic acid - ethyl acrylate copolymer (Eudragit®L 100-55, Evonik Industries AG, Darmstadt, Germany), methacrylic acid-methyl methacrylate copolymer (Eudragit®S 100, Evonik Industries AG, Darmstadt, Germany), hypromellose acetate succinate-LF, -MF, and -HF (HPMCAS, Aqoat®, Harke Pharma GmbH, Mülheim/Ruhr, Germany), hypromellose phthalate-HP50 and HP-55 (HPMCP, Harke Pharma GmbH, Mülheim/Ruhr, Germany), hydroxypropylmethylcellulose (Methocel™ E5, Colorcon Ltd., Orpington, UK), ethycellulose (EC, Ethocel™ Standard 7 cP premium, Dow Chemical Company, Midland, MI, USA), polyvinyl acetate/polyvinylpyrrolidon (KSR, Kollidon® SR, BASF AG, Ludwigshafen, Germany)

2.1.3. Plasticizer

Triethyl citrate (TEC, Morflex, Inc., Greensboro, NC, USA)

2.1.4. Surfactants

Sodium lauryl sulfate (Carl Roth GmbH + Co.KG, Karlsruhe, Germany), cetrimonium bromide (Merck KGaA, Darmstadt, Germany)

2.1.5. Other excipients

Microcrystalline cellulose pellets (MCC core 710-850 μm , Cellets® 780, Harke Pharma, Mülheim/Ruhr, Germany), non-parials, sieved cut size 425-500 μm (Suglets®, NP Pharm S.A.S., Bazainville, France), magnesium stearate (Herwe Chemisch-technische Erzeugnisse, Sinsheim Dühren, Germany), fumed silica (Aerosil® 200, Evonik Industries AG, Darmstadt, Germany)

2.2. METHODS

2.2.1. Comparison of controlled release properties of matrices prepared by hot melt extrusion, wet granulation and direct compression

2.2.1.1. Hot melt extrusion

The polymers were pre-plasticized by mixing polymer and TEC with a mortar and pestle. Drug was added and the mixture was then processed in a co-rotating twin screw extruder (30 rpm, Minilab Haake Rheomex CTW 5, Thermo Electron (Karlsruhe) GmbH, Karlsruhe, Germany). The molten mixture was extruded through a 1.83 mm diameter rod die. After air cooling, the extrudates were manually cut into pieces with 3 mm length. TEC content and processing temperature is shown in **Table 7**.

Table 7   TEC content and processing temperature for hot melt extruded matrices

Polymer	TEC, % (based on polymer)	Processing temp.,°C
Eudragit® RS	10	120
Kollidon® SR	10	120
Ethylcellulose	10	130
Ethylcellulose (containing metoprolol tartrate)	30	90

In order to simulate hot melt extrudates of a larger size, 9 mm Eudragit RS tablets containing propranolol HCl were prepared by milling the respective 2 mm extrudates (Retsch MM 2000 small ball mill, Retsch GmbH, Haan, Germany) with the aid of liquid nitrogen. Then 200 mg of the powder was filled in a flat 9 mm die, molten in the hot air oven at 150 °C for 20 min and then immediately compressed with 3 kg force.

2.2.1.2. Wet granulation

Wet granulation was manually prepared using a mortar and pestle. Drug and polymer powder were mixed before wet-massing with a 15 % w/w polymer solution (isopropranol: water; 88:12 w/w). The wetted mass was manually passed through a 500

μm screen and the granules were dried at 60 °C for 3 h. The dried granules were sieved again (500 μm) to separate agglomerated granules. Then the granules were lubricated for 2 min in a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) with 1 % w/w magnesium stearate and 1 % w/w fumed silica. Biconvex mini-tablets of 2 mm diameter and 10 mg weight were compressed (Korsch EK0, Korsch AG, Berlin, Germany) to a hardness of 50-100 N.

2.2.1.3. Direct compression

Prior compression, drug and polymer were mixed using a mortar and pestle. The mixture was then lubricated and compressed to mini-tablets as described above in wet granulation (2.2.1.2.).

2.2.1.4. Drug release

Drug release study (n=3) was performed in a paddle apparatus (USP XXX III, 37 °C, 50 rpm) (Vankel® VK 600, Vankel Industries, Edison, NJ, USA) using 900 ml pH 6.8 phosphate buffer for 24 h. Drug release was measured using a UV-spectrophotometer (UV-2101PC, Shimadzu Scientific Instrument, Columbia, MD, USA) at 238, 270, 272, 274, 285, 288 nm for diltiazem HCl, theophylline anhydrous, caffeine anhydrous, metoprolol tartrate, carbamazepine and propranolol HCl, respectively. Drug release rates were obtained from the linear slope of drug release ($\leq$ 60%) versus square root of time plots.

2.2.1.5. Drug solubility

An excess amount of drug was added to 5 ml pH 6.8 phosphate buffer and shaken in an incubator (37 °C, 80 rpm, GFL 3033, GFL Gesellschaft für Labortechnik, Burgwedel, Germany). After 48 h, the pH of suspension was adjusted to initial pH and, if necessary, further shaken. The suspension was then filtered (0.2 μm), diluted and analyzed by UV-spectrophotometer (Shimadzu UV-2101 PC, Shimadzu Europa GmbH, Duisburg, Germany) as described in 2.2.1.4.

2.2.1.6. Differential scanning calorimetry (DSC)

The thermal properties were characterized with a differential scanning calorimeter (Mettler DSC 821^e with STAR® software, Mettler Toledo, Giessen, Germany) under a nitrogen atmosphere at a heating rate of 10 °C/min. The samples (5-10 mg) were weighed

into 40 µl aluminum pans. The pans were crimped with lids through which a pin hole was made for the escape of water vapor.

2.2.1.7. Similarity factor (*f₂*)

The similarity of drug release profiles were evaluated using the similarity factor (*f₂*) calculated as follow:

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

where n is the number of observations, R_t represent the percentage of drug released from the reference profile and T_t is the percentage of drug release from the test profile. Drug release profiles are judged similarly when the f_2 is $\geq$ 50.

2.2.2 Hot melt extrusion for enteric and controlled release mini-matrices preparation

2.2.2.1. Hot melt extrusion

The polymers were pre-plasticized by mixing polymer and TEC with a mortar and pestle. Drug was added and the mixture then processed in a co-rotating twin screw extruder (Minilab Haake Rheomex CTW 5, Thermo Electron (Karlsruhe) GmbH, Karlsruhe, Germany) at 30 rpm screw speed. The torque was measured as an indicator of the processability of each formulation. The molten mixture was extruded through a 1.83 mm diameter rod die. After air cooling, the extrudates were manually cut into pieces of 3 mm length. The die swell was calculated as follow:

$$\text{Die swell, } \% = \frac{diameter_{matrix} - diameter_{die}}{diameter_{die}} \times 100$$

2.2.2.2. Drug release

Drug release (n=3) was studied in a paddle apparatus (USP 30, 37 °C, 50 rpm) (Vankel® VK 7010, Vankel Industries Inc., Edison, NJ, USA) using 900 ml 0.1N HCl for 2 h before changing to 900 ml pH 6.8 phosphate buffer. In case of 5-ASA, drug release

was conducted in 0.1N HCl (2 h) then in pH 6.8 phosphate buffer (3 h) and followed by pH 7.4 phosphate buffer for 24 h. Drug release was measured using a UV-VIS spectrophotometer (Varian Cary 500 UV/Visible spectrophotometer, Varian Deutschland GmbH, Darmstadt, Germany) at 275 nm, 270 nm, 285 nm and 328 nm for diprophylline, theophylline, carbamazepine and 5-aminosalicylic acid, respectively.

2.2.2.3. Differential scanning calorimetry (DSC)

The thermal properties of the extrudates were characterized with a differential scanning calorimetry (Mettler DSC 821^e with STAR$^®$ software, Mettler Toledo, Giessen, Germany) under a nitrogen atmosphere at a heating rate of 10 °C/min. The samples (5-10 mg) were weighed into 40 µl aluminum pans. The pans were crimped with lids through which a pin hole was made for the escape of water vapor. The heat of fusion (ΔH_f) of drug melting peak was use to calculate the remaining of crystalline drug in the matrix as follow:

$$\text{Crystalline drug remaining} = \frac{\Delta H_f(matrix)}{\Delta H_f(physical.mixture)}$$

2.2.2.4. Drug solubility

An excess amount of drug was added to 5 ml 0.1N HCl, pH 6.8 or pH 7.4 phosphate buffer and shaken in an incubator (37 °C, 80 rpm, GFL 3033, GFL Gesellschaft für Labortechnik, Burgwedel, Germany). After 48 h, the pH of the suspension was adjusted to 1, 6.8 or 7.4, if necessary, and further shaken. The suspension was then filtered (0.2 µm), diluted and analyzed UV-spectrophotometrically as described under **2.2.2.2.**

2.2.2.5. Mechanical properties

The mechanical properties of the matrices upon compression were determined with a texture analyzer (TAXT Plus, Winopal Forschungsbedarf GmbH, Ahnsbeck, Germany) (n = 10). A flat, cylindrical probe (3 mm diameter) was fixed to a 50 kg load cell. The test parameters were as follows: pretest speed 10 mm/sec, test speed 0.1 mm/sec, posttest speed 10 mm/sec, target mode distance 26 mm. Force - displacement curves were recorded. In wet state, the matrices were kept in 0.1N HCl and shaken in an

incubator (37 °C, 80 rpm, GFL 3033, GFL Gesellschaft für Labortechnik, Burgwedel, Germany) for 2 h. Before measurement, the excess medium was blotted using filter paper.

2.2.2.6. Erosion study

Erosion studies in pH 6.8 phosphate buffer were performed at 50 rpm and 37 °C (Vankel® VK 7010, Vankel Industries Inc., Edison, NJ, USA). The initial weight (w_i), the wet weight (w_w) and weight after drying (w_d) (80 °C until constant weight) was calculated as percentage of mass remaining and medium content as follows:

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

$$\text{Medium content (\%)} = \frac{w_w - w_d}{w_w} \times 100$$

2.2.3 Enteric failure of Eudragit L100-55 coated propranolol HCl pellets

2.2.3.1. Pellet preparation

Drug-loaded pellets (propranolol HCl or diprophylline, 10-30 % w/w drug loading based on core weight were prepared by layering a drug-binder solution/suspension (16.4 % w/w drug, 1.6 % w/w hydroxypropylmethylcellulose, 41.0 % w/w isopropranol, 41.0 % w/w water) on MCC cores in a fluidized bed coater (Aeromatic® Strea1, Aeromatic AG Muttenz, Switzerland). The layering conditions were: product temperature 45-50 °C, outlet temperature 38-40 °C, nozzle diameter 1.2 mm, spray pressure 1.5 bar, spray rate 12.3 g/min, final drying at 40 °C for 15 min.

In addition, propranolol HCl pellets (60 % w/w drug loading) on non-pareils (425-500 μm) were prepared with the same procedure as described above.

The drug-layered pellets were coated with ethanolic Eudragit® L100-55 solution (6.25 % w/w solid content), plasticized with 10 % w/w TEC based on polymer, in a fluidized bed coater (Mini-Glatt®, Glatt GmbH, Binzen, Germany) to a predetermined coating level (1.8-7.2 mg/cm²). The coating conditions were: inlet temperature 30 °C, outlet temperature 23-25 °C, nozzle diameter 1.2 mm, spray pressure 0.9 bar, spray rate 0.85 g/min, final drying at 25 °C for 15 min.

For comparison, one batch of drug-layered pellets was seal-coated prior to the usual coating step with aqueous hydroxypropylmethylcellulose solution (7.0 % w/w solid content) in a fluidized bed coater (Mini-Glatt®, Glatt GmbH, Binzen, Germany) until 1.8 mg/cm² seal-coating level was obtained. The coating conditions were: inlet temperature 68 °C, outlet temperature 45 °C, nozzle diameter 1.2 mm, spray pressure 0.9 bar, spray rate 1 g/min, final drying at 45 °C for 15 min.

2.2.3.2. Drug release

Dissolution studies (n=3) were performed in a USP 30 paddle apparatus (Vankel® VK7010, Vankel Industries Inc., Edison, NJ, USA) (900 ml, 0.1 N HCl, 0.001 N HCl, water or pH 6.8 phosphate buffer, 37 °C, 100 rpm). The amount of drug released was determined by a UV spectrophotometer (Varian Cary 500 UV/Visible spectrophotometer, Varian Deutschland GmbH, Darmstadt, Germany) at a wavelength of 288 and 275 nm for propranolol HCl and diprophylline, respectively.

2.2.3.3. Pellet morphology

Macroscopic pictures of coated pellets before and after (dissolution) drug release studies were taken by a macroscope (DFK 31F03 camera, The Imaging Source Europe GmbH, Bremen, Germany coupled with an image analysis software (IQ Easy measure®, INTEQ Informationstechnik GmbH, Berlin, Germany).

2.2.3.4. Fourier transform infrared spectroscopy (FTIR)

The interaction between propranolol HCl and Eudragit® L100-55 was evaluated using an FTIR spectrophotometer (Excalibur 3100 FT-IR, Varian Inc., Palo Alto, CA, USA) equipped with a diamond crystal ATR unit (Pike MIRacle, Pike Technologies, Madison, WI, USA). Computer-based processing of the collected data was performed with the spectrometer software (Resolutions Pro, version 4.0, Varian Inc., Palo Alto, CA, USA). The samples were (i) drug-polymer complex, which was prepared by mixing solutions of propranolol HCl and Eudragit® L100-55 in pH 6.8 phosphate buffer at different ratios and stirring overnight. The precipitate was then collected and washed with deionized water before drying in a hot air oven at 60 °C, (ii) sample prepared by dissolving Eudragit® L100-55 in concentrated propranolol HCl solution, deionized water or 0.1N HCl. The solutions were then poured on a Teflon sheet and dried at ambient conditions for 1 day before drying in a hot air oven at 60 °C.

2.2.3.5. Surface tension measurement of drug/surfactant solutions

The surface tension of propranolol HCl and diprophylline solutions (Milli Q water) at various concentrations was determined at room temperature with a Krüss K9 tensiometer (Krüss GmbH, Hamburg, Germany) using the platinum ring method (du Nouy's) (n=2).

2.2.3.6. Drug solubility

An excess amount of drug was added to 5 ml 0.1 N HCl and shaken in an incubator (37 °C, 80 rpm, GFL 3033, GFL Gesellschaft für Labortechnik, Burgwedel, Germany)(n=2). After 48 h, the pH of the suspension was adjusted to the initial pH, if necessary, and further shaken. The suspension was then filtered, diluted and analyzed by a UV-spectrophotometer (Shimadzu UV-2101 PC, Shimadzu Europa GmbH, Duisburg, Germany) at wavelengths of 275 and 288 nm for diprophylline and propranolol HCl, respectively.

2.2.3.7. Polymer solubility in propranolol HCl or surfactant solutions

Polymer powder was gradually added to solutions of propranolol HCl or surfactant in 0.1 N HCl (50 mg surfactant/ml). The sample tubes were shaken (SM shaker, Edmund Bühler GmbH, Hechingen, Germany) until a clear solution was obtained prior to adding more polymer powder. The maximum amount of polymer added before the solution became turbid was taken as the solubility value.

2.2.3.8. Determination of the mean micelle size

The mean micelle size was determined by photon correlation spectroscopy (PCS) using a Malvern Nanosizer ZS (Malvern Instruments Ltd., Worcestershire, UK). The detection optics was set at a position of 173°. The samples were prepared by dissolving 0.5 % or 1 % w/v Eudragit L100-55 in 10 ml propranolol HCl, cetrimonium bromide and sodium lauryl sulphate solution (100 mg/ml) and shaken overnight (SM shaker, Edmund Bühler GmbH, Hechingen, Germany). The particle sizes were computed using the Stokes–Einstein equation.

3. Results and Discussion

3.1. Comparison of controlled release properties of matrices prepared by hot melt extrusion, wet granulation and direct compression

3.1.1. Introduction

Oral solid dosage forms are more preferable due to their convenient administration, easy handling, physical and chemical stability and lower production cost with high throughput production (Andrews, 2007). Controlled release dosage forms are developed with the aim to reduce the dose frequency and to maintain the therapeutic drug level in blood plasma for an extended time period (Jantzen and Robinson, 1996).

Various techniques have been used to prepare controlled release formulations, e.g. coating, matrices, and osmotic systems, (Lecomte et al., 2004; Santus and Baker, 1995; Sriwongjanya and Bodmeier, 1998; Wesseling and Bodmeier, 1999). Among these, the controlled release matrix tablets are the most accepted because of the simplest and least expensive systems (Kim, 2000). The controlled release matrix tablets can be produced by convention technique, direct compression or wet granulation. Depending on the matrix carrier, they are classified into water-soluble and water-insoluble matrix tablets. Examples for water-soluble materials used in matrix tablets are hydroxypropylmethylcellulose (HPMC), polyacrylic acid (e.g. Carbopol®) and polyethylene oxide (POE). Water-insoluble matrix tablets are composed of e.g. waxes or synthetic resins such as methacrylate copolymers. Drug release from water-insoluble matrix tablets involves the penetration of release media into the polymer matrix, dissolution and diffusion of drug through the matrices channels without changes in matrix appearance. For that reason water-insoluble matrix tablets are less affected by the gastrointestinal motility than water-soluble ones which are slowly dissolved in the gastrointestinal fluid. (Chang and Choi, 2011).

Hot melt extrusion is a continuous, solvent-free technique used for processing thermoplastic polymers into matrices with the aid of heat and pressure (Crowley et al., 2007). It has been used to prepare oral controlled release matrices such as tablets and pellets (Almeida et al., 2011b; Brabander et al., 2003; Follonie et al., 1995; Fukuda et al., 2006b; Mehuys et al., 2004b). Drug release from hot melt extruded matrices is slower than from compressed matrices due to the dense structure (Crowley et al., 2004; Young et al., 2002).

The Higuchi equation has been successfully used to describe the kinetics of drug release from matrix systems (Higuchi, 1963):

$$Q = \sqrt{D \frac{\varepsilon}{\tau}(2C_o - C_s)C_s t} = \sqrt{D_{app}(2C_o - C_s)C_s t} = k\sqrt{t} \quad (1)$$

Q is amount of drug released at time t per unit surface area, D is the drug diffusivity in the permeating medium, C_0 is the initial drug concentration in the matrix, C_s is the saturation drug concentration, ε is the porosity, τ is the tortuosity of the matrix, D_{app} is the apparent diffusivity and k is the dissolution rate constant. Accordingly, drug release can be influenced by varying the initial drug loading in the matrix, drug solubility, preparation method and the polymer type used as matrix carrier. In the present study, the influence of the preparation methods (i.e., direct compression, wet granulation and hot melt extrusion), polymer type, drug solubility, drug loading and tablet size on drug release was investigated. The feasibility and limitations of the different preparation methods for producing controlled release dosage forms of drugs with various solubilities were also examined. Furthermore, an applicability-map was created in this study in order to select the suitable preparation technique for controlled release matrices with desired release profiles.

3.1.2. Results and discussion

In hot melt extrusion, molten thermoplastic polymer and drug were blended and extruded through the die, resulting in dense matrices. Lower porosity and high tortuosity of matrices were attributed to the intense mixing within extruder (Crowley et al., 2004; Saraiya and Bolton, 1990; Young et al., 2002). As a result, hot melt extrudates provided slower drug release comparing to wet granulation and direct compression (**Fig 4a-c**).

Drug release from extrudates was affected by the polymer type. The release was in the order: Eudragit® RS > Kollidon® SR > ethylcellulose. Hydrophilic and swellable Eudragit® RS provided the highest drug release because of its water permeability. Kollidon® SR contains 80 % insoluble polyvinyl acetate and 19 % soluble polyvinylpyrrolidone. The soluble part could dissolve and leach out, resulting in porous polyvinyl acetate matrices. This led to a faster release compared to insoluble ethylcellulose matrices. The influence of polymer type on drug release was clearly seen with hot melt extruded matrices (**Fig 4a).** Slight difference of drug release with different polymer types from wet granulation and direct compression was probably explained by the porosity of the matrices (**Fig 4b, c**). Interestingly, the fastest drug release from wet granulated Kollidon® SR matrices was presented (**Fig 4b**). This could be explained by the

migration of polyvinylpyrrolidone to the surface of granules during the drying process, leading to fast hydration and thus more porous matrix tablets during dissolution (Kranz and Wagner, 2006). A linear relationship between drug release and square root of time irrespective of the preparation method indicated that the drug release was controlled by diffusion (**Fig 5**).

