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Implications of Plasticization on the Properties of Hot-Melt Extruded Oral Dosage Forms

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Implications of Plasticization on the Properties of Hot-Melt Extruded Oral Dosage Forms

by

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Dedication

To my parents.

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Implications of Plasticization on the Properties of Hot-Melt Extruded Oral Dosage Forms

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The influence of plasticization and other formulation factors on the properties of hot-melt extruded dosage forms for the controlled release of water-soluble active compounds was investigated.

Citric acid monohydrate was demonstrated to function as a solid-state plasticizer in hot-melt extruded Eudragit® RS PO tablets and in cast films when concentrations below the compatibility limit were employed. Melting of the organic acid and solubilization in the polymer during extrusion were necessary to observe the plasticizing effect. The release rate of diltiazem hydrochloride, used as a high-melting, water-soluble model drug, from melt extruded Eudragit® RS PO matrix tablets increased and became independent of the original drug particle size in the presence of citric acid monohydrate. Thermal analysis of physical mixtures demonstrated that citric acid promoted drug melting during extrusion by interaction and melting point depression. Diltiazem hydrochloride remained amorphous in the final dosage form, and leaching of citric acid monohydrate enhanced drug diffusion by increasing the matrix porosity.

Delayed-release matrix pellets with particle sizes below one mm were prepared by hot-melt extrusion, and the influence of the matrix forming polymer and the type and level of plasticizer on the processibility and release properties was investigated. Pellets complied with the USP requirement for delayed release articles to release less than 10% drug at pH 1.2 after 2 hours when plasticized Eudragit® S100 was used as the release-controlling material. High levels of efficient plasticizers had to be employed to decrease the polymeric melt viscosity, increase the process yield and enable extrusion at moderate temperatures to avoid instabilities during processing and storage. The aqueous solubility of the plasticizer further impacted the drug release rate in acid.

A novel application of hot-melt extrusion for the preparation of monolithic matrices comprising enteric coated particles was studied. The influence of the mechanical strength of the multiparticulates, pellet loading and nature of the hydrophilic carrier material on the preservation of the delayed-release properties after extrusion was investigated. Soft particles coated with brittle films remained intact when low-melting carriers that did not solubilize the enteric film during extrusion were used, and the dissolution profile was stable over one year.

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Chapter 1: Introduction

1.1 CONTROLLED RELEASE DOSAGE FORMS FOR ORAL DRUG DELIVERY

1.1.1 Advantages of controlled release systems

Controlled or modified release systems are characterized by their ability to either control the rate or the area of drug release. With respect to oral drug delivery, the release can either be sustained during the transit of the dosage form in the gastro-intestinal tract (extended, sustained or prolonged drug release), or delayed to regions subsequent to the stomach including the small intestine or the colon (delayed release). Dosage forms with controlled release properties provide numerous advantages over conventional, immediate release systems [1]. From a biopharmaceutical standpoint, controlled release systems generate more consistent drug plasma concentrations over a prolonged period of time. Toxic peaks in drug concentration as occurring in the initial phase after administration of immediate release products or inefficient plasma levels at later time points can be avoided. The plasma concentration fluctuates less and remains within the therapeutic window over a prolonged time interval. As a result, not only drug efficacy and safety, but also patient compliance will be enhanced since dosing can be simplified to a once or twice a day regimen. Delayed release applications are indicated when the drug is instable in the acidic environment of the stomach, causes local side effects to the stomach mucosa, or if particular regions in the intestine or in the colon need to be targeted to improve drug absorption and bioavailability. Another field of application for delayed delivery systems focuses on active ingredients with chronotherapeutic effects. In this case, the lag-time between drug administration and release allows the coordination of the

release with the body's circadian rhythms to maximize effectiveness and minimize side effects.

1.1.2 Classifications and release mechanisms

Numerous approaches have been pursued to control the drug release in a temporal or spatial manner. The drug may be embedded in a release-controlling matrix (matrix systems) or inside a core which is surrounded by a release-controlling shell or membrane (reservoir system). Natural or synthetic polymers are mainly used as drug carriers or coating materials to provide the dosage form with the desired release properties. The drug is liberated from these systems by diffusion, matrix or coat dissolution, osmosis or by a combination of these mechanisms. Alternative delivery approaches include gastro-retentive systems, bioadhesive and particulate dosage forms.