Drug solubility (**Table 8**) highly influenced the drug release from matrices. Increasing drug solubility resulted in an increased drug release (**Fig 6**). Sustained release over 24 h for highly soluble drugs such as metoprolol tartrate was achievable with the denser hot melt extruded mini-matrices. However, a limitation for the hot melt extrusion of metoprolol tartrate containing matrices was the applied heat. The preparation of metoprolol tartrate (Tm = 123 °C)/ethylcellulose at 130 °C resulted in the separation of molten drug and polymer. The molten polymer was sticking onto the screws while the liquid drug dripped at the die. Higher TEC was incorporated in order to reduce the processing temperature below the melting point of metoprolol tartrate. The release of propranolol HCl from wet granulated matrices was faster than from direct compressed matrices (**Fig 6b, c**) because of tablet disintegration. This was attributed to the drug migration and re-crystallization on the surface of the granules during the granule drying process thus causing the loss of binding force between granules upon drug release (Shlieout and Zessin, 1996).
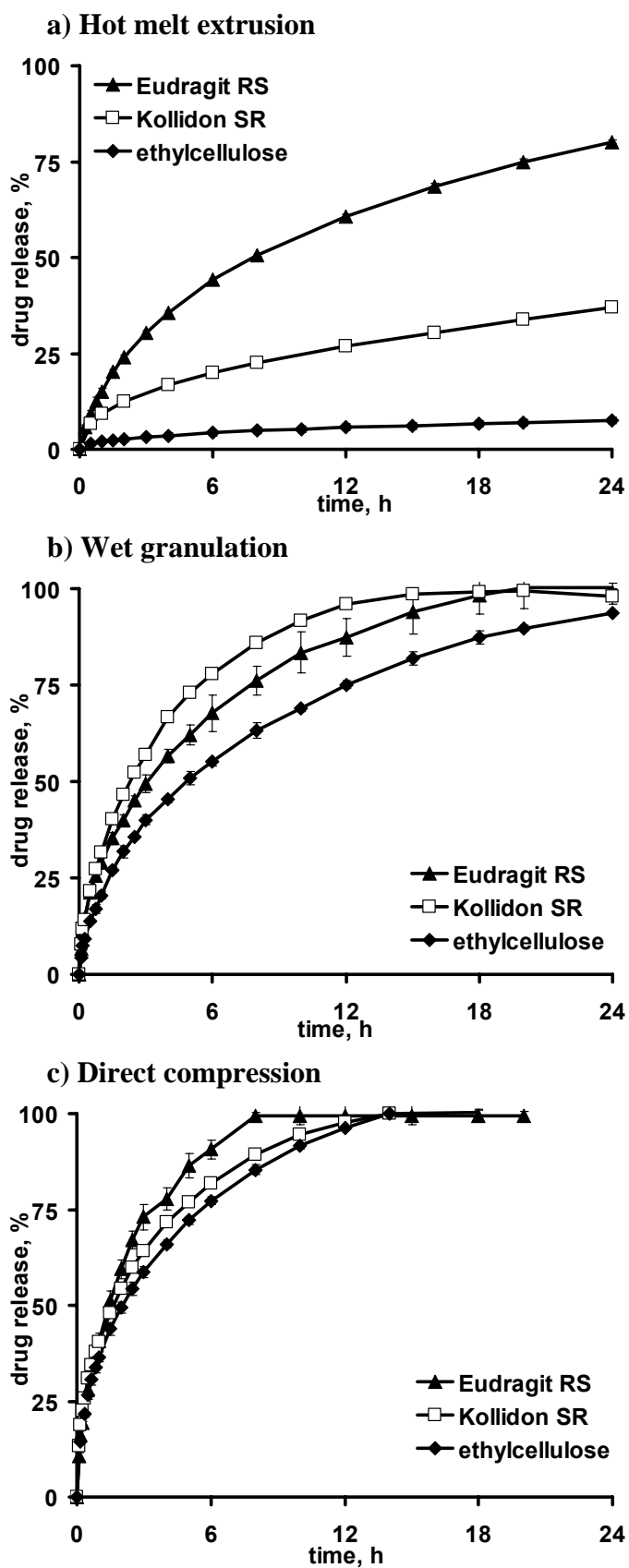
a) Hot melt extrusion

b) Wet granulation

c) Direct compression

Fig 4 Influence of polymer type and preparation method on drug release containing 50 % theophylline (2 mm tablets)
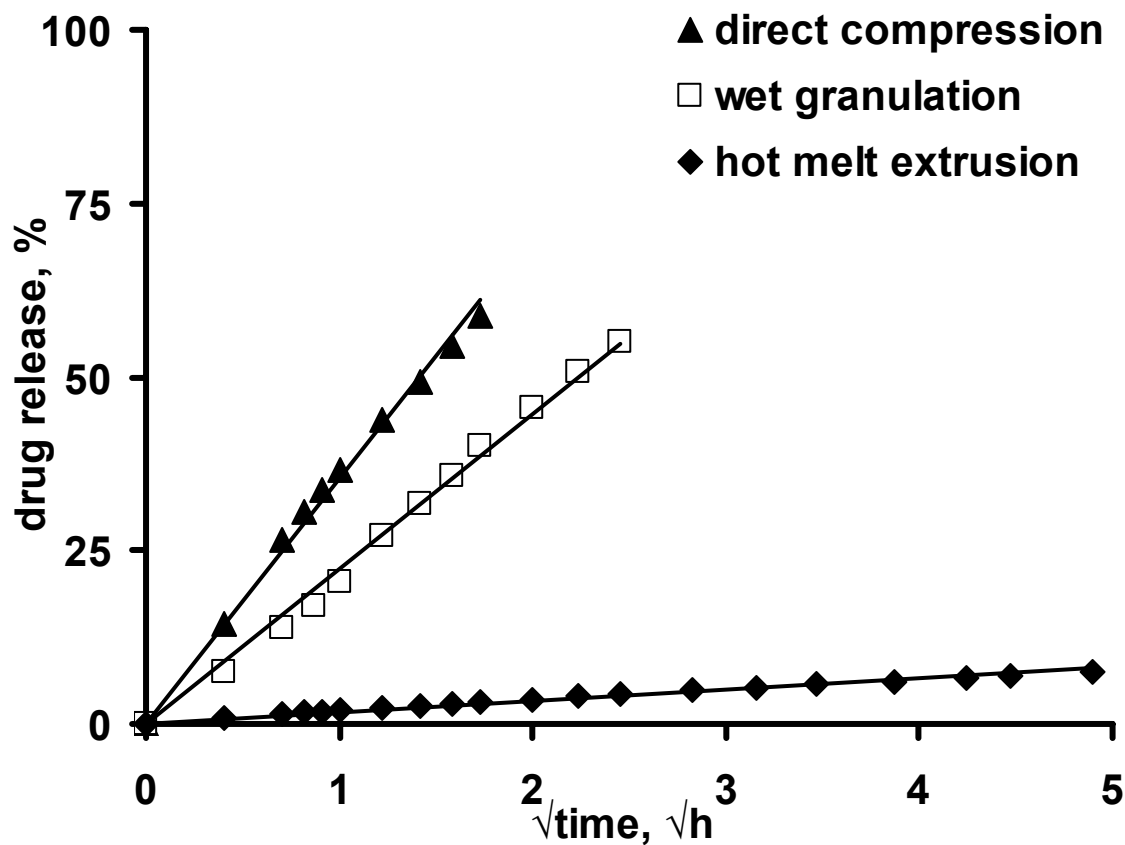
Fig 5 Drug release from ethylcellulose matrices prepared by hot melt extrusion, wet granulation and direct compression as a function of the square-root of time (50 % theophylline)

Table 8   Solubility of the model drugs in pH 6.8 phosphate buffer

Drug	Solubility, mg/ml
metoprolol tartrate	>1000
diltiazem HCl	437*
propranolol HCl	250
caffeine	35
theophylline	12
carbamazepine	0.2

*solubility in water, 37 °C (Sugimoto et al., 2006)

a) Hot melt extrusion

b) Wet granulation

c) Direct compression
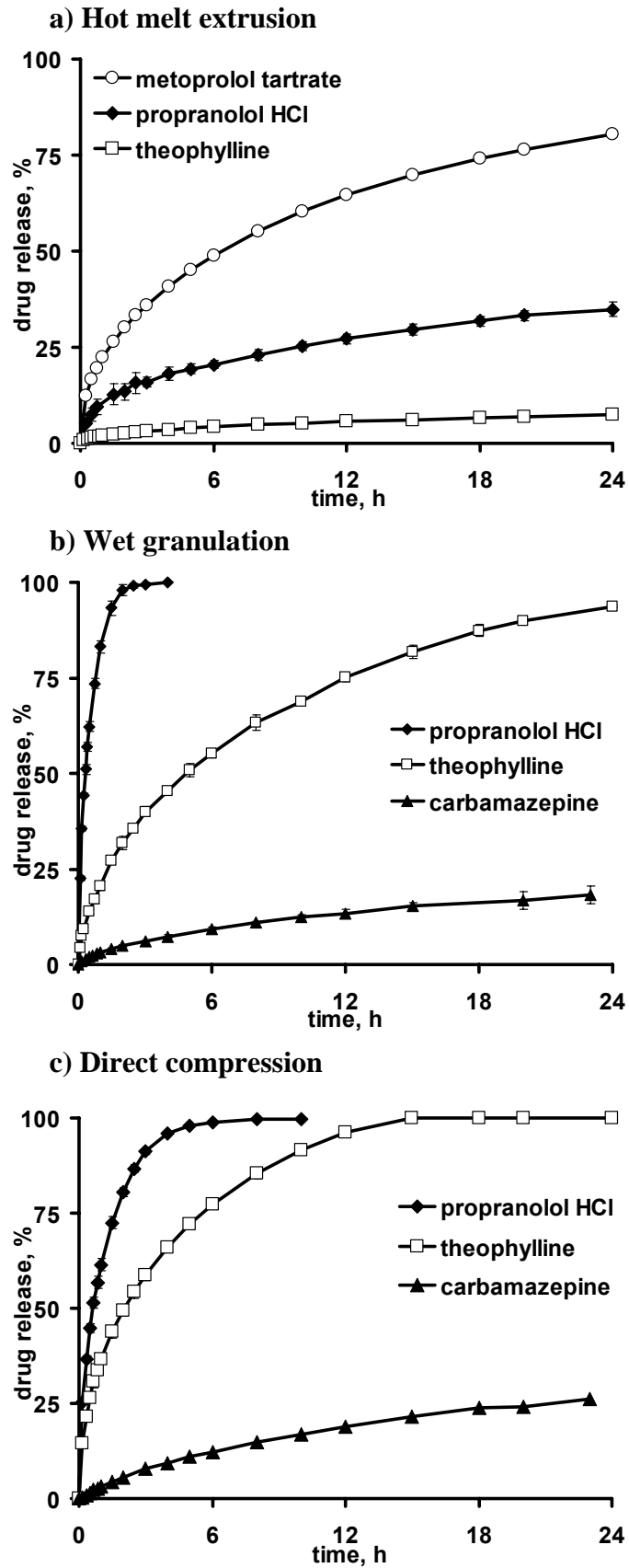
Fig 6 Influence of drug type and preparation method on drug release from ethylcellulose matrices with 50 % drug loading

Another potential limitation of hot melt extrusion processes was the drug loading capacity. While wet granulated and direct compressed ethylcellulose matrices could contain up to 97 % and 90 % drug loading, respectively, hot melt extruded matrices could contain up to 50 % drug for propranolol HCl, theophylline and carbamazepine or 60 % for of metoprolol tartrate. Above these loadings, severe surface fracture of the hot melt extruded matrices was observed. The higher metoprolol tartrate loading may be due to an entrapment of partially melted drug which was probably induced by the friction heat during processing. As expected, increasing the drug loading increased the drug release (**Fig 7**).
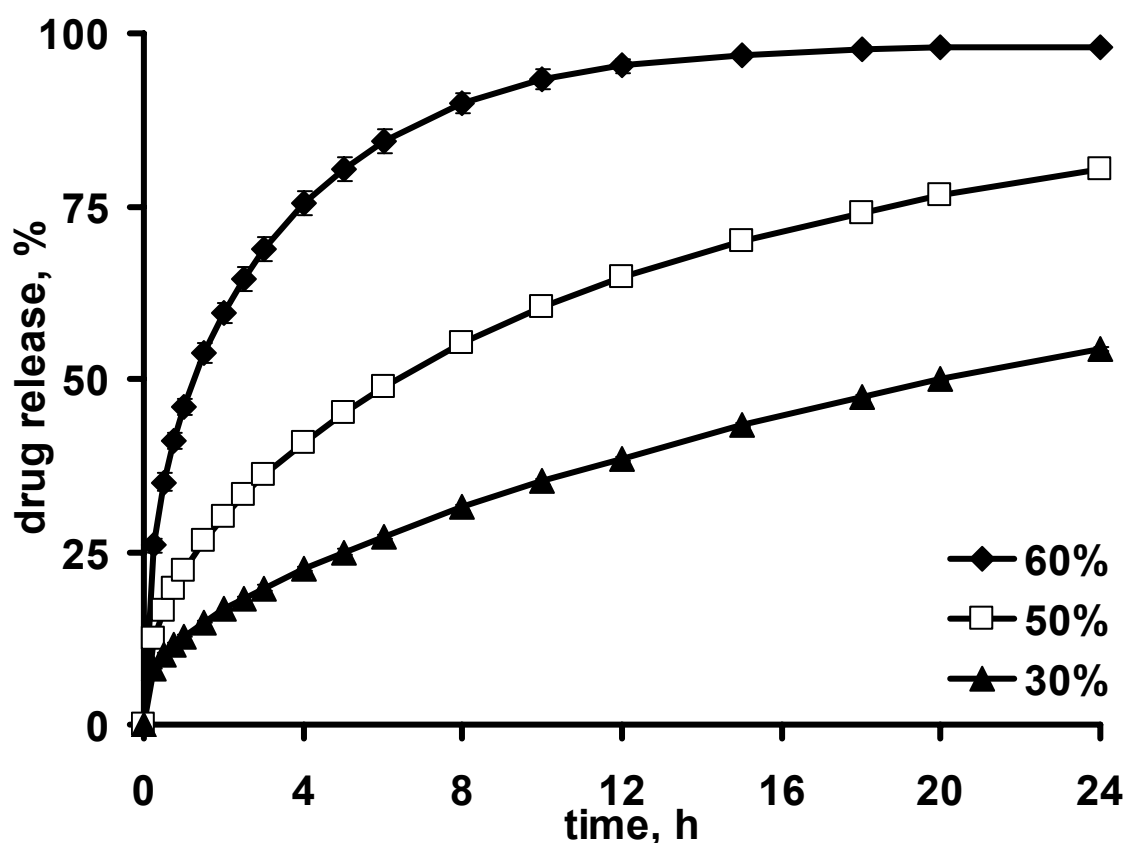
Fig 7   Influence of drug loading on metoprolol tartrate release from hot melt extruded ethylcellulose matrices

Increasing the matrix size resulted in decreasing drug release (**Fig 8**) because of the decreased surface area of matrices in relation to the volume. This was in agreement with the Higuchi equation Eq. 2.

$$\frac{M_t}{M_\infty} = \frac{A}{V\rho f}\sqrt{D_{app}(2c_o - c_s)c_s t}$$ (Eq. 2)

where M_t/M_∞ is the percentage of drug released at time t, A/V is the surface to volume ratio, ρ is the matrix density, f is the initial drug loading, D_{app} is the drug apparent diffusivity, c_o is the initial drug concentration and c_s is the saturation concentration. The Higuchi equation could be simply modified to Eq. 3.

$$\frac{M_t}{M_\infty} = \frac{A}{V}k\sqrt{t}$$ (Eq. 3)

The release rate is proportional to the surface to volume ratio of the matrix. Thus the release rate can be calculated as;

$$k_1\frac{A_2}{V_2} = k_2\frac{A_1}{V_1}$$ (Eq. 4)

Therefore, drug release rate of different matrix size could be estimated from the experimental release rate of a certain size matrix. Drug release from the experiment and estimation was in good agreement (**Fig 8**), indicating the acceptability of estimation from Eq. 3. Some of the calculated release rates for different matrix sizes were later used for applicability-map.
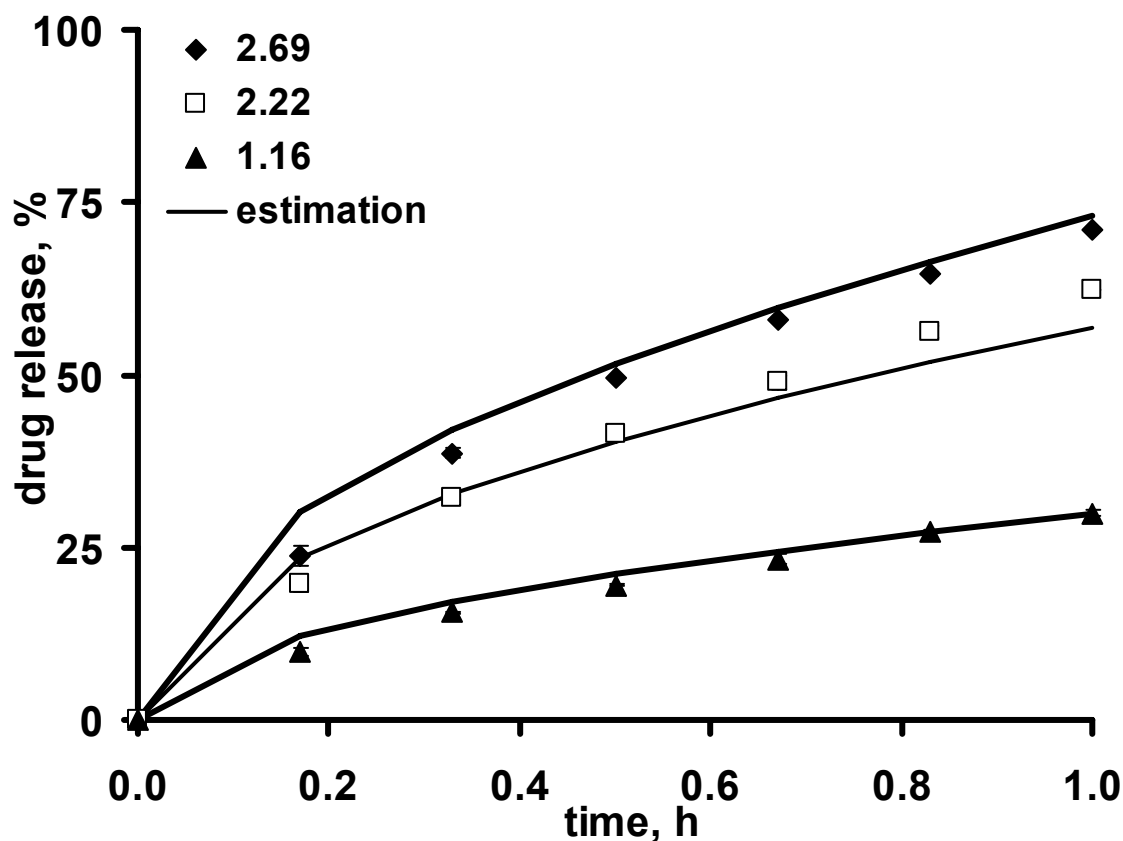
Fig 8 Influence of surface to volume ratio (A/V) on drug release from hot melt extruded Eudragit® RS matrices containing 50 % propranolol HCl (A/V of 2.69, 2.22 and 1.16 corresponds to the matrix with diameter and length of 2, 3 mm, 2, 10 mm and 9, 3 mm, respectively)

The influence of preparation method, polymer type and drug solubility on the drug release rate was summarized in an applicability-map which provides simple information for matrix production (**Fig 9**). Controlled release matrices (drug released within 8-24 h) containing highly soluble drugs (metoprolol tartrate) could be obtained using hot melt extrusion with a low permeability polymer such as (ethylcellulose). In case of propranolol HCl, drug release within 8-24 h was not successfully prepared. In order to get the suitable controlled release profiles, the permeability of the hot melt extruded matrices should be adjusted. This could e.g. be achieved by blending the ethylcellulose with more permeable or soluble polymers. In addition, the propranolol release rate could be adjusted by varying the drug loading or the matrix size as will be discussed in the later part. Controlled release matrices of soluble drug (theophylline) could be prepared by hot melt extrusion with a highly permeable polymer (Eudragit® RS) or by wet granulation with all three polymers.

Poorly soluble drug carbamazepine showed very low drug release rates with more than 24 h drug release from all matrices. In the applicability-map, the release rate was a linear function of the square root of drug solubility (**Fig 9, Table 9**). Thus, the release rate of a drug with certain solubility could be estimated from the linear equations (**Table 9**). The reliability of this approach was examined using diltiazem HCl (437 mg/ml) and caffeine (35 mg/ml) as additional model drugs. An acceptable agreement in drug release of experimental data and the estimation was obtained (**Fig 10**) (f_2 factor; 54-69). Therefore, the applicability-map and equations in this study could be applied to design controlled release matrices containing drugs with certain solubility.
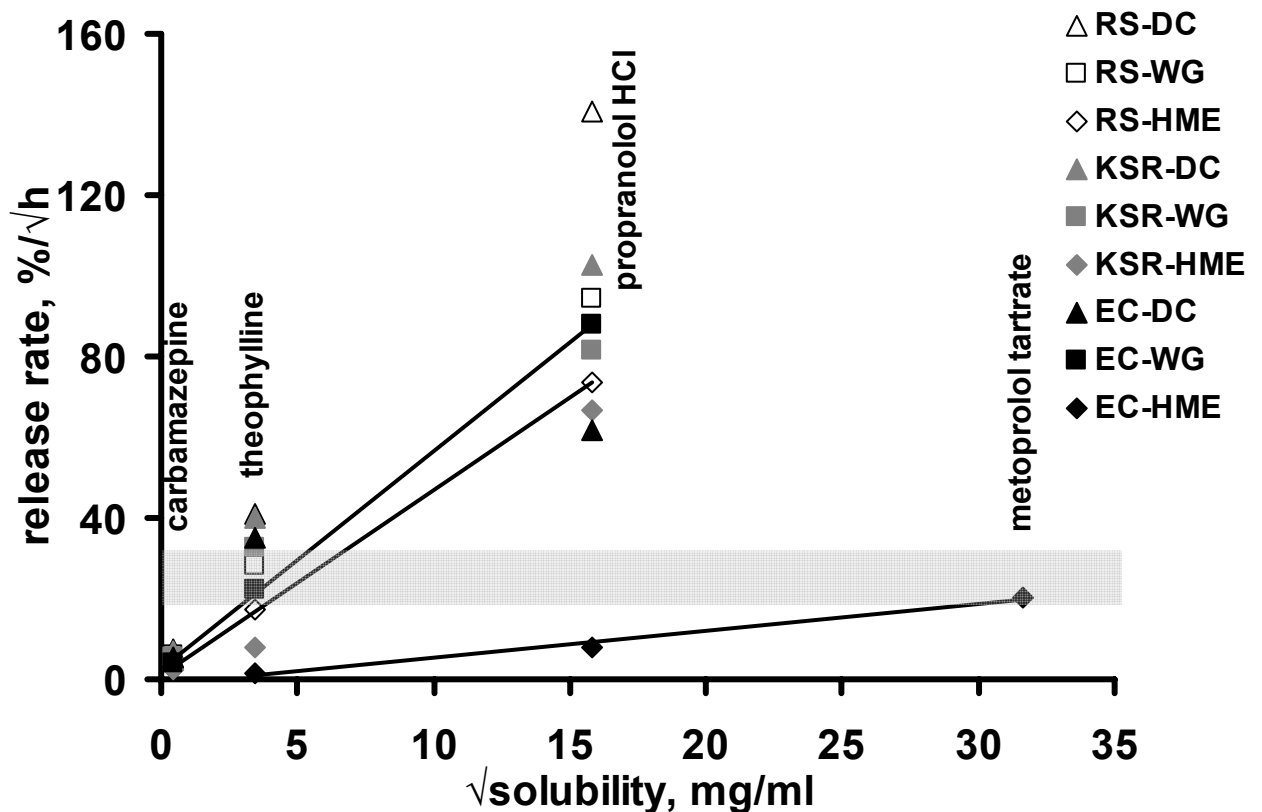
Fig 9   Relationship of drug release rate and square root of drug solubility for matrices (50 % drug loading, 2 mm matrix tablet) prepared by different methods and with different polymers; gray bar represents the 90 % drug release within 8-24 h

Table 9 Linear equations and correlation coefficients obtained from the plots of drug release rate versus square root of drug solubility (**Fig 6**)

Polymer / method	equation	R^2
Eudragit RS		
Hot melt extrusion	4.6058x + 0.8666	0.9998
Wet granulation	5.6489x + 5.7484	0.9963
Direct compression	8.5151x + 7.1940	0.9964
Kollidon SR		
Hot melt extrusion	4.3394x – 2.8773	0.9871
Wet granulation	4.6592x + 9.1778	0.9711
Direct compression	5.8889x + 11.163	0.9749
Ethylcellulose		
Hot melt extrusion	0.6641x -1.3946	0.9869
Wet granulation	5.4107x +2.3831	0.9994
Direct compression	7.4049x + 5.2617	0.9961

a) Caffeine
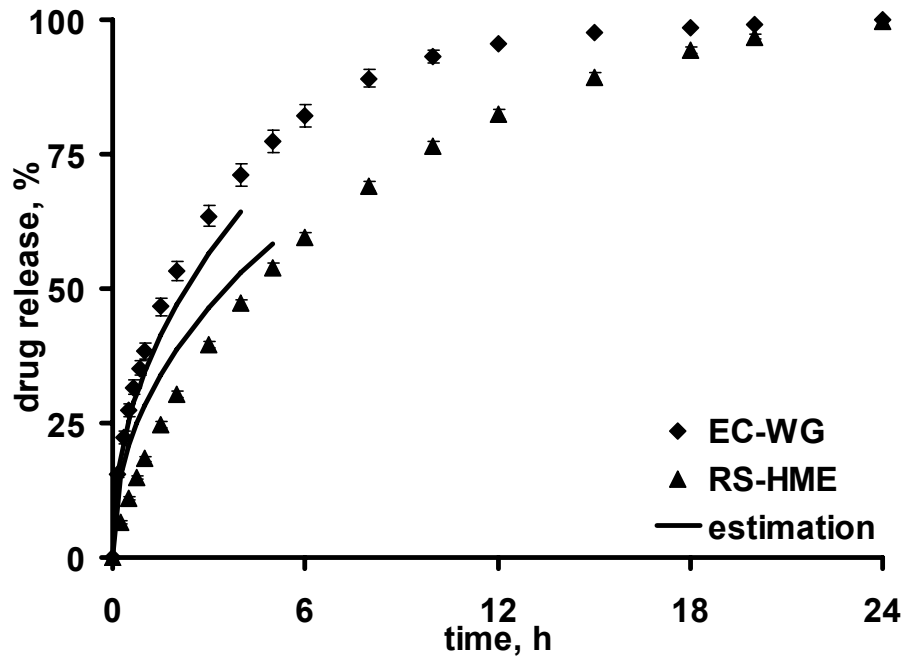
b) Diltiazem HCl
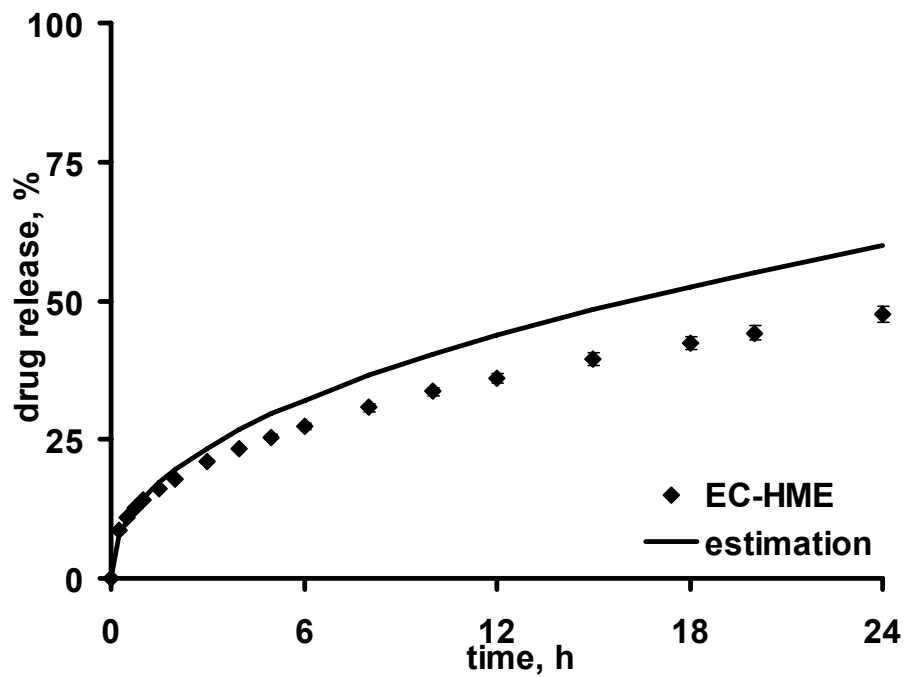
Fig 10 Estimation and experimental drug release from 2 mm-matrices containing a) caffeine and b) diltiazem HCl (50 % drug loading)

The influence of drug loading and matrix size on the drug release rate of matrices was also summarized in applicability-maps (**Fig. 11 and 12**). Hot melt extruded matrices were able to control the release of water soluble drugs with loadings of 10-50 % (metoprolol tartrate, propranolol HCl and theophylline) whereas the release rates of a poorly soluble drug were too low (**Fig 11a**). The soluble drug (theophylline) could be prepared as the controlled release matrices by wet granulation with the loading of 50% (**Fig 11b**). Unexpectedly, the controlled release of propranolol HCl was achieved with 10% loading in Kollidon® SR and ethylcellulose direct compressed matrices. The controlled release of theophylline was also achieved with 10-50% loading as well (**Fig 11c**).

The desired controlled release rate could also be obtained by varying the matrix size (**Fig 12**). Increasing the matrix size increased the applicability of wet granulation and direct compression for the preparation of controlled release matrices. On the other hand, a benefit of smaller matrices was that a desired dose was adjustable by combining several matrices. Moreover, decreasing the matrix size was beneficial for poorly soluble drugs. Suitable controlled release (8-24 h) of carbamazepine was achieved with granules (≤ 500 μm) prepared by wet granulation.

In accordance with the influence of the drug solubility (**Fig 9 and Table 9**), linear relations were obtained for the influences of drug loading and matrix size (**Fig 11 and 12**). Thus, drug release could be estimated from linear equations for all loadings or matrix sizes within the experimental range.
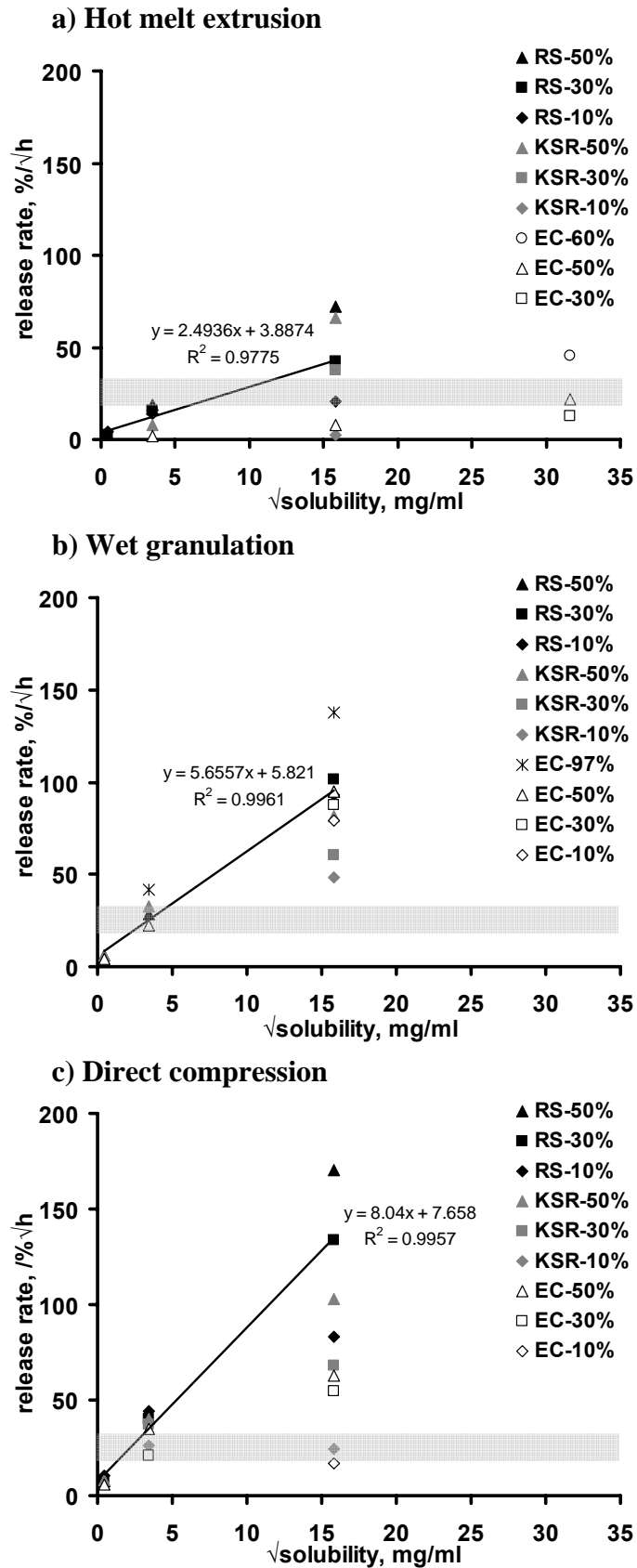
a) Hot melt extrusion

b) Wet granulation

c) Direct compression

Fig 11 Relationship of drug release rate and square root of drug solubility for 2 mm-matrices with different drug loadings (gray bar represents the 90 % drug release within 8-24 h)
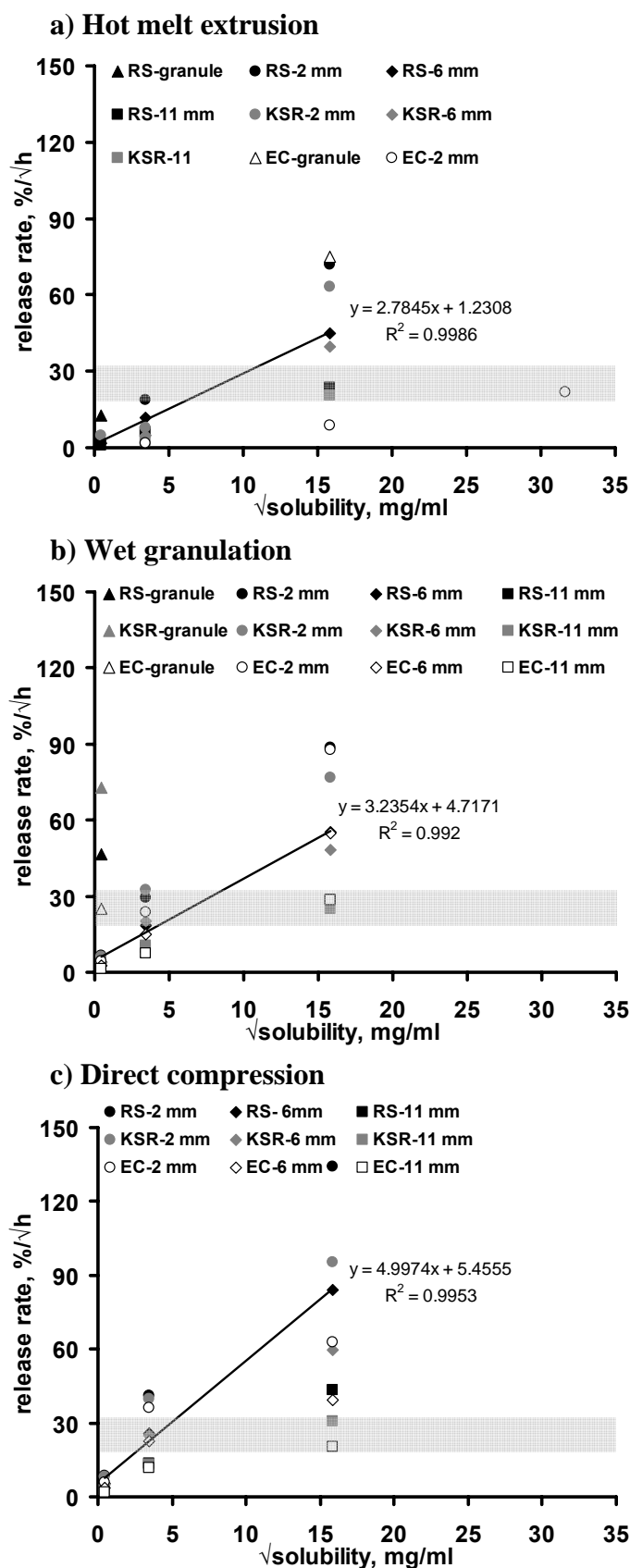
a) Hot melt extrusion

b) Wet granulation

c) Direct compression

Fig 12 Relationship of drug release rate and square root of drug solubility for matrices of different size (50 % drug loading, gray bar represents the 90 % drug release within 8-24 h)

3.1.3. Conclusion

The influence of the preparation methods hot melt extrusion, wet granulation and direct compression on drug release was studied. The release properties were depending on the polymer permeability, drug solubility, drug loading, and matrix size. Hot melt extruded matrices exhibited the slowest drug release than the matrices from other two methods. Hot melt extrusion was most suitable for highly soluble drug whereas wet granulation and direct compression were the methods of choice to prepare controlled release of drugs with an intermediate solubility. For poorly soluble drugs, suitable controlled release properties could only be achieved with small granules. Increasing the size of the matrices, on the other hand, decreased the release rates as expected. This broadened the applicability of wet granulation and direct compression to the preparation of controlled release matrix tablets of soluble drugs. The benefits of hot melt extrusion were restricted by the limitations of drug loading and processing with low melting point drugs. An acceptable estimation of drug release using the applicability-map was shown and facilitated the selection of the most suitable preparation method for matrix tablet production of a specific drug.

3.2. Hot melt extrusion for enteric and controlled release mini-matrices preparation

3.2.1. Introduction

Enteric dosage forms have been developed to prevent drug release in the stomach and to release the drug in the intestine in order to prevent drug decomposition in strong acidic environment and also to protect the patient from stomach-irritating drugs. In addition, they have potential for intestinal or colonic targeting (Brogmann and Beckert, 2001). Controlled release preparations have been developed to keep the drug plasma levels constant within the therapeutic range for extended time period (Jantzen and Robinson, 1996). This results in a lower dose frequency and thus improves the patient compliance. Combining enteric and controlled release properties would be desirable for drugs, which should not be release in the stomach but in a controlled release fashion in the intestine. Various possibilities to combine enteric and controlled release preparations include (i) enteric coating on controlled release matrices (Devraj and Bhatt, 2010; Marvola et al., 1999), (ii) a multilayer coating of enteric and controlled release layers (Dashevsky et al., 2004b; Farag and Leopold, 2011) (iii) coating blends of enteric and controlled release polymers (Dashevsky et al., 2004a; Wu and McGinity, 2003a). All methods involve multiple steps. Dense, slowly eroding enteric matrices might be an interesting option to obtain both enteric and controlled release properties because erosion could be decreased in intestinal fluids (Yang et al., 2008).

Hot melt extrusion is a continuous, solvent-free technique used for processing thermoplastic polymers into dense matrices with the aid of heat and pressure. It has been used to prepare controlled release dosage forms, such as implants, films and capsules (Schilling et al., 2010a; Schilling et al., 2010b); (Ghalanbor et al., 2010; Gosau and Müller, 2010b); (Mididoddi et al., 2006; Mididoddi and Repka, 2007); (Mehuys et al., 2005; Mehuys et al., 2004a). Enteric and controlled release was achieved with Eudragit[®] L100-55 matrices prepared by HME (Andrews et al., 2008). Eudragit[®] L100-55 extrudates containing ketoprofen (however, an acidic drug with lower solubility as low and higher solubility at higher pH) showed excellent gastric protection (<1% release in 0.1 N HCl) and sustained release up to 9-11 h in pH 6.8 (Yang et al., 2008). The colonic delivery of 5-ASA was achieved with Eudragit[®] S100 as carrier. Drug release was not more than 10% in 0.1 N HCl and matrices were not completely dissolved after 12 h in pH 7.4 buffer (Bruce et al. 2005). These studies were performed with single and not multiple

unit dosage forms such as mini-matrices. Schilling et al. produced enteric matrices with a diameter ≤ 1 mm with good gastric protection but the controlled release properties were not considering (Schilling et al., 2010b).

The aim of this study was to investigate the feasibility of hot melt extrusion to produce mini-matrices with both enteric and controlled release properties. Various enteric polymers and model drugs of different solubility (e.g., diprophylline, theophylline, carbamazepine) were compared with regard to processability and the influence of polymer pH-solubility threshold on drug release was investigated. In addition, the potential of hot melt extruded mini-matrices for colonic drug delivery of 5-ASA was investigated.

3.2.2. Results and discussion

Cellulosic and methacrylate enteric polymers were investigated as carrier materials in order to obtain enteric and sustained release matrices prepared by hot melt extrusion. The composition, properties and processing data of the enteric matrices containing 30% theophylline are shown in **Table 10**. Because of the high Tg and high molecular weight of the polymers, the plasticizer TEC was added to reduce the Tg and the melt viscosity in order to facilitate processing. The cellulosic polymers had a much lower molecular weight than the methacrylate polymers and thus required lower process temperatures and less TEC to achieve the target torque value of approx. 1 Nm. The extrusion temperature should be at least 50°C higher than the Tg of the matrix, as already reported previously (Chen et al., 2004; McGinity and Zhang, 2003). Die swelling is described as the expansion of the extrudate to a diameter larger than the die diameter. A higher die swell was observed with methacrylate polymers than with cellulosic polymers, which this could be due to their higher molecular weight (Nijenhuis et al., 2007).