Controlled delivery dosage forms can further be classified as single-unit (monolithic) or multiple-unit systems. Multiple-unit dosage forms with modified release properties yield advantages over monolithic systems in terms of beneficial pharmacokinetic properties and formulation flexibility [2]. Particles small enough to pass through the stomach pylorus spread more rapidly and homogeneously in the intestine independently of gastric emptying and feeding state. The drug absorption can be maximized while plasma level fluctuations and intra- and inter-subject variations are reduced. In contrast to monolithic dosage forms including film-coated tablets, high local concentrations and dose dumping are avoided. The blending of pellets containing different drugs or providing different drug release rates allows the simultaneous delivery of incompatible drugs and the creation of tailored release profiles.

Downstream processing of multiple-unit systems into monolithic, multi-particulate dosage forms is necessary to improve patient compliance and dosing accuracy.

The most common techniques are the filling of multi-particulates into capsules or the compression into tablets. Capsules are more cost-intensive than tablets and may be less secure due to their higher susceptibility to tampering. Capsule shells are further hygroscopic and provide little protection to light, oxygen and moisture. The compression of pellets into multi-particulate tablets has gained popularity, but remains technologically challenging [3]. Compaction forces during tableting can fracture the film of functionally coated pellets and result in the loss of their modified release properties. The requirement of large amounts of cushioning agents to absorb compaction forces and physically separate the pellets during compression limits the amount of pellets that can be loaded into the tablet.

1.2 HOT-MELT EXTRUSION FOR PHARMACEUTICAL APPLICATIONS

1.2.1 Advantages and applications of hot-melt extrusion

Hot-melt extrusion is a well established process that is widely used in the plastic, rubber and food industry. More recently, the process has been adapted for the preparation of pharmaceutical matrix systems providing immediate or controlled drug release. During hot-melt extrusion, a blend consisting of a drug, a thermoplastic carrier and further optional excipients is transported through a heated barrel by one or two rotating screws. The drug is homogeneously dispersed in the softened carrier and then extruded under high pressure through a product-shaping die to yield a matrix-type dosage form.

The interest in hot-melt extrusion for pharmaceutical applications has increased recently as evident from a growing number of patents, scientific publications and marketed drug products [4-6]. Hot-melt extrusion allows the manufacture of dosage forms in a continuous and efficient manner, provides potential for scale-up and

experiences high industrial acceptance. The process is highly versatile as numerous different dosage forms including tablets, granules, pellets, transdermal and transmucosal films, powders and implants can be obtained by utilizing appropriate dies and downstream processing equipment. The technology has been successfully applied for the preparation of solid dispersions to improve the solubility, dissolution rate and bioavailability of poorly soluble compounds [7]. Alternatively, matrix systems providing controlled release for high loadings of soluble drugs may be manufactured by melt extrusion. The initial porosity of melt extruded matrices is low due to the high degree of carrier coalescence during thermal compounding as compared to wet-massed [8] or directly compressed matrices [9], minimizing percolation effects and hence drug diffusion. Subsequent processing steps including film coating and the use of organic or aqueous solvents can be avoided, making the process amenable for hydrolysable drugs and reducing time and efforts associated with coating procedures and solvent removal. The rotating screw inside the extrusion barrel exerts shearing, kneading and mixing forces on the processed material, promoting a deaggregation, particle size reduction and homogenous dispersion of the drug within the thermoplastic carrier.

1.2.2 Composition of formulations and general requirements for hot-melt extrusion

A formulation for a hot-melt extruded dosage form typically comprises the drug embedded in a thermoplastic carrier. Optionally, further functional excipients may be utilized including processing aids (plasticizers, glidants or thermal lubricants), stability enhancers (antioxidants, pigments) or release-modifying agents (pore-formers, gelling polymers, superdisintegrants, retardants or electrolytes for pH modification, solubilizing agents or surfactants). The carrier can be a thermoplastic polymer or other meltable

substances including waxes, lipids, organic acids, urea and inorganic salts. Polymeric carriers may be completely amorphous or semi-crystalline, and have been traditionally used for other pharmaceutical applications including film-coating, granulation, direct compression, or in liquid dosage forms. All formulation components need to meet the following requirements in order to be acceptable for hot-melt extruded pharmaceutical systems:

1. Be of a pharmaceutical grade and generally regarded as safe for the intended dose and route of administration.
2. Stability under processing conditions.
3. Stability during shelf-life.

1.2.3 Characterization of hot-melt extruded dosage forms

Hot-melt extruded delivery systems should be carefully characterized regarding chemical stability, solid state properties including degree of crystallinity and interactions between formulation components, drug release properties and content uniformity. The characterization work includes the evaluation of the status quo subsequent to manufacture as well as the monitoring of these properties as a function of storage time and storage conditions.