Table 10   Composition, properties and processing data of enteric matrices containing 30% theophylline

polymer	MW	pH threshold	Tg, °C (polymer powder)	TEC, %	Tg, °C (matrix)	Extrusion temp., °C	Torque, Nm	Die swell, %
Eudragit® S100	135000	7.0	172*	30	93	160	1.55	46
Eudragit® L100-55	250000	5.5	110	30	50	130	0.91	49
HPMCAS-LF	18000	5.0	120	20	54	100	1.03	26
HPMCAS-MF	17000	5.5	130	20	41	100	0.92	25
HPMCAS-HF	17000	6.5	135	20	56	100	1.14	25
HPMCP-HP50	84000	5.0	135	20	66	130	0.96	26
HPMCP-HP55	78000	5.5	130	20	57	130	0.78	26

* (Schilling et al., 2010b)

According to the USP 30 requirements, drug release from enteric dosage forms in 0.1N HCl should not exceed 10% after 2 h. All formulations exhibited good enteric properties except HPMCAS-MF which released slightly more than 10% theophylline after 2 h (**Fig 13**). In pH 6.8 phosphate buffer, theophylline was rapidly released within 2-3 h from Eudragit® L100-55, HPMCP as well as the HPMCAS-grades LF and MF whereas release was controlled up to 8 h with the HF grade. Incomplete release of only 20% theophylline after 24 h was obtained from Eudragit® S100 matrices. The different release rates were attributed to the different pH-solubility of the polymers (**Table 10**). The polymers with high pH thresholds exhibited slower drug release because of the slower polymer dissolution/ erosion). The type of enteric polymer is thus an important parameter in achieving enteric only or enteric/controlled release properties.
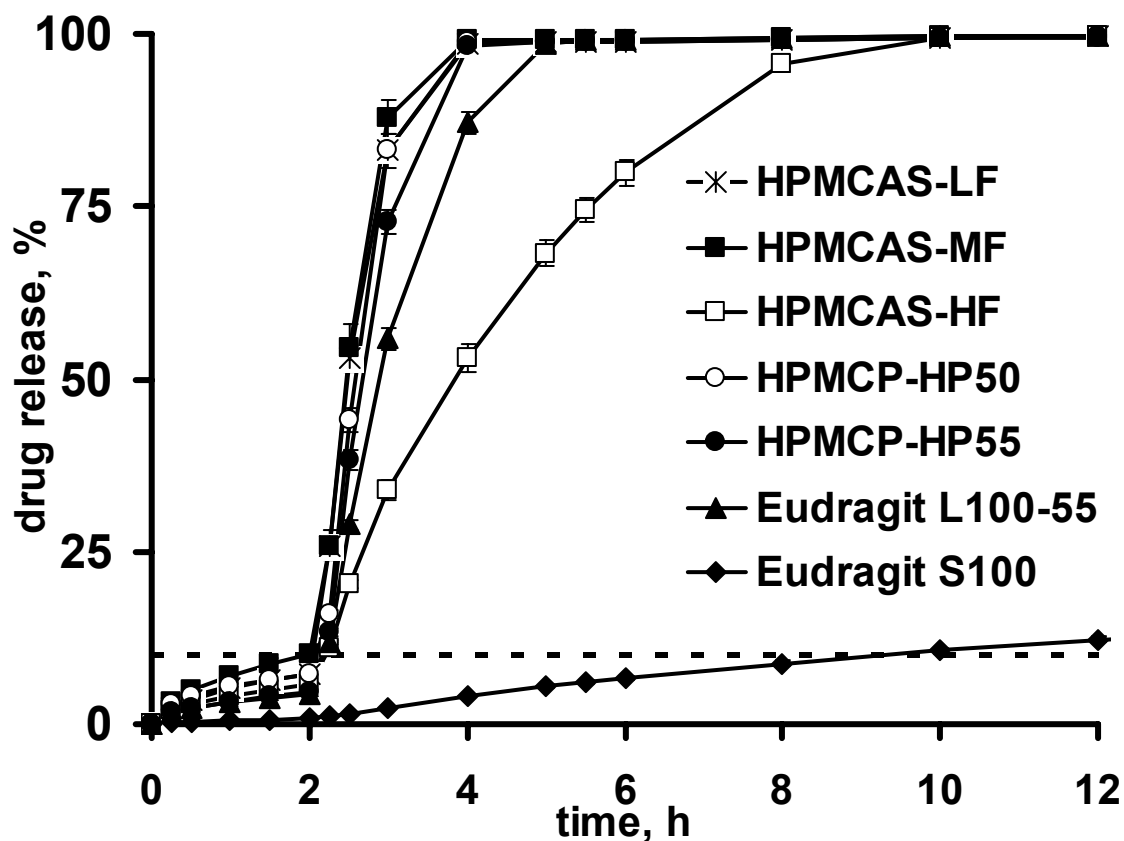
Fig 13 Influence of type of enteric polymer on theophylline release (30% loading, formulation detail in Table 1)

Mechanical stress on the mini-matrices in the stomach could result in the failure of enteric properties. Therefore, the mechanical properties of matrices were investigated (**Fig 14**). In the dry state, the Eudragit® polymers broke at a force of 250-300 N while the cellulosic polymers deformed plastically. All matrices had a more pronounced plastic deformation in the wet compared to the dry state. The higher mechanical resistance ensures a more reliable drug release from hot melt extruded matrices compared to enterically coated pellets (break at 12-13 N, experiment), which could rupture upon mechanical stress in the stomach.
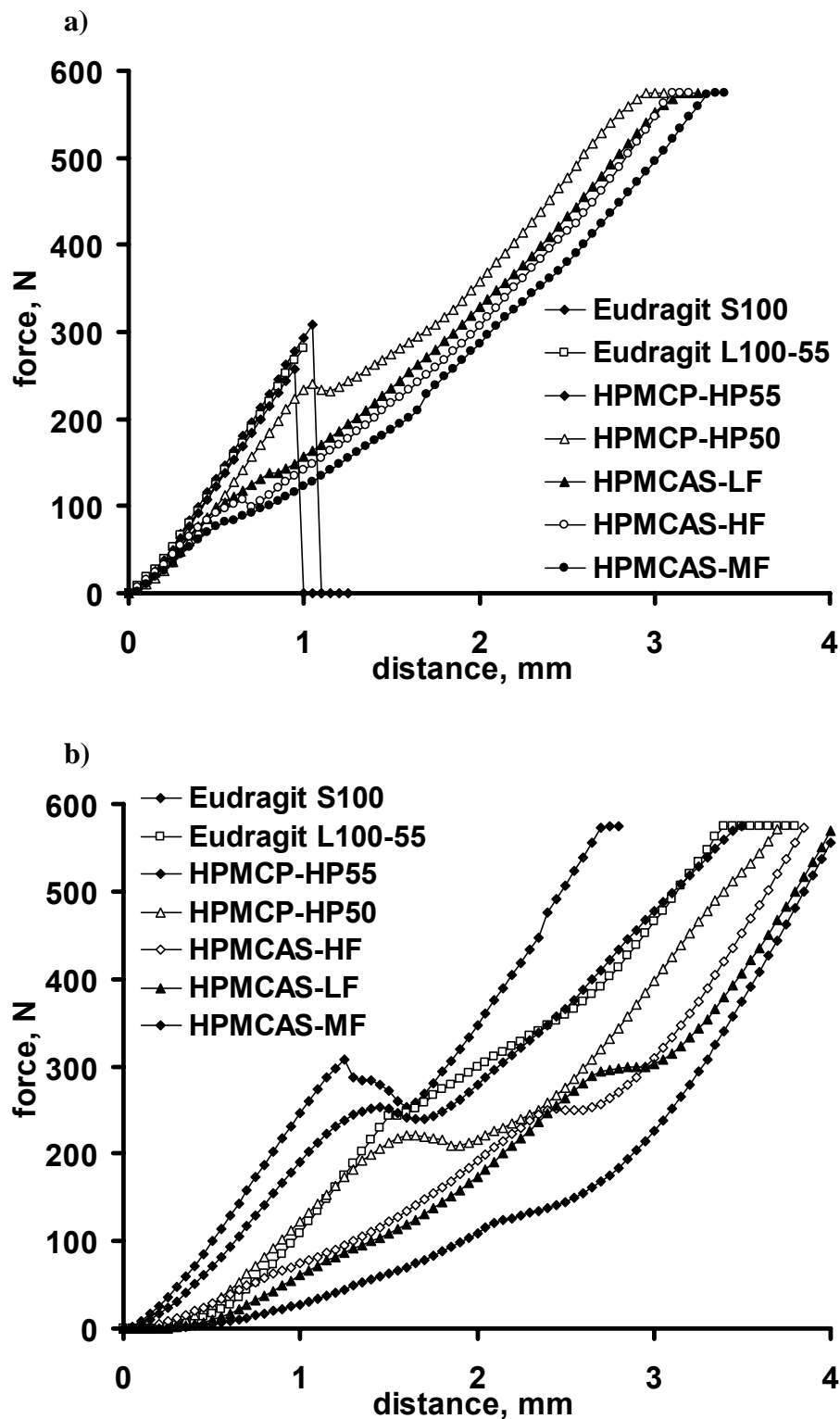
Fig 14 Mechanical properties of enteric mini-matrices (30% theophylline) in a) dry state and b) wet state (2 h in 0.1N HCl)

The application range of these matrix systems was further investigated using the model drugs diprophylline and carbamazepine with higher and lower solubilities than theophylline (**Table 11**). Eudragit® L100-55, Eudragit® S100 and HPMCAS-HF were selected as carriers because of their coverage of the pH solubility threshold range from pH 5.5 to 7.0.

Table 11 Melting temperature and solubility in different media of the model drugs

Drug	Tm, °C	Solubility, mg/ml		
		0.1N HCl	pH 6.8 phosphate buffer	pH 7.4 phosphate buffer
Diprophylline	160	215	210	-
Theophylline	273	14	12	-
5-Aminosalicylic acid	280	11	24	97
Carbamazepine	187	0.2	0.2	-

Diprophylline and carbamazepine reduced the Tg of the polymer matrix more than theophylline because of their higher solubility in the polymer matrices as confirmed by a decrease in drug crystallinity (**Table 12**). The reduction of the Tg indicated the ability of these two drugs to function as a plasticizer and thus resulted in easier processing (e.g. lower torque). For Eudragit® S 100 matrices containing theophylline (Tm = 273°C), 160 °C was chosen as the processing temperature. In contrast, the preparation of diprophylline (Tm= 160°C)/Eudragit® S 100 matrices at 160 °C resulted in complete drug melting and dissolving in the matrix. Consequently, ≥ 50% was released within 2 h in 0.1N HCl. Higher amounts of TEC were incorporated in order to reduce the processing temperature below the melting point of diprophylline. The Eudragit® S100 matrices containing carbamazepine could also not be produced at 160 °C. Extruding at this temperature resulted in air bubbles within the matrices. This might be due to the lowering of the melt viscosity resulting in a lower pressure inside the extruder and enhanced melt flow rate. As a consequence, the air in the drug/polymer mixture bed was not effectively expelled. The matrices containing theophylline showed less die swell than the ones containing diprophylline and carbamazepine. The difference between these matrices was that theophylline was not soluble in the polymer. Therefore higher fractions of solid drug particles were present in the matrices. Increasing amounts of particles could change the

rheological behavior and also weaken the elasticity of the polymer, thereby reducing the die swell (Rahim et al., 2011).

Table 12   Properties and processing data of enteric polymer matrices containing different drugs (30 % loading)

Formulation	TEC, %	Tg, °C	Crystalline drug remaining	Extrusion temp., °C	Torque, Nm	Die swell, %
Eudragit L 100-55	0	110				
	30	50				
diprophylline	30	30	0.51	130	0.24	61
theophylline	30	50	-*	130	0.91	49
carbamazepine	30	32	0.10	130	0.29	81
Eudragit S 100	0	172				
	30	96				
	50	83				
diprophylline	50	59	0.29	130	0.54	60
theophylline	30	93	0.92	160	1.55	46
carbamazepine	30	52	0.17	140	0.45	75
HPMCAS-HF	0	135				
	20	56				
diprophylline	20	46	0.80	100	1.16	29
theophylline	20	54	1.01	100	1.14	25
carbamazepine	20	44	0.81	100	1.09	31

* could not be determined because of interfering polymer degradation

All matrices exhibited acceptable drug release of ≤ 10% during the first 2 h in 0.1N HCl (**Fig 15**). In pH 6.8 phosphate buffer, Eudragit® L100-55 rapidly released diprophylline and theophylline whereas controlled release up to 12 h was obtained only for carbamazepine. HPMCAS-HF, on the other hand, achieved controlled drug release for ≥ 10 h for all drugs. Interestingly, similar drug release of diprophylline and theophylline from Eudragit® L100-55 and HMPCAS- HF matrices was observed (**Fig 15a and c**). This could be attributed to the similar erosion rates of these matrices (**Fig 15d and f**). In contrast, carbamazepine matrices exhibited a slower matrix erosion rate which is probably attributed to the lower wettability of the matrices containing the poorly soluble drug. The slower release of carbamazepine is in agreement with the slower erosion. Drug release from Eudragit® S100 was slow for diprophylline and negligible for theophylline and

carbamazepine (**Fig 15c**) because of the insolubility and thus lack of erosion of this polymer below the pH of 7.0 (**Fig 15e**). Drug was released mainly by diffusion through pores within the matrix. The solubility of the drug thus determines the choice of enteric polymer in order to obtain both enteric and controlled release properties. For poorly soluble drugs, polymers with a low pH threshold were successfully applied as matrix formers whereas the polymer with higher pH threshold was suitable only for highly soluble drugs.

Blends of enteric polymers with different pH thresholds (e.g., Eudragit® S100/pH 7.0 and HPMCAS-MF/pH 5.5) were investigated to obtain flexible release properties. The detection of two Tgs for the polymer blend matrices indicated that Eudragit® S100 and HPMCAS-MF was not miscible (**Table 13**). At low temperatures, Eudragit® S100 with a Tg of 150 °C (plasticized, **Table 13**) did not melt and thus remained as solid particles in the matrix. These insoluble particles and the associated increase in internal friction caused an increase in torque. As mentioned above, the presence of particles in the melt could reduce the die swell. Increasing the processing temperature resulted in a lower torque and increased die swell (**Table 13**) and a decrease in drug release (**Fig 16**). This might be attributed to the partial melting of Eudragit® S100 and the increased density of the matrices. However, above 130 °C, browning of the extrudates was observed which could be due to the degradation of the cellulosic polymer (Schilling et al., 2010b). Varying the ratio Eudragit® S100: HPMCAS-MF affected the torque but not the die swell (**Table 13**). The HPMCAS-MF was completely molten at the processing temperature (120°C) and thus processing became easier with increasing HPMCAS-MF portion as indicated by a lower torque. In contrast the torque increased with increasing Eudragit® S100 amount due to the increasing non-melting polymer portion. Die swell was constant with varying polymer ratios since Eudragit® S100 was not completely melted the die swell was thus mainly the effect of HPMCAS-MF. Increasing the HPMCAS-MF content resulted in an increased drug release in both media (**Fig 17**). This was due to the increased medium uptake in 0.1N HCl (**Fig 18a**) and faster matrix erosion in pH 6.8 phosphate buffer (**Fig 18b**). Although drug release in 0.1N HCl was increased at higher HPMCAS-MF contents, matrices with Eudragit® S100: HPMCAS-MF ratios up to 1:2 still passed the enteric requirement (≤ 10% release after 2 h in 0.1N HCl). This showed the capability of such blends give adjustable controlled release patterns while still keeping enteric properties.
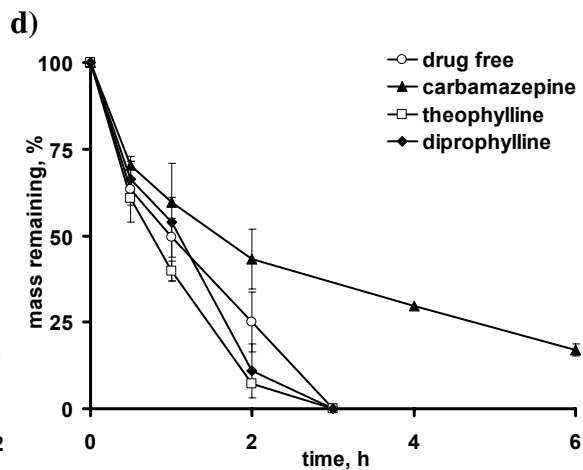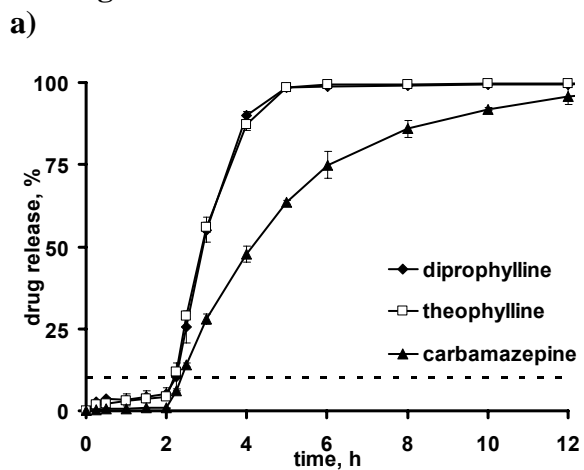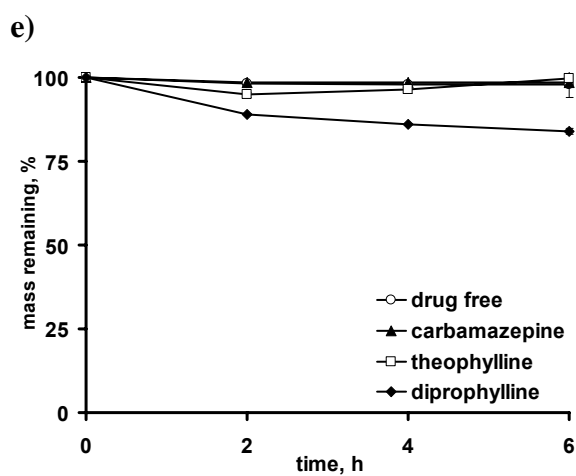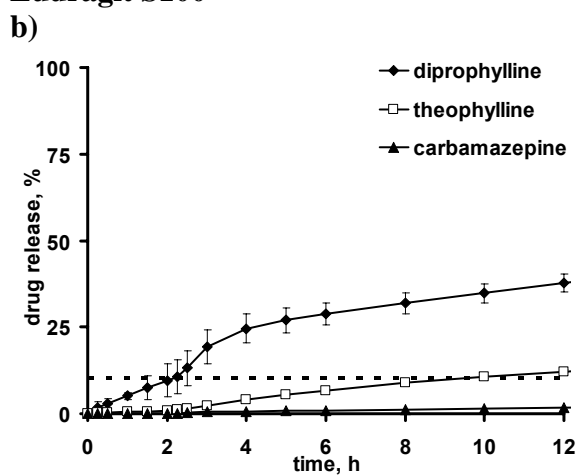
Eudragit L100-55

a)

d)

Eudragit S100

b)

e)

HPMCAS-HF

c)

f)
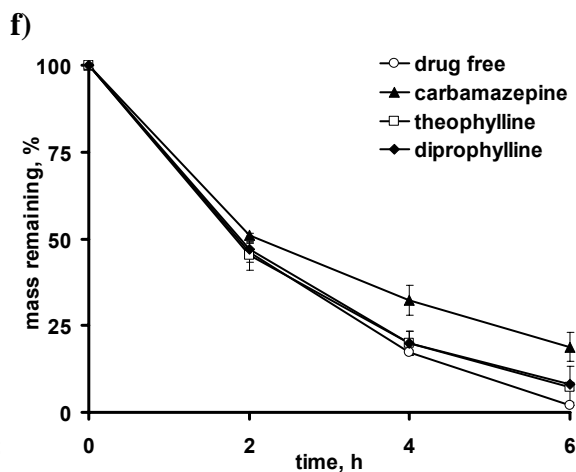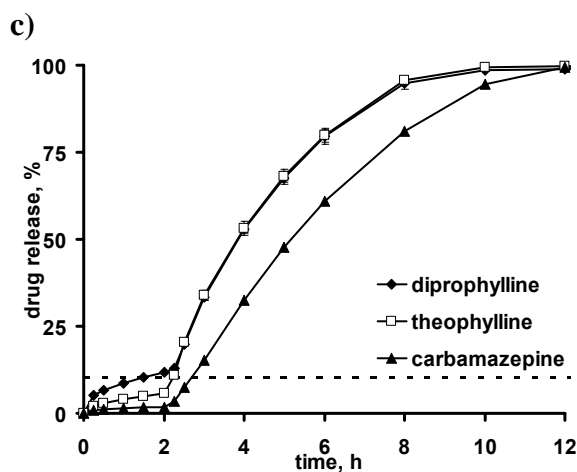
Fig 15 Influence of drug type on drug release (a-c) and mass remaining (d-f)

Table 13   Processing data of Eudragit$^{\circledR}$ S100: HPMCAS-MF blends (30% theophylline, 30%TEC based on polymer)

Eudragit S100: HPMCAS-MF blend	Tg, °C	Extrusion temp., °C	Torque, Nm	Die swell, %
1:1	150/ 41	100	3.96	17
		120	1.50	36
		140	0.60	35
1:2	143/ 31	120	0.72	30
2:1	147/ 48	120	3.02	36
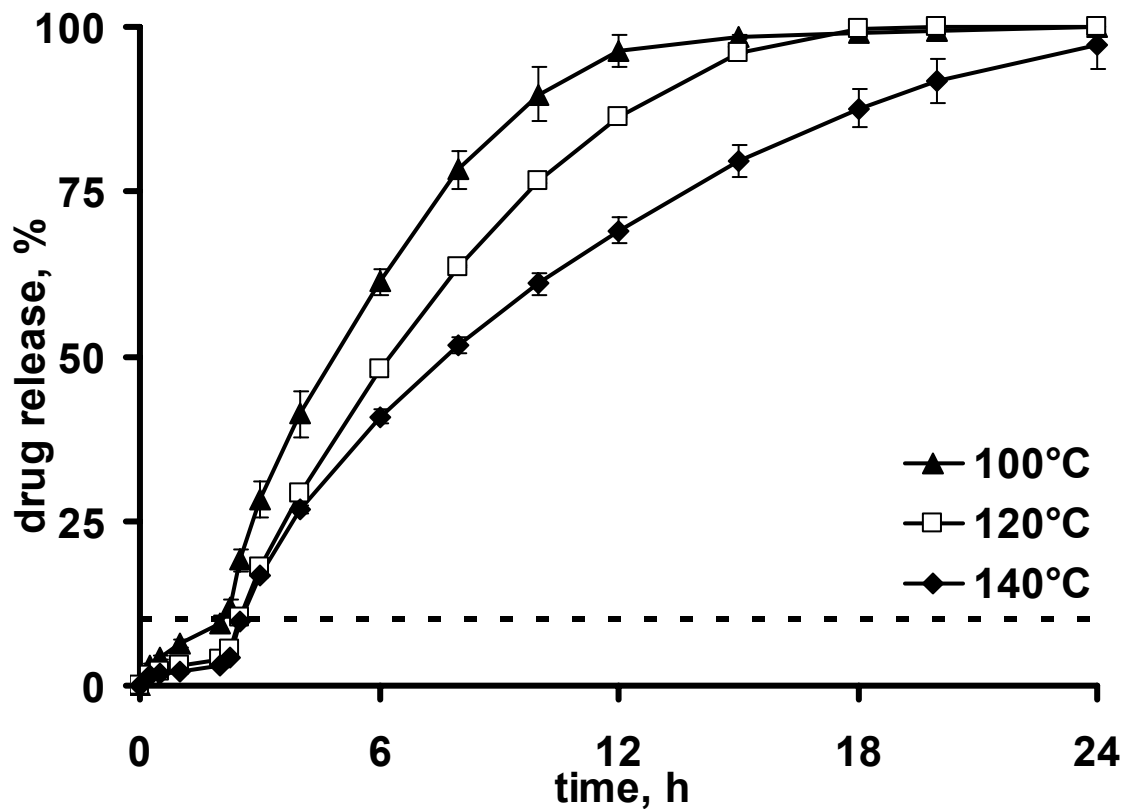
Fig 16 Influence of extrusion temperature on drug release from Eudragit$^{\circledR}$ S100:HPMCAS-MF (1:1) matrices (30% theophylline)
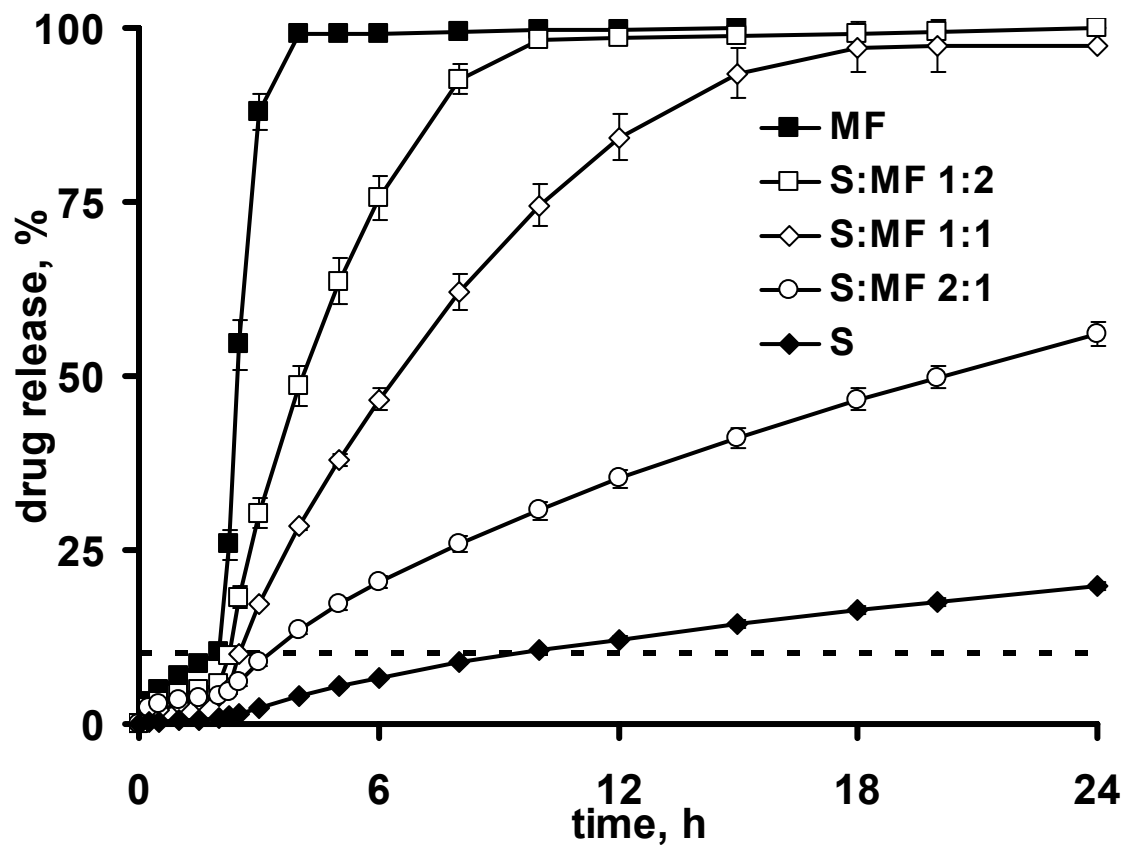
Fig 17 Influence of Eudragit® S100:HPMCAS-MF ratio on drug release (30% theophylline, formulation details in Table 1 and 4)
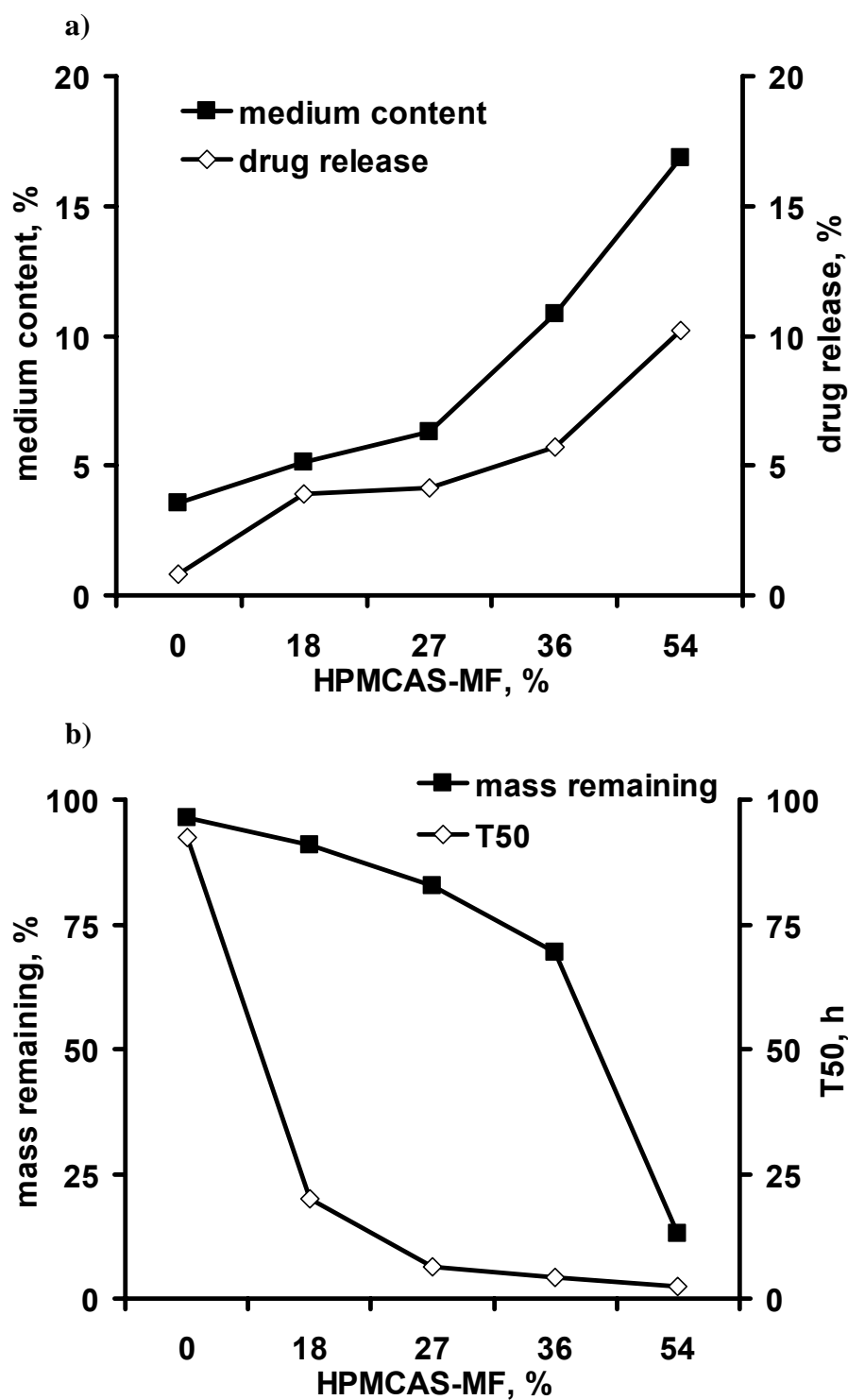
Fig 18 Influence of the Eudragit® S100: HPMCAS-MF ratio on medium content, mass remaining and drug release (or T50) (30% theophylline) a) 2h in 0.1N HCl and b) 1 h in pH 6.8 phosphate buffer (0%, 18%, 27%, 36% and 54% HPMCAS-MF is equivalent to Eudragit® S:MF 1:0, 2:1, 1:1, 1:2 and 0:1, respectively)

The potential of hot melt extruded matrices for colonic drug delivery was also investigated with 5-ASA as model drug and matrices of Eudragit® S100 and its blends with HPMCAS **(Table 14)**. Irrespective of the HPMCAS-HF or HPMCAS-MF content, 5-ASA was not released in 0.1N HCl thus passing gastric resistance. A slight increase in drug release was observed when changing to pH 6.8. This was due to the increase in drug solubility and partial erosion of HPMCAS. The rapid increase in drug release in pH 7.4 was due to the erosion of both HPMCAS and Eudragit® S100. While the gastric resistance was unaffected by the HPMCAS-HF or HPMCAS-MF content, the release rate in phosphate buffer was adjustable (**Fig 19**). When compared to the release of theophylline from Eudragit® S100: HPMCAS-MF (1:1) matrices in pH 6.8, 5-ASA release were released slower although its solubility was higher. This was probably caused by the lowering of micro-environmental pH by the acidic 5-ASA, which suppressed ionization and erosion of the enteric polymer (Dangel et al., 2001a, 2001b). Excellent gastric protection and complete release of 5-ASA at higher pH proved that hot melt extruded mini-matrices could potentially be used for colonic drug delivery.

Table 14   Processing data of enteric matrices containing 5-ASA (30% loading, 30%TEC (based on polymer), screw speed 30 rpm)

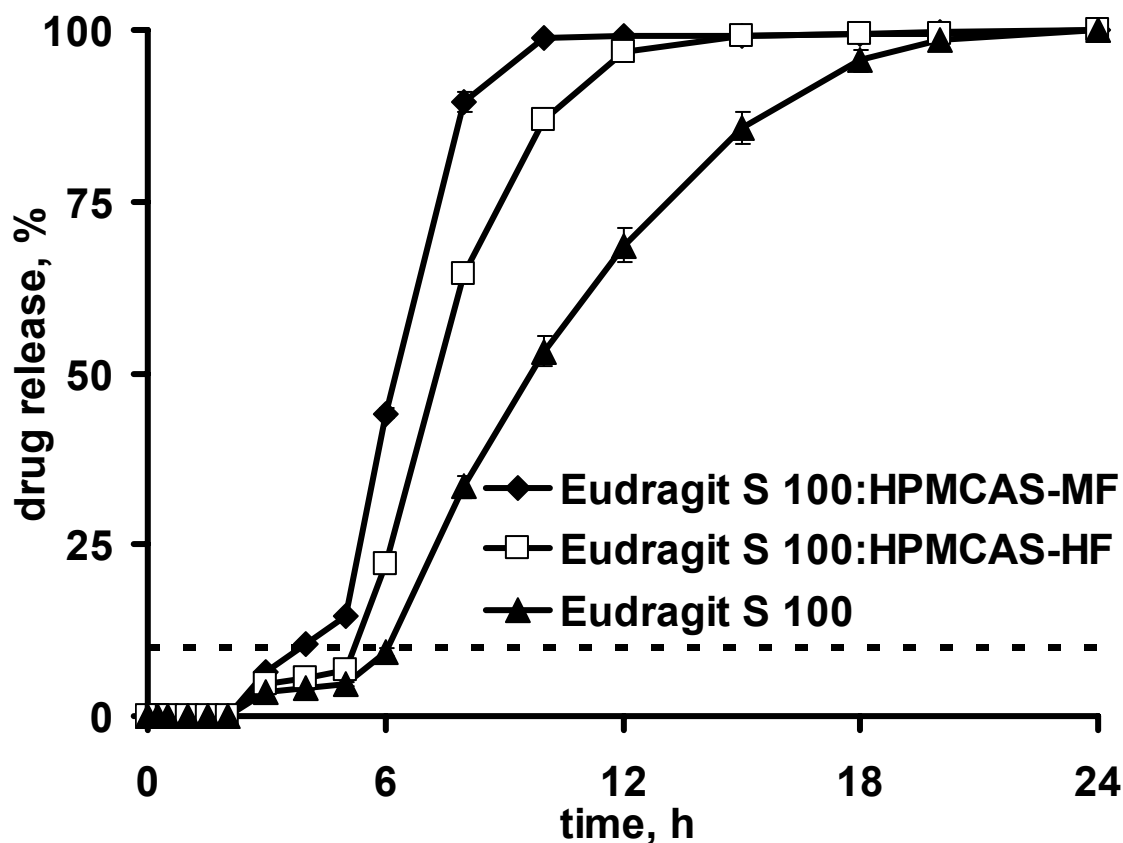| Polymer	Extrusion temp., °C	Torque, Nm	Die swell, %
Eudragit S100	160	1.77	41
Eudragit S100: HPMCAS-MF (1:1)	120	1.63	30
Eudragit S100: HPMCAS-HF (1:1)	120	1.68	28

Fig 19 5-ASA release from enteric Eudragit® S100 or Eudragit® S100: HPMCAS (1:1) matrices (30% loading, 30% TEC). 0-2 h in 0.1N HCl, 2-5 h in pH 6.8 phosphate buffer then pH 7.4 phosphate buffer

3.2.3. Conclusion

Mini-matrices with both enteric and controlled release properties were successfully prepared by hot melt extrusion. The good mechanical resistance in dry and state and plastically deformation in wet state of mini-matrices ensured the reliable drug release without rupturing by the mechanical stress in stomach. Mini-matrices demonstrated acceptable enteric properties with different release rates in pH 6.8 which attributed to the different pH-solubility of the polymers. The solubility of the drug affected the drug release rate and thus determines the choice of polymer carrier. In order to get the enteric and controlled release of poorly soluble drugs, the polymer matrices with a low pH threshold was required. In contrast, efficient enteric and controlled release of soluble drug could be obtained with using a higher pH threshold as polymer carriers. Blends of Eudragit® S100 and HPMCAS-MF were investigated to obtain flexible release

properties. Although increase HPMCAS-MF increased drug release, mini-matrices with Eudragit® S100: HPMCAS-MF ratios up to 1:2 released < 10 % drug in 0.1 N HCl after 2 h. This implied the capability of using the blends to adjust the controlled release rate while still having enteric properties. Mini-matrices with Eudragit® S100 or its blend with HPMCAS were potentially used for colonic drug delivery as they showed excellent gastric protection and released 5-ASA at higher pH.

3.3. Enteric failure of Eudragit L100-55 coated propranolol HCl pellets

3.3.1. Introduction

Enteric coated dosage forms were developed with the intention to either protect active drugs from potential decomposition in the gastric juice or the stomach from drug-induced irritations (Healey, 1989). Enteric polymers contain acidic functional groups, which are unionized at acidic pH but ionized and thus soluble at elevated pH. Eudragit® L100-55, an anionic copolymer based on methacrylic acid and ethylmethacrylate with a 1:1 ratio of carboxylic to ester functional groups, is widely used as an enteric coating and dissolves at pH values above 5.5 (Bruce et al., 2003a).

The drug release mechanisms from coated dosage form are i) release through the intact polymeric film, ii) release through medium-filled pores, iii) release through the hydrated or swollen coating and iv) release through ruptures in the coating (Zhang et al., 1991). For highly water soluble drugs, the migration of drug into the coating could cause a premature drug release due to the pore formation in the coating film during drug release (Bruce et al., 2003a). In order to prevent such premature drug release, thicker coating levels or seal coatings under the functional coating could be applied (Bianchini et al., 1991; Bodmeier and Paeratakul, 1990; Bruce et al., 2003b; Crotts et al., 2001; Ghebre-Sellassie et al., 1987; Li et al., 1997). Apart from preventing drug migration, seal coats can also avoid potential drug-polymer-interactions which could lead to a failure of the desired property. Propranolol HCl, for example, forms a complex via ionic bonding between its amine group and the anionic functional group of substances such as polymetharcrylate copolymers, fatty acids or sodiumcarboxymethylcellulose (Lee et al., 1991; Stott et al., 2001; Takka, 2003). However, this complex was only investigated at a higher pH where both substances were ionized. Data explaining the interaction of this drug with anionic substances in acidic environment have not been reported to our knowledge. Propranolol HCl was reported to be a surface active drug, which has a self association property and could thus cause biological membrane disruption and solubilization (Mosquera et al., 1999; Ruso et al., 2000; Ruso et al., 1999). In addition, polymers like polymethacrylic acid, polyvinylpyrrolidone-acetate, polyvinylalcohol-acetate and polyvinylalcohol-butylate have been solubilized by surfactants (Saito and Mizuta, 1967; Vlachy et al., 2006).

In this study, an initially surprising lack of gastric resistance was seen for propranolol HCl pellets coated with the enteric polymer Eudragit® L100-55. The

objective thus was to investigate the reason for this gastric resistance failure by studying the interactions between propranolol HCl and Eudragit® L100-55.