Thermogravimetry (TG) or chromatographic methods represent popular analytical techniques to assess the chemical stability of the components in hot-melt extruded dosage forms. Instabilities of low-molecular weight components including the drug or processing aids may be detected using stability-indicating high-pressure liquid chromatography (HPLC) assays [10-12]. Polymer degradation in form of depolymerization or chain scission has been studied by gel permeation chromatography (GPC) [11, 13] or HPLC assaying of free monomers [14]. Thermally induced reactions in the polymeric side

chains often involve functional groups and can be monitored by Fourier transform infrared spectroscopy (FT-IR) coupled with differential scanning calorimetry (DSC) [15, 16] or TG [17], mass spectroscopy (MS) coupled with TG [18], solid-state nuclear magnetic resonance spectrometry (NMR) [19] or by titration.

Processing under elevated pressure and temperature may induce changes to the solid-state of the drug or the processing aids. Extrusion at temperatures below the drug's melting point in carriers that show low compatibility with the drug will primarily result in a dispersion of the crystalline drug at reduced particle size and in its original polymorphic modification. These systems are favorable for controlled release delivery systems due to their advantageous storage stability. However, elevated temperature and polymer-drug interactions may favor polymorphic conversions or induce complete or partial melting or solubilization of the drug in the polymer matrix. The drug may be dispersed on a molecular level to form a true solid solution with the polymer, or be present as a separate phase to form an amorphous mixture with the carrier. This approach has been pursued for the bioavailability enhancement of poorly soluble drugs attributed to the higher solubility and dissolution rate of amorphous compounds. On the downside, these systems are susceptible to physical instabilities in the form of drug recrystallization or polymorphic conversion to the most stable modification after cooling and during storage. In any case, the solid state of the drug and the excipients should be characterized, the degree of crystallinity quantified and monitored during shelf-life. Popular analytical techniques that are used for the assessment of drug and excipient solid state properties include DSC or modulated DSC (MDSC), powder X-ray diffraction analysis (PXRD), solid-state NMR, FT-IR and Raman spectroscopy [20].

The same analytical tools may be employed to investigate solid-state interactions between the drug and functional excipients. These interactions may be of a chemical

nature due to reactions between functional groups as it has been reported for 5-aminosalicylic acid and citric acid during hot-melt extrusion [21]. Attractive intermolecular forces between blend components including hydrogen bonding, electrostatic and hydrophobic forces are typical physical interactions that may occur in the solid state. These interactions may decrease the melting point and viscosity of the blend, promote drug solubilization and amorphization during the extrusion process and oppose complete drug release from the matrix due to drug adsorption phenomena.

When selecting an analytical method, several criteria need to be taken into consideration: How is the sample prepared, and does the preparation technique introduce solid-state changes into the system? Methods involving as little sample manipulation as possible should be preferred such as diffraction or diffuse reflectance techniques. Milling of the extrudates or the exposure to high pressure can potentially reduce drug crystallinity or induce polymorphic conversions. Heating procedures as used for DSC experiments may manipulate the solid state of the drug due to solubilization during testing. The characteristic limit of detection of the analytical method plays an important role if the drug loading in the matrix is low or small changes in crystallinity need to be detected. Although all of the listed techniques have the potential to be used for quantitative solid-state analysis when calibrated carefully, some methods may provide signals that are more sensitive to the degree of crystallinity within the sample than others such as FT-IR. Signal independence from particle size represents an important advantage of NMR spectroscopy. When the nature of interactions needs to be identified, some methods including FT-IR or MS provide more useful information than others.

Imaging techniques including scanning electron microscopy (SEM), transmission electron microscopy (TEM), energy dispersive spectroscopy (EDS) or atomic force microscopy (AFM) have proven useful to study the microstructure of hot-melt extruded

delivery systems. SEM has been demonstrated to be a highly sensitive method for the detection of drug recrystallized on the surface of supersaturated, hot-melt extruded tablets at concentrations below the limit of detection of PXRD or DSC [22]. EDS or AFM can be employed to investigate the drug particle size and degree of dispersion within the extruded matrix. Alternatively, peak broadening in PXRD patterns has been used to calculate the average particle size of drug nanocrystals in solid dispersions [23]. The porosity of hot-melt extrudates has been studied quantitatively by helium pycnometry and mercury intrusion porosimetry [9] or qualitatively by SEM. In addition, hot-melt extruded systems are generally characterized with respect to content uniformity and drug release profile. Fitting of the release data to mathematical models provides a tool to identify underlying drug release mechanisms.