3.3.2. Results and discussion

According to the USP 30 requirements, enteric coated dosage forms have to release ≤ 10 % drug within 2 h in 0.1 N HCl and ≥ 75 % after 45 min in pH 6.8 phosphate buffer. To achieve enteric properties for Eudragit® L 100-55 with pellets with diameters in the range of 0.5-1.2 mm, coatings with a 10-30 % polymer weight gain are suggested by the supplier (equivalent to 1.8-5.4 mg/cm^2 in this study) (Evonik, 2009). Surprisingly, gastric protection could not be achieved at these recommended coating levels with pellets containing the highly water soluble drug propranolol HCl (**Fig. 20**). The pellets required a coating with ≥ 7.2 mg/cm^2 Eudragit® L100-55 in order to pass the enteric test (**Fig. 20**). Gastric resistance failure of enteric coated pellets containing highly water soluble drug has previously been explained by the migration of drug into the coating during the film formation (Ghebre-Sellassie et al., 1987). However, drug migration could not explain the surprising partial dissolution of the enteric polymer in 0.1 N HCl which was visible as a polymer gel layer in macroscopic pictures of the coated pellets after release (**Fig. 21**). The gelled part around the pellets was completely dissolved in pH 6.8 phosphate buffer (**Fig. 21**), confirming that it was Eudragit® L100-55. In agreement with the drug release data, more pronounced dissolution of the enteric film was observed at the lower coating levels**.**
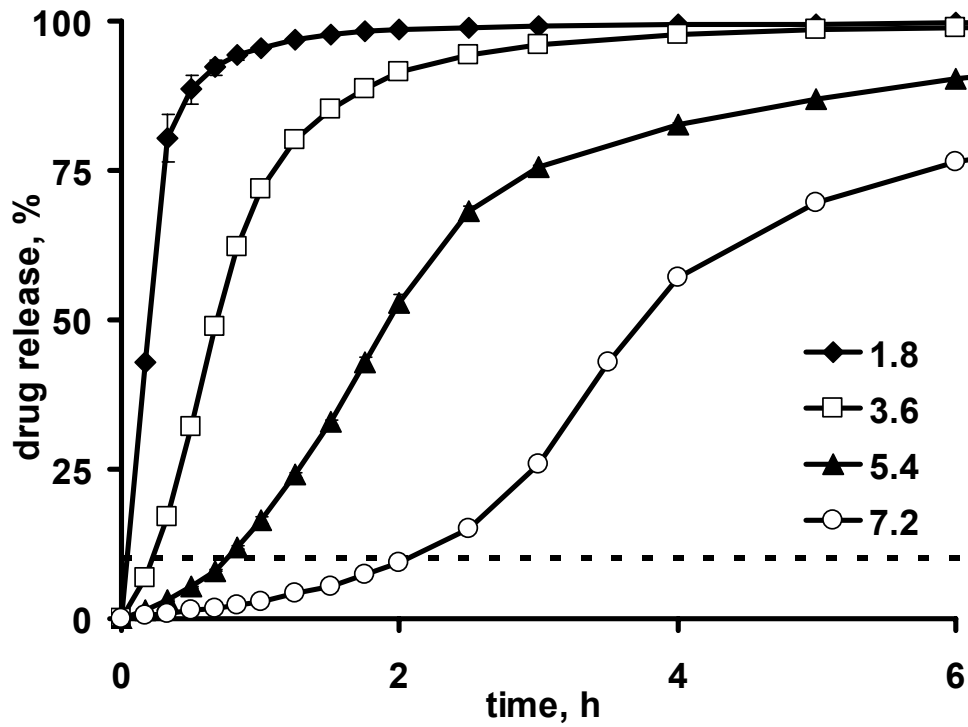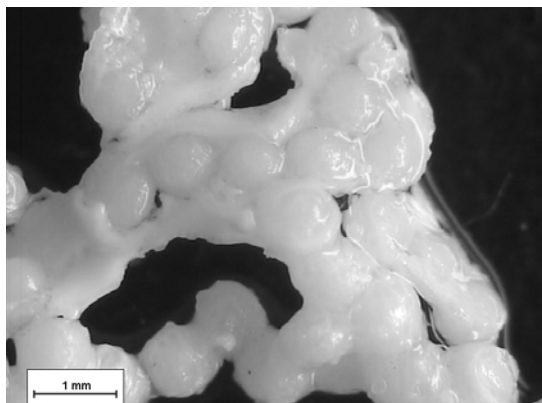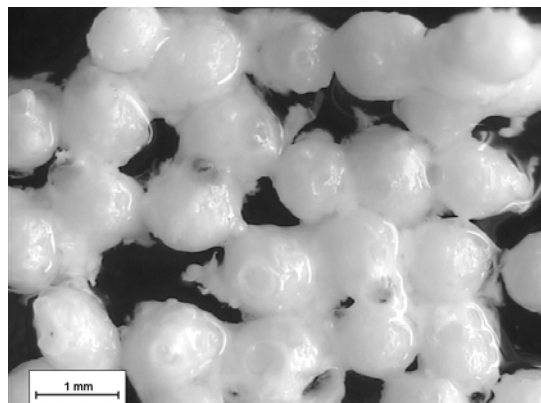
Fig 20 Influence of Eudragit® L100-55 coating level (mg/cm²) on propranolol HCl (30% loading) release in 0.1 N HCl (dashed line represent 10% drug release limit for enteric dosage forms)
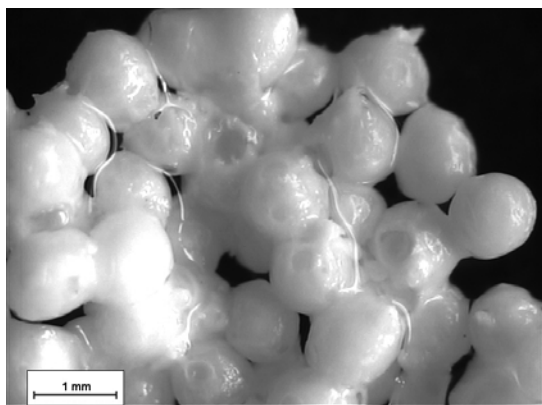
After release in 0.1 N HCl

1.8 mg/cm^2
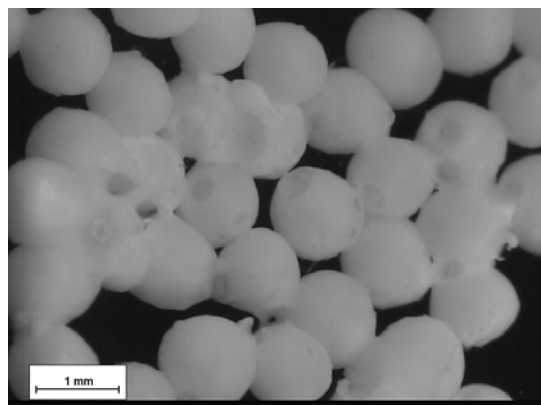

3.6 mg/cm^2

5.4 mg/cm^2

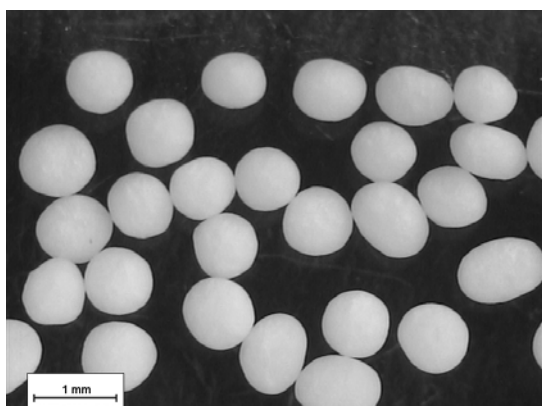**7.2 mg/cm^2**

After release in pH 6.8

Fig 21 Macroscopic pictures of Eudragit® L 100-55 coated propranolol HCl/MCC pellets after release in 0.1 N HCl and pH 6.8 phosphate buffer

The propranol HCl release from Eudragit® L100-55 coated pellets in 0.1 N HCl has been described by a drug diffusion mechanism through the swollen Eudragit® L100-55 film (Lecomte et al., 2004). In the present study, the drug induced not only swelling but dissolution of the polymer. Decreasing the propranolol HCl loading from 30 % to 10 % led to a decreased release in 0.1 N HCl (**Fig. 22a**).This was consistent with a visible reduction of polymer dissolution (**Fig 22b**) and implied an influence of the drug loading on the gastric protection of Eudragit® L100-55 coated pellets. To clarify whether this polymer-dissolving effect is related specifically to propranolol HCl or also to other water-soluble drugs, propranolol HCl (solubility: 160 mg/ml) was replaced with diprophylline (solubility: 215 mg/ml). Diprophylline pellets exhibited a slower drug release compared to propranolol HCl pellets, even though diprophylline has a higher solubility. This was attributed to the fact that diprophylline pellets did not result in any visible dissolution of the polymer coating (**Fig 22b**). However, diprophylline pellets still failed the enteric test which could be due to the high water solubility of diprophylline. It was thus concluded that propranolol HCl exerts a drug-specific effect on the dissolution of Eudragit® L100-55.

The dissolution of the polymer coating did not only depend on the propranolol HCl concentration but also on the release medium. The propranolol HCl release from Eudragit® L100-55 coated pellets was in the order: pH 6.8 phosphate buffer > 0.1N HCl > 0.001N HCl > water (**Fig 23a**). Similar results were observed with propranolol HCl pellets based on soluble non-pareils cores instead of MCC cores (**Fig 24**). The order of release is in agreement with the degree of polymer dissolution in the different media as can be seen from macroscopic pictures (**Fig. 23b and 24b**). The fastest release rate in pH 6.8 phosphate buffer was expected due to the complete solubility of Eudragit L100-55 in this medium. In acidic media or deionized water, in which Eudragit® L100-55 is not soluble, polymer dissolution was only enabled by the presence of propranolol HCl inside the coated pellets.

a)

b)

10 % propranolol HCl   **30 % propranolol HCl**

30 % diprophylline

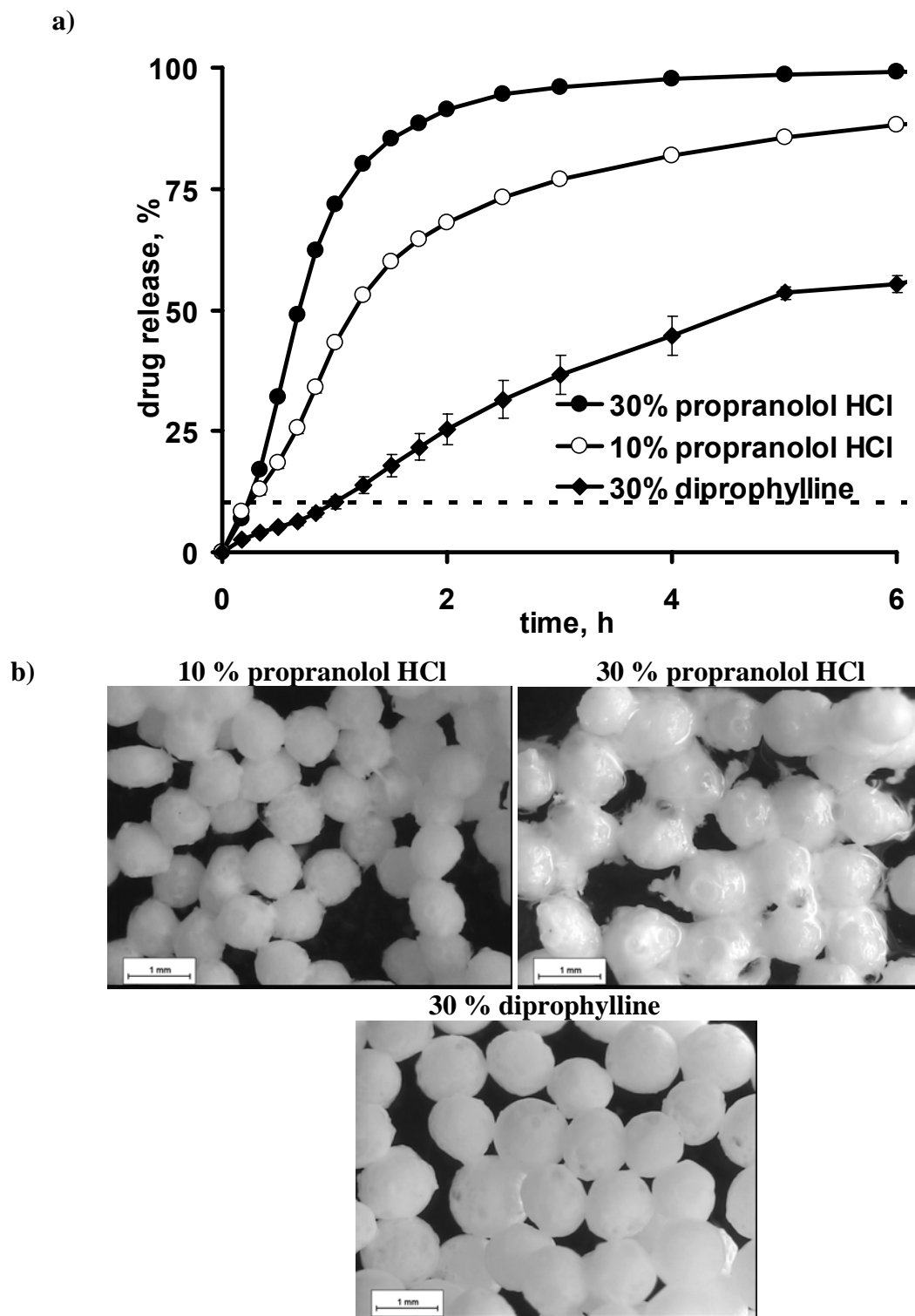**Fig 22** Influence of drug loading and drug type on drug release from Eudragit® L100-55 coated pellets (3.6 mg/cm^2) in 0.1 N HCl. a) drug release and b) macroscopic picture after release

a)
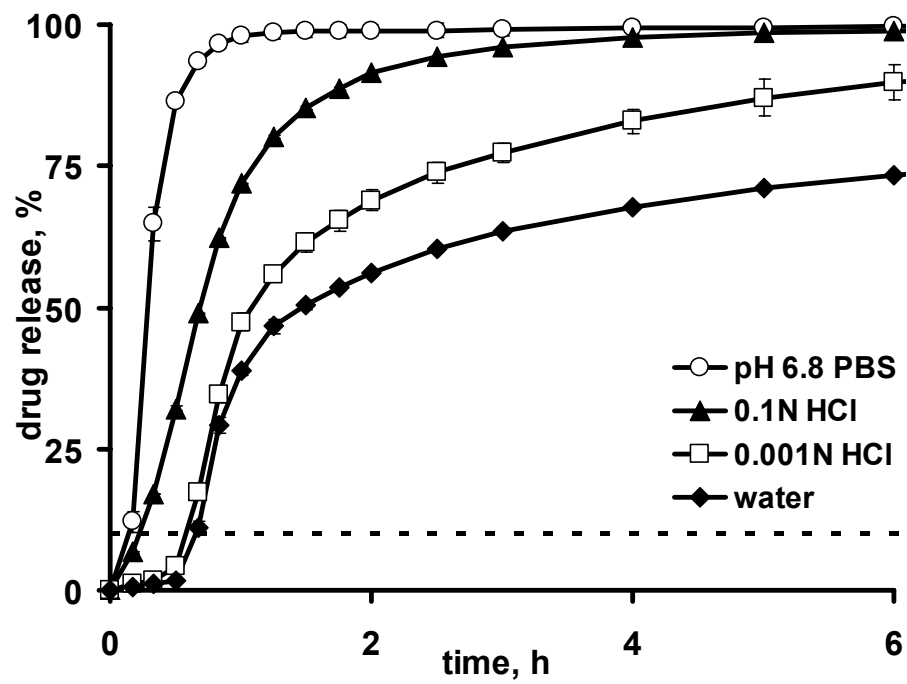
b)

Fig 23 Influence of release medium on a) drug release and b) polymer dissolution as seen in macroscopic picture after release from Eudragit® L100-55 coated pellets (30 % drug loading, 3.6 mg/cm² coating level, MCC core)

a)

b)

Fig 24 Influence of release medium on a) drug release and b) polymer dissolution as seen in macroscopic picture after release for Eudragit® L100-55 coated pellets (60 % drug loading, 1.8 mg/cm² coating level, NP core)

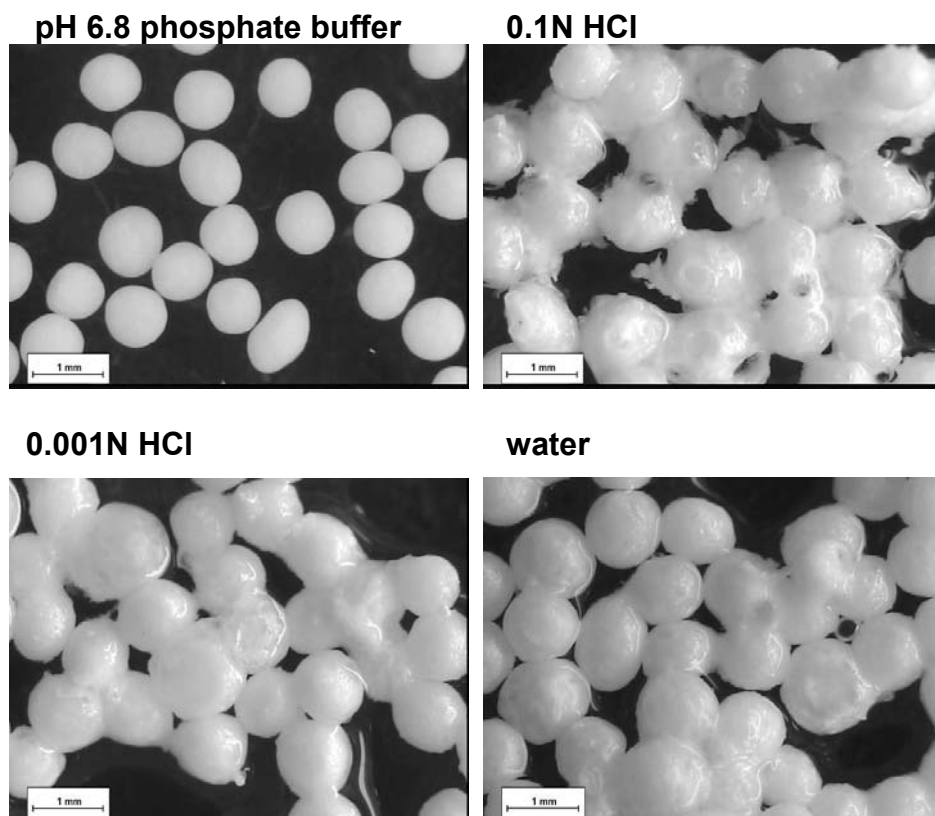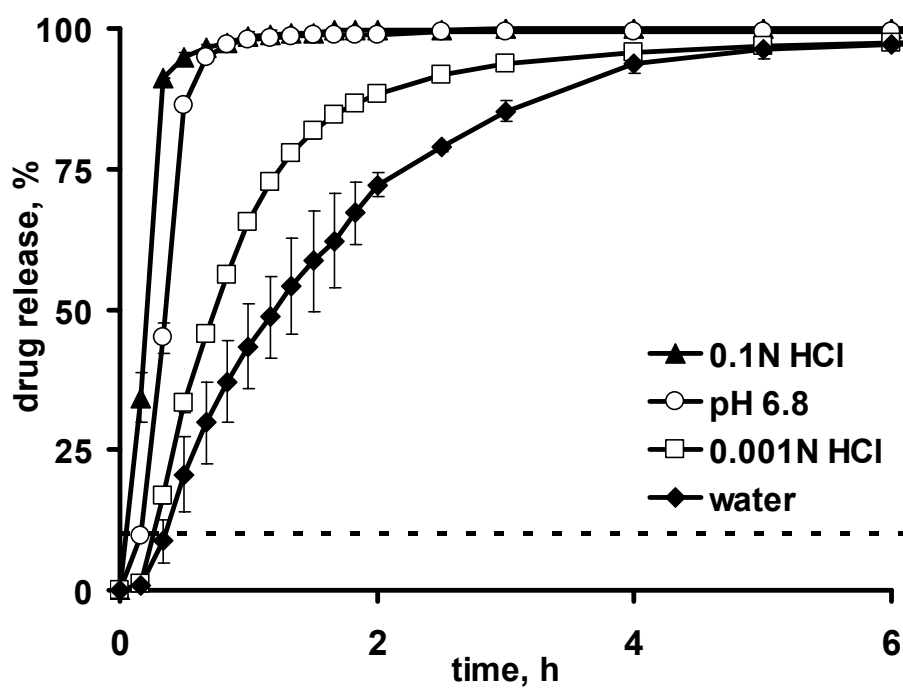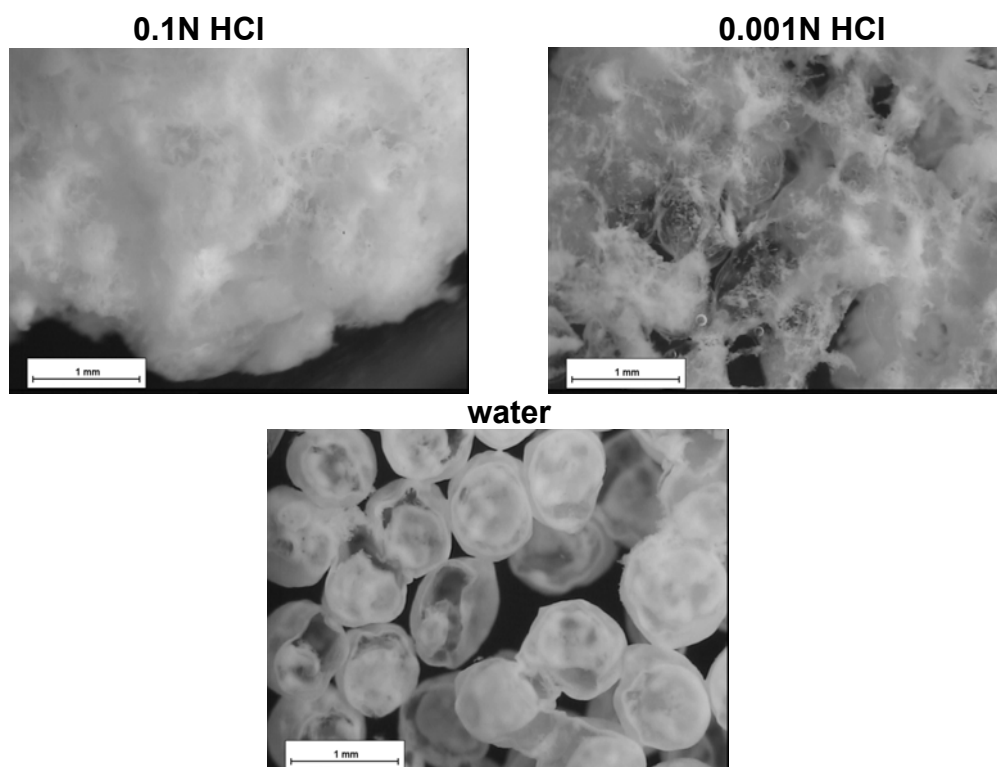Interestingly, Eudragit® L100-55 powder dissolved in concentrated propranolol HCl solutions but precipitated upon dilution (**Table 15**). This phenomenon explained the appearance of the Eudragit® L100-55 coated propranolol HCl pellets after release in 0.1 N HCl (**Fig 21**). The Eudragit® L100-55 coat dissolved partially due to the exposure to concentrated propranolol HCl solutions inside the pellets. Upon exposure to the bulk medium, the propranolol HCl solution was diluted and thus resulted in precipitates of Eudragit® L100-55 as gelled layer around the pellets as seen in the macroscopic pictures. This polymer dissolution could not be attributed to drug-induced changes of the pH inside pellets. Increasing the propranolol HCl concentration in 0.1 N HCl or deionized water led to decreasing pH values **(Table 15).** This should in fact prevent Eudragit® L 100-55 from dissolution instead of promoting it. The pH of samples in 0.1 N HCl remained constant after Eudragit® L 100-55 addition, whereas the pH was decreased by the polymer for samples in deionized water. This is attributed to partially ionization of carboxylic group in Eudragit® L 100-55 in deionized water, in consequence, pH was decreased.