1.2.4 Hot-melt extrusion process technology

Hot-melt extrusion represents a complex process combining co-melting with particle size reduction, homogenization and compression at elevated pressure. The formulation is ususally pre-blended and then fed into the extruder, or blend components can be metered separately using different feeders. Extruders may be flood-fed, implying that the feedstock is delivered into the screw channel by gravity, and that the rate of transport is controlled by the rotation speed of the screw(s). This method is commonly employed for free-flowing powder blends and when using single screw extruders. Starve-feeding involves the delivery of material by a rate controlling feeder, making the throughput independent of the extruder screw rotation speed. Most commonly used devices are screw feeders which meter the blend either volumetrically or gravimetrically to achieve the target mass flow. Alternative feeding devices include vibration-assisted feeders, belt feeders, hoppers with agitators or roll feeders [24].

The heart of the extruder consists of a single- or twin-screw system rotating inside a heated barrel. The screw design strongly impacts the performance of the extruder, the properties of the extruded material and the throughput rate. Characteristic screw parameters represent the screw diameter, the screw length and the ratio thereof (L/D). The screw may be one piece or modular to allow application-oriented tailoring of the extrusion process. Typical screw elements include a feeding and conveyance zone in the initial section exhibiting a large channel volume, followed by melting, mixing and metering elements towards the die end. Twin-screw extruders may be operated using a co- or counter-rotating screw design. The co-rotating principle provides better mixing, can be operated at higher screw speeds and exhibits self-wiping properties [25]. Two different mixing processes occur during the extrusion process, dispersive and distributive mixing. Dispersive mixing results in a reduction in drug particle size due to the shear stress exerted by the rotating screw. Since shear stress is the product of shear rate and melt viscosity, dispersive mixing is highest within the initial segments of the extruder when the polymer melt exhibits the highest viscosity [26]. On the other hand, distributive mixing is essential to produce a homogeneous product of high content uniformity, and can be achieved by screw designs promoting splitting and recombination of the softened material. The barrel may also be in one piece or modular, is electrically heated and usually comprises several heating zones to generate temperature profiles. Venting modules may be incorporated into the barrel design to remove volatiles including moisture and residual monomers during extrusion.

In addition to the extruder design, typical process control parameters include the feeding rate, screw rotation speed, and the temperature profile. Readout parameters that assist process monitoring are melt pressure and temperature, torque or motor load and energy consumption. The material exits the barrel through a product-shaping die whose

geometry is dictated by the application. The die poses a resistance to the material that needs to be overcome by the pressure which is generated by the moving melt. Depending on the dosage form requirements, dies with circular, annular and slit-shape orifices are available.

1.2.5 Formulation stability during processing

In spite of the tremendous research activity within the field of pharmaceutical hot-melt extrusion during the past 20 years, the number of melt extruded products on the market remains slim until today. Most aspects contributing to this circumstance are directly or indirectly related to concerns of chemical or physical instabilities of single components or the drug product. Instabilities may occur during processing and become immediately apparent subsequent to the melt extrusion process, or manifest themselves during shelf-life. The extent of degradation is primarily dependent on the formulation, extrusion equipment and process design. The stability of the formulation components during the hot-melt extrusion process may be affected adversely by one or a combination of the following factors:

1. Elevated temperature.
2. Extensive mechanical shear rate or stress.
3. High pressure.

The extent of thermally induced degradation reactions is a function of the extrusion temperature, duration of heat exposure and heat susceptibility of the extruded material. The processing temperature is mainly dictated by the melt viscosity-temperature behavior and the glass transition temperature or melting point of the polymeric carrier. Selecting polymers with low melt viscosities and transition temperatures represents a viable approach to reduce the extrusion temperature and hence thermal degradation of the

drug and/ or the functional excipients. The use of processing aids including plasticizers and thermal lubricants enlarge the temperature window for hot-melt extrusion by decreasing the glass transition temperature of the polymer and the viscosity of the blend. Oxidation reactions may be reduced by either using anti-oxidants or by processing under vacuum or in an inert-gas atmosphere.

The duration of heat exposure is determined by the residence time of the material inside the extruder. Short residence times of a few minutes are pivotal to limit degradation and may be realized by an appropriate extruder design and the use of well-plasticized blends. Increasing the screw speed can reduce the residence