Table 15   pH of propranolol HCl solutions in 0.1 N HCl and deionized water before and after addition of 1 % w/v Eudragit® L100-55

Propranolol HCl, mg/ml	0.1N HCl			deionized water		
	0% Eudragit® L100-55	1% w/v Eudragit® L100-55	Polymer dissolution	0% Eudragit® L100-55	1% w/v Eudragit® L100-55	Polymer dissolution
0	0.95	0.94	no	6.75	3.57	no
25	0.90	0.90	no	5.50	2.71	no
50	0.91	0.88	yes	4.95	2.53	partial
75	0.86	0.88	yes	4.76	2.63	yes
100	0.86	0.87	yes	4.57	2.63	yes

Due to the opposite charge ion, a salt formation between cationic propranolol HCl and anionic Eudragit® L100-55 could occur and might be responsible for the polymer dissolution (**Fig 25**). When this salt was formed deliberately by mixing solutions of the drug and the polymer in pH 6.8 phosphate buffer, precipitation occurred immediately. This complex was insoluble in deionized water and 0.1 N HCl and also could not be dissolved by the addition of more propranolol HCl solution. This was in agreement with a previous report that the salt formation of propranolol HCl and the anionic surfactant, sodium lauryl sulfate resulted in an insoluble complex (Aungst and Hussain, 1992). FTIR-measurements confirmed that this precipitate were a complex of Eudragit® L 100-55 and propranolol HCl by a band at 1550 cm^{-1} (**Fig 26**). This band corresponded to be a salt formation between carboxylic and amine group in Eudragit L100-55 and propranolol HCl, respectively (Takka, 2003). Mixing of the drug and the polymer in 0.1N HCl or deionized water did not cause a precipitation and the band at 1550 cm^{-1} was not present indicating no salt formation. Therefore, the propranolol HCl-induced dissolution of Eudragit® L100-55 in 0.1 N HCl was not caused by a salt formation between drug and polymer.
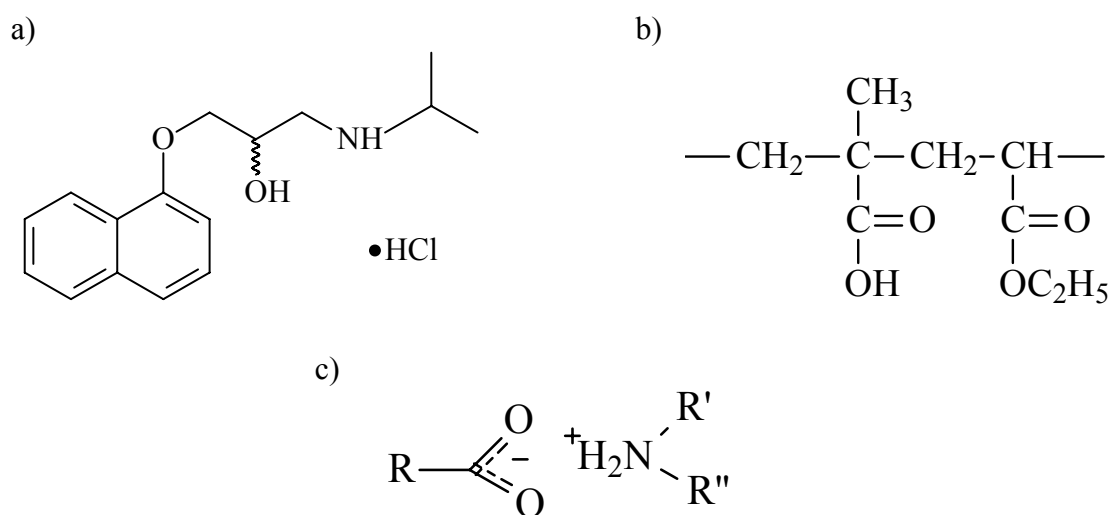
a)   b)

c)

Fig 25 Possibility of salt formation between a) propranolol HCl and b) Eudragit® L100-55 c) salt form
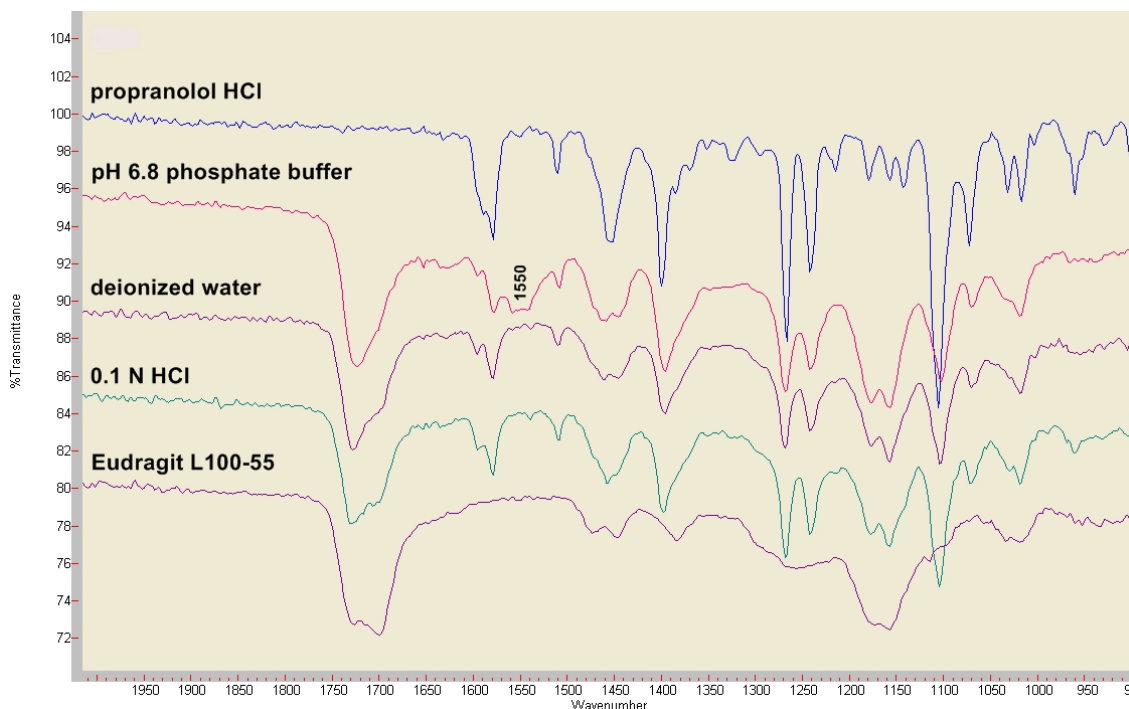
Fig 26 FTIR spectra of propranolol HCl, Eudragit® L100-55 and complex (1:1) prepared in different solvent

In the literature, polymer dissolution with the aid of surfactants as well as the surfactant behavior of propranolol HCl has been reported**.** Therefore, the surface tension of propranolol HCl solutions was investigated. In accordance with previous reports, a decrease in surface tension was observed with increasing propranolol HCl concentrations (**Fig 27**) (Ubrich et al., 2004). In contrast diprophylline, which did not cause dissolution of Eudragit® L 100-55, did not reduce the surface tension and thus did not have surfactant properties. To further evaluate the influence of propranolol HCl and surfactants on polymer dissolution, the polymer solubility in propranolol HCl and surfactant solutions was determined (**Table 16**). Sodium lauryl sulfate (SDS) was the most powerful surfactant to dissolve Eudragit® L100-55 followed by cetrimonium bromide and propranolol HCl. Moreover, other enteric polymers (hydroxypropylmethylcellulose acetate succinate and hydroxypropylmethylcellulose phthalate) and water insoluble polymers (Eudragit® RL, Kollidon® SR and ethylcellulose) were soluble in sodium lauryl sulfate solutions to some extent. Both cetrimonium bromide and propranolol HCl were considered as cationic surfactants and the Eudragit® L100-55 solubility was only slightly higher in cetrimonium bromide**.** This may be attributed to the stronger surfactant properties of cetrimonium bromide. Other authors also reported that the solubilization of

a water-insoluble poly (methacrylic acid) and acrylate copolymer in acidic solution occurred in the presence of surfactant (Vlachy et al. 2007). The structure of polymer and surfactant was described in the form of the 'pearl-necklace model'. In water or in acidic environment, the ionization of polymer was negligible. Therefore, hydrophobic forces played a role for the polymer-surfactant complex. Micelles were formed with the hydrophobic polymer parts facing inside and the head charge facing the medium, thus leading to polymer solubilization (Vlachy et al., 2006; Vlachy et al., 2007). The polymer-surfactant aggregation was confirmed by an increase in the mean size of micelles after adding Eudragit® L100-55 to the surfactant solutions (**Fig 28**).
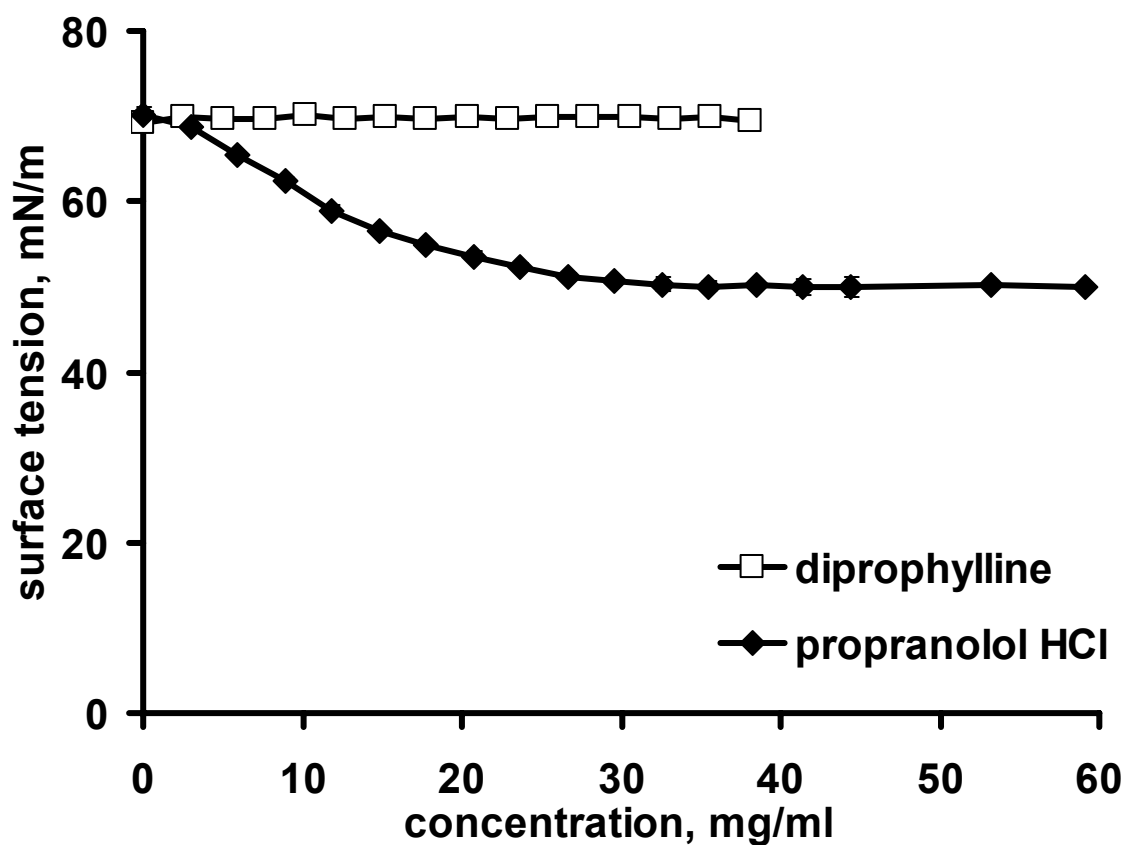
Fig 27 Surface tension of propranolol HCl and diprophylline solutions

Table 16   Polymer solubility in drug and surfactant solutions (50 mg surfactant/ml; 0.1N HCl)

Polymer	Polymer solubility, % w/v		
	Propranolol HCl	Cetrimonium bromide	Sodium lauryl sulfate
Eudragit® L100-55	3	4	5
HPMCP HP 50	-	-	1
HPMCAS-LF	0.5	0.5	1
HPMCAS-MF	0.5	0.5	1
HPMCAS-HF	0.5	0.5	1
Eudragit® RL	-	-	1
Kollidon® SR	-	-	3
Ethylcellulose 4 cP	-	-	1
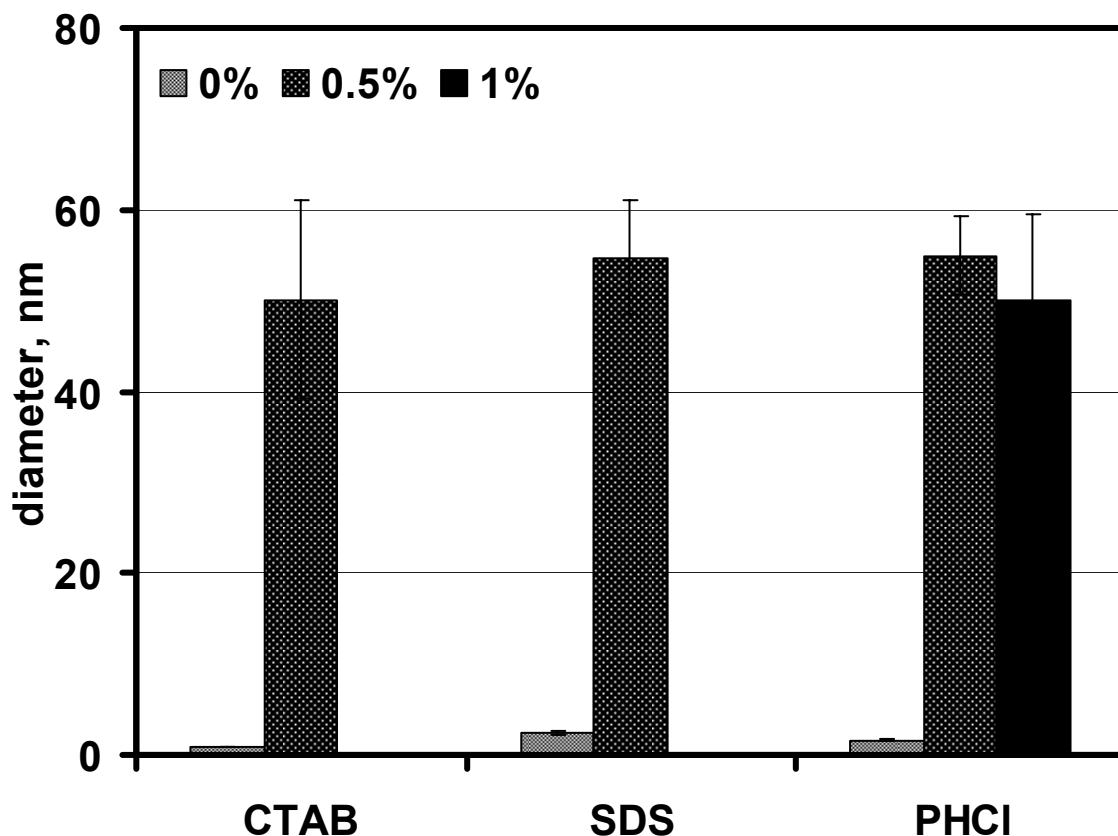
Fig 28 Mean micelle size of cetrimonium bromide (CTAB), sodium lauryl sulphate (SDS) and propranolol HCl (PHCl) with and without Eudragit® L100-55 (0.5 % and 1 % w/v)

The higher extent of polymer dissolution in 0.1 N HCl was attributed to the higher solubility of Eudragit® L100-55 in 0.1 N HCl compared to deionized water (**Table 17**). This solubility difference could be explained by the influence of electrolytes present in 0.1 N HCl on micelle formation. Electrolytes hindered the repulsion between the charged head groups of surfactants, thus increasing the micelle size and decreasing the critical micelle concentration (Elliott et al., 1973). In case of polymer-surfactant interaction, more adsorption of surfactant on polymer was reported in the presence of electrolytes (Carlsson et al., 1986). To confirm the effect of electrolytes on the solubility of Eudragit® L100-55 in propranolol HCl solutions, 0.1 N NaCl was used as dissolution medium. At the same ionic strength and osmolarity of 0.1 N HCl and 0.1 N NaCl, similar Eudragit® L100-55 solubility values were obtained in the presence of propranolol HCl.

Table 17   Influence of drug concentration and medium on Eudragit$^{®}$ L100-55 solubility

Propranolol HCl, mg/ml	Polymer solubility, % w/v	
	0.1 N HCl	Deionized water
25	0	0
50	3	0.5
75	6	5
100	11	10

In order to prevent the failure in gastric resistance, a HPMC seal coat was placed between the drug layer and the Eudragit$^{®}$ L100-55 coating layer. The seal coat prolonged the propranolol HCl release (**Fig 29a**), but could not completely prevent the polymer dissolution and premature drug release (**Fig 29a and b**). Apparently, the seal coat was either too thin or the water solubility of the HPMC still allowed sufficient interaction between propranolol HCl and Eudragit$^{®}$ L 100-55 for the polymer to dissolve. The retardation of the drug release may be attributed to the increase in coating thickness.
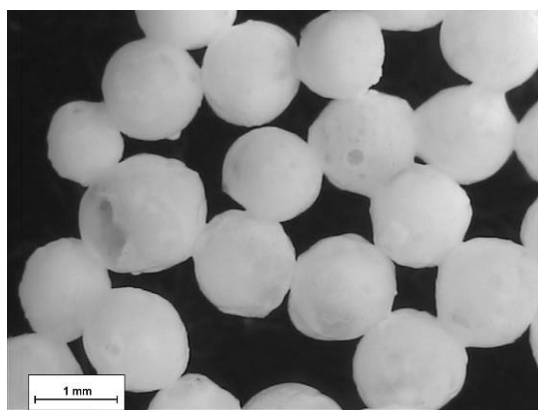
a)
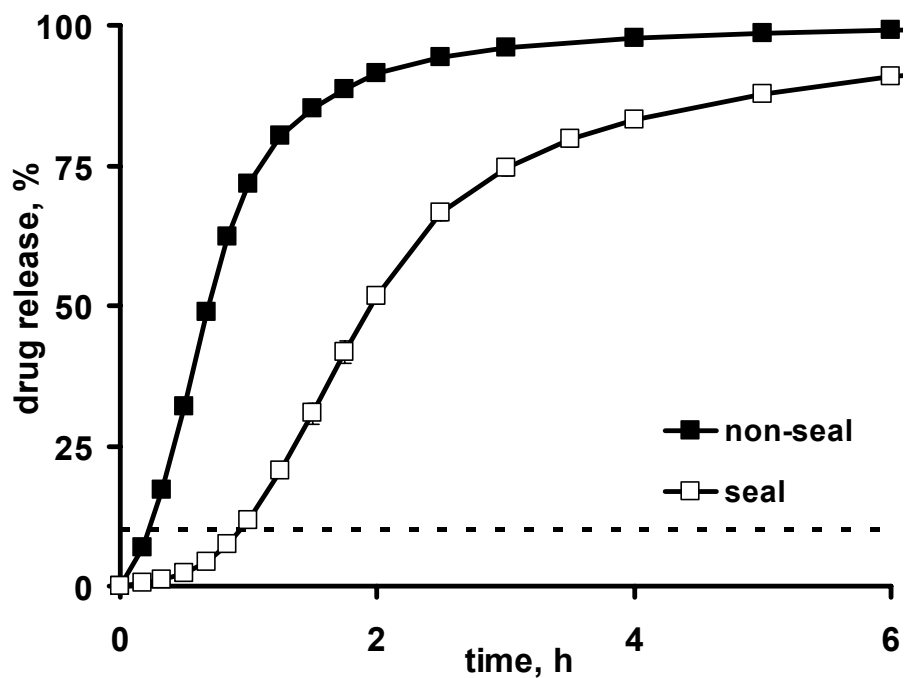
b)

Fig 29 Influence of sealing coat (1.8 mg/cm^2 HPMC E5) on a) drug release from propranolol HCl pellets (3.6 mg/cm^2 Eudragit L100-55) in 0.1 N HCl and b) polymer dissolution as seen in macroscopic picture after release for Eudragit$^{®}$ L100-55 coated propranolol HCl pellets seal with HPMC (30% drug loading, MCC core)

3.3.3. Conclusion

A failure of gastric resistance of Eudragit® L100-55 coated propranolol HCl pellets was observed. A premature drug release in 0.1 N HCl could be explained by the dissolution of polymer coating. The polymer coating dissolution was not occurred with Eudragit® L100-55 coated diprophylline pellets indicating that water soluble drug did not induce the polymer dissolution. The drug release and dissolution of polymer coating depended also on the type of release medium (0.1N HCl > 0.001N HCl > water), but irrespective of the core type (non-pareils or microcrystalline cellulose core). Eudragit® L100-55 could dissolve in the concentrated propranolol HCl solution and precipitate upon dilution. Therefore, the polymer coating dissolution was due to the exposure to the concentrated propranolol HCl solution inside the pellets. Upon propranolol HCl dilution by exposure to the bulk medium, polymer was thus precipitate as gel layer around the pellets. The polymer dissolution could be induced by the surfactant behavior of propranolol HCl as Eudragit® L100-55 and some other polymers could dissolve in the surfactant solutions. pH measurement, FTIR investigation and particle size analysis revealed that the polymer dissolution was not caused by the drug-induced pH change, salt formation between drug and polymer, but may be attributed to the polymer-surfactant aggregation. In order to prevent the enteric failure, a HPMC seal coat was placed between the drug layer and the Eudragit® L100-55 coating layer. The seal coat prolonged the propranolol HCl release, but could not completely prevent the polymer dissolution and premature drug release.

4. Summary

4.1. Comparison of controlled release properties of matrices prepared by hot melt extrusion, wet granulation and direct compression

Oral solid controlled release dosage forms aims to maintain the therapeutic drug level in blood plasma for an extended time period. This result in a lower dose frequency and thus improves the patient compliance. The aims of this study were to compare controlled drug release properties of matrices prepared by different preparation methods (direct compression, wet granulation and hot melt extrusion) and to investigate the influence of polymer type, drug solubility, drug loading and tablet size on drug release. In addition, an applicability-map was created in order to be a guideline of a suitable preparation technique for controlled release matrices. Matrices prepared from hot melt extrusion showed slower drug release comparing to wet granulation and direct compression because of the denser and lower porosity as well as thehigh tortuosity of matrices. Drug release was influenced by the polymer type and related to the polymer permeability. Drug release was in the order: Eudragit$^{®}$ RS > Kollidon$^{®}$ SR > ethylcellulose. Increasing drug solubility and drug loading, irrespective of the preparation methods, increased the drug release. Direct compression and wet granulation provided higher drug loading than hot melt extrusion. Increasing the matrix size decreased surface area of the matrix and thus decreased the drug release. An applicability-map was created by plotting the drug release rate versus the square root of drug solubility. The applicability-map indicated that hot melt extrusion was most suitable for highly soluble drug whereas wet granulation and direct compression were the alternative methods to prepare controlled release of drugs with an intermediate solubility. The controlled release of poorly soluble drug could be achieved with granules made by wet granulation. An acceptable estimation of drug release using the applicability-map was shown. This indicated that the applicability-map facilitated the selection of the most suitable preparation method for matrix tablet production of a specific drug.

4.2. Hot melt extrusion for enteric and controlled release mini-matrices preparation

Dosage forms with enteric and controlled release properties would be desirable for drugs, which should not be release in the stomach but in a controlled release fashion in the intestine. Dense, slowly eroding enteric matrices might be an interesting option to obtain both enteric and controlled release properties. The aim of this study was to investigate the feasibility of hot melt extrusion to produce mini-matrices with both enteric and controlled release properties. Cellulosic (HPMCAS and HPMCP) and methacrylate (Eudragit® L100-55, Eudragit® S100) enteric polymers were investigated as carrier materials. The cellulosic polymers had a much lower molecular weight than the methacrylate polymers and thus required lower process temperatures, less plasticizer and showed less die swell. Mini-matrices showed good mechanical properties in both wet and dry state that can ensure a reliable drug release without rupturing by mechanical stress. Mini-matrices showed acceptable enteric properties with different release rates in pH 6.8. This was attributed to the different pH-solubilities of the polymers (pH threshold). Drugs with various solubilities i.e., diprophylline, theophylline, carbamazepine) were incorporated in Eudragit® L100-55, Eudragit® S100 and HPMCAS-HF matrices. Diprophylline and carbamazepine exhibited a plasticizing effect on the polymer matrix by decreasing the Tg of the polymer matrix thus leading to easier processing. All mini-matrices provided acceptable enteric properties. The solubility of the drug determines the choice of enteric polymer in order to obtain both enteric and controlled release properties. In pH 6.8, polymer matrices with low pH threshold polymer rapidly released diprophylline and theophylline whereas controlled release of carbamazepine was obtained. On the other hand, a higher pH threshold polymer achieved controlled release for all drugs. Blends of Eudragit® S100/pH 7.0 and HPMCAS-MF/pH 5.5 were investigated to obtain flexible release properties. Increasing HPMCAS-MF led to easier processing. Although drug release was increased with increasing HPMCAS-MF, matrices with Eudragit® S100: HPMCAS-MF ratios up to 1:2 still passed the enteric requirement. Increasing the processing temperature resulted in easier processing, but a decrease in drug release. This might be attributed to an increase in melting of Eudragit® S100 in the blend and the increased density of the matrices. The potential of hot melt extruded matrices (Eudragit® S100 or its blend with HPMCAS) for colonic drug delivery was also investigated using 5-ASA as a model drug. 5-ASA was not released in 0.1 N HCl but slightly released in pH 6.8 and completely released in pH 7.4, indicating the potential use for colonic drug delivery.

4.3. Enteric failure of Eudragit® L100-55 coated propranolol HCl pellets

In this study, Eudragit® L100-55 coated propranolol HCl pellets did not fulfill the enteric requirement. Drug release in 0.1 N HCl from Eudragit® L100-55 coated propranolol HCl pellets was >10% within 2 h (USP criteria for enteric coated dosage forms ≤ 10% within 2 h in 0.1 N HCl). The premature drug release was attributed to the dissolution of the polymer coating showing in the macroscopic picture after drug release. Decreasing the coating level and increasing the drug loading resulted in increased drug release and was consistent with the degree of dissolution of the polymer coating. To investigate the influence of a water soluble drug on the dissolution of the polymer coating, propranolol HCl (solubility: 160 mg/ml) was replaced with diprophylline (solubility: 215 mg/ml). Diprophylline pellets exhibited a slower drug release compared to propranolol HCl pellets. This was attributed to the fact that diprophylline pellets did not result in any visible dissolution of the polymer coating. It was thus concluded that propranolol HCl exerts a drug-specific effect on the dissolution of Eudragit® L100-55. The dissolution of Eudragit® L100-55 coating depended also on the type of the release medium (0.1N HCl > 0.001N HCl > water), but irrespective of the core type (non-pareils or microcrystalline cellulose core). Eudragit® L100-55 could dissolve in the concentrated propranolol HCl solution and precipitate upon dilution. Therefore, the dissolution of the polymer coating was due to the exposure to the concentrated propranolol HCl solution inside the pellets. Upon propranolol HCl dilution by exposure to the bulk medium, polymer was thus precipitate as gel layer around the pellets. The polymer dissolution can possibly be explained by the surfactant behavior of propranolol HCl. The surfactant behavior of propranolol HCl was confirmed by decreasing surface tension of propranolol HCl solution with increasing drug concentration. In addition, Eudragit® L100-55 and some other polymers dissolved in surfactant solutions (cetrimonium bromide and sodium lauryl sulfate). pH measurement, FTIR investigation and particle size analysis revealed that the polymer dissolution was not caused by the drug-induced pH change, salt formation between drug and polymer, but could be attributed to the polymer-surfactant aggregation. In order to prevent the failure in gastric resistance, a HPMC seal coat was placed between the drug layer and the Eudragit® L100-55 coating layer. The seal coat prolonged the propranolol HCl release, but could not completely prevent the polymer dissolution and premature drug release.

5. Zusammenfassung

5.1. Vergleich der kontrollierten Freisetzung aus Matrices hergestellt mittels Schmelzextrusion, Feuchtgranulierung und Direkttablettierung

Orale feste Arzneiformen mit kontrollierter Freisetzung haben zum Ziel, den therapeutischen Wirkstoffspiegel im Blutplasma für ein verlängertes Zeitintervall aufrecht zu erhalten. Daraus resultiert eine niedrigere Dosierungshäufigkeit und folglich eine Verbesserung der Patientencompliance. Ziele dieser Studie waren die kontrollierte Freisetzung aus Matrices zu vergleichen, die mittels verschiedener Herstellungsverfahren hergestellt wurden (Direkttablettierung, Feuchtgranulierung und Schmelzextrusion) und den Einfluss der Polymerart, Wirkstofflöslichkeit, Wirkstoffbeladung und Tablettengröße auf die Wirkstofffreisetzung zu untersuchen. Zusätzlich wurde eine Anwendbarkeitskarte entwickelt um als Richtlinie für geeignete Herstellungsverfahren für kontrolliert freisetzende Matrices zu dienen. Matrices, die mittels Schmelzextrusion hergestellt wurden, wiesen eine langsamere Wirkstofffreisetzung im Vergleich zu mittels Feuchtgranulierung und Direkttablettierung hergestellter auf infolge der dichteren und niedrigeren Porosität sowie der höheren Tortuosität der Matrices. Die Wirkstofffreisetzung wurde durch die Polymerart und die damit verbundene Polymerpermeabilität beeinflusst. Die Wirkstofffreisetzung erfolgte in folgender Reihenfolge: Eudragit® RS > Kollidon® SR > Ethylcellulose. Eine erhöhte Wirkstofflöslichkeit und Wirkstoffbeladung erhöhte die Wirkstofffreisetzung unabhängig vom Herstellungsverfahren. Die Direkttablettierung und Feuchtgranulierung ermöglichte eine höhere Wirkstoffbeladung als die Schmelzextrusion. Eine Erhöhung der Matrixgröße erniedrigte die Matrixoberfläche und erniedrigte somit die Wirkstofffreisetzung. Eine Anwendbarkeitskarte wurde entwickelt, indem die Wirkstofffreisetzungsrate gegen die Quadratwurzel der Wirkstofflöslichkeit aufgetragen wurde. Die Anwendbarkeitskarte weist darauf hin, dass die Schmelzextrusion am meisten für sehr gut lösliche Wirkstoffe geeignet war, wohingegen sich die Feuchtgranulierung und Direkttablettierung als alternative Methoden zur kontrollierten Freisetzung von Wirkstoffen mittlerer Löslichkeit eignen. Die kontrollierte Freisetzung schwerlöslicher Wirkstoffe kann mit durch Feuchtgranulierung hergestellten Granulaten erreicht werden. Eine akzeptable Einschätzung der Wirkstofffreisetzung mittels der Anwendbarkeitskarte wurde gezeigt. Das bedeutet, dass die Anwendbarkeitskarte die Auswahl des am meisten geeigneten Herstellungsverfahrens für die Herstellung von Matrixtabletten spezieller Wirkstoffe erleichtert.

5.2. Schmelzextrusion für die Herstellung von enterisch und kontrolliert freisetzenden Minimatrices

Arzneiformen mit enterischer und kontrollierter Freisetzung wären erstrebenswert für Wirkstoffe, die nicht im Magen sondern im Darm auf eine kontrollierte Weise freigesetzt werden sollten. Dichte, langsam erodierende enterische Matrices könnten eine interessante Option darstellen, um beides, eine enterische und kontrollierte Freisetzung, zu erreichen. Ziel dieser Studie war es die Möglichkeit zu untersuchen, mittels Schmelzextrusion Minimatrices mit enterischer und kontrollierter Freisetzung herzustellen. Cellulosen (HPMCAS und HPMCP) und Methacrylate (Eudragit® L100-55, Eudragit® S100) als enterische Polymere wurden als Trägermaterial untersucht. Die Cellulosen hatten ein viel kleineres Molekulargewicht als die Methacrylate und benötigten somit eine niedrigere Verarbeitungstemperatur, weniger Weichmacher und wiesen eine geringere Strangaufweitung auf. Die Minimatrices wiesen sowohl im feuchten als auch im trockenen Zustand gute mechanische Eigenschaften auf, was eine verlässliche Wirkstofffreisetzung gewährleisten kann ohne Risse durch mechanischen Stress. Die Minimatrices zeigten akzeptable enterische Eigenschaften mit unterschiedlichen Freisetzungsraten in pH 6.8. Das war den unterschiedlichen pH-Löslichkeiten (pH-Schwellenwert) der Polymere zuzuschreiben. Wirkstoffe mit unterschiedlichen Löslichkeiten (z.B. Diprophyllin, Theophyllin, Carbamazepin) wurden in Eudragit® L100-55, Eudragit® S100 und HPMCAS-HF Matrices eingearbeitet. Diprophyllin und Carbamazepin zeigten einen weichmachenden Effekt auf die Polymermatrix durch eine Tg-Erniedrigung der Polymermatrix, und führten somit zu einer erleichterten Verarbeitung. Alle Minimatrices wiesen akzeptable enterische Eigenschaften auf. Die Löslichkeit des Wirkstoffes bestimmt die Wahl des enterischen Polymers um beides, enterische und kontrollierte Freisetzung, zu erhalten. In pH 6.8 setzten die Polymermatrices mit einem niedrigeren pH-Schwellenwert Diprophyllin und Theophyllin schnell frei, wohingegen eine kontrollierte Freisetzung von Carbamazepin erreicht wurde. Auf der anderen Seite, erreichte ein Polymer mit höherem pH-Schwellenwert eine kontrollierte Freisetzung aller Wirkstoffe. Mischungen aus Eudragit® S100/pH 7.0 und HPMCAS-MF/pH 5.5 wurden untersucht um flexible Freisetzungseigenschaften zu erhalten. Eine Erhöhung von HPMCAS-MF führte zu einer erleichterten Verarbeitung. Obwohl die Wirkstofffreisetzung erhöht war mit erhöhtem HPMCAS-MF, erfüllten Matrices mit einem Verhältnis von Eudragit® S100: HPMCAS-MF bis zu 1:2 immernoch die enterischen Anforderungen. Eine Erhöhung der

Verarbeitungstemperatur resultierte in einer einfacheren Verarbeitung, erniedrigte allerdings die Wirkstofffreisetzung. Das könnte dem verstärkten Schmelzen von Eudragit® S100 in der Mischung zugeschrieben werden und der erhöhten Dichte der Matrices. Das Potenzial der schmelzextrudierten Matrices (Eudragit® S100 oder dessen Mischungen mit HPMCAS) für gezielte Wirkstofffreisetzung im Kolon wurde ebenfalls untersucht mit 5-ASA als Modelwirkstoff. 5-ASA wurde nicht in 0.1 N HCl aber schwach in pH 6.8 freigesetzt und komplett in pH 7.4, was auf den möglichen Nutzen für eine gezielte Freisetzung im Kolon hinweist.

5.3. Enterisches Versagen von Eudragit® L100-55 überzogenen Propranolol HCl Pellets

In dieser Studie erfüllten die mit Eudragit® L100-55 überzogenen Propranolol HCl Pellets nicht die enterischen Anforderungen. Die Wirkstofffreisetzung in 0.1N HCl aus Eudragit® L100-55 überzogenen Propranolol HCl Pellets war >10 % innerhalb von 2 h (USP-Kriterien für enterisch überzogene Arzneiformen ≤10 % innerhalb von 2 h in 0.1N HCl). Die vorzeitige Wirkstofffreisetzung war der Auflösung des Polymerüberzugs zuzuschreiben, zu sehen auf den makroskopischen Bildern nach der Wirkstofffreisetzung. Eine Erniedrigung des Überzugslevels und eine Erhöhung der Wirkstoffbeladung resultierte in einer erhöhten Wirkstofffreisetzung und war übereinstimmend mit dem Grad der Auflösung des Polymerüberzugs. Um den Einfluss eines wasserlöslichen Wirkstoffes auf die Auflösung des Polymerüberzugs zu untersuchen, wurde Propranolol HCl (Löslichkeit: 160 mg/ml) ersetzt durch Diprophyllin (Löslichkeit: 215 mg/ml). Die Diprophyllin-haltigen Pellets wiesen eine langsamere Wirkstofffreisetzung auf im Vergleich zu den Propranolol HCl-haltigen. Das ist dem Fakt zuzuschreiben, dass die Diprophyllin-haltigen Pellets keine sichtbare Auflösung des Polymerüberzugs aufzeigten. Dementsprechend wurde geschlussfolgert, dass Propranolol HCl einen wirkstoffspezifischen Effekt auf die Auflösung von Eudragit® L100-55 aufweist. Die Auflösung vom Eudragit® L100-55-Überzug hängt auch vom Freisetzungsmedium ab (0.1 N HCl > 0.001 N HCl > Wasser), ist aber unabhängig vom Starterkern-Typ (Zuckerstarterkern oder Starterkern aus mikrokristalliner Cellulose). Eudragit® L100-55 konnte in konzentrierter Propranolol HCl-Lösung aufgelöst werden und präzipitierte bei Verdünnung dieser. Daher ist die Auflösung des Polymerüberzugs dem Ausgesetztsein der konzentrierten Propranolol HCl-Lösung im Inneren des Pellets zuzuschreiben. Bei der Verdünnung von Propranolol HCl durch das vorhandene Medium, präzipitierte das

Polymer als Gelschicht um die Pellets herum. Die Auflösung des Polymers kann möglicherweise durch das Tensid-Verhalten von Propranolol HCl erklärt werden. Das Tensid-Verhalten von Propranolol HCl wurde bestätigt durch die Erniedrigung der Grenzflächenspannung von Propranolol HCl-Lösungen bei Erhöhung der Wirkstoffkonzentration. Außerdem lösen sich Eudragit® L100-55 und einige andere Polymere in Tensidlösungen auf (Cetrimoniumbromid und Natriumlaurylsulfat). pH-Messungen, FTIR-Untersuchungen und Partikelgrößenanalyse deckten auf, dass die Polymerauflösung nicht bedingt war durch wirkstoffinduzierte pH-Veränderungen, Salzbildung zwischen Wirkstoff und Polymer, sondern der Polymer-Tensid-Aggregation zugeschrieben werden kann. Um das Versagen der Magensaftresistenz zu verhindern, wurde ein HPMC-Schutzüberzug zwischen die Wirkstoffschicht und die Eudragit® L100-55-Überzugsschicht gelegt. Der Schutzüberzug verlangsamte die Propranolol HCl-Freisetzung, konnte aber die Polymerauflösung und vorzeitige Wirkstofffreisetzung nicht komplett verhindern.

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7. Publications and Presentations

7.1. Publications

Apichatwatana, N., Bodmeier, R. Comparison of controlled release properties of matrices prepared by hot melt extrusion, wet granulation and direct compression (in preparation)

Apichatwatana, N., Bodmeier, R. Hot melt extrusion for enteric and controlled release mini-matrices preparation (in preparation)

Apichatwatana, N., Rujivipat, S., Bodmeier, R. Enteric failure of Eudragit$^{®}$ L100-55 coated propranolol HCl pellets (in preparation)

7.2. Presentations

Apichatwatana, N., Bodmeier R. Parameters affecting the drug release from hot melt extruded enteric mini-matrices. Polymers in Biomedicine and Electronics Biannual Meeting of the GDCh-Division of "Macromolecular Chemistry" and Polydays, Berlin, Germany (2010).

Herrmann, J., Apichatwatana, N., Körber, M., Bodmeier, R. Insoluble polymer mini-matrices as controlled delivery systems for high loading water soluble drug prepared by tabletting or hot melt extrusion. Annual Meeting of the American Association of Pharmaceutical Scientists, AAPS, New Orleans, Louisiana ,USA, (2010)

8. Curriculum Vitae

For reasons of data protection,

the curriculum vitae is not included in the online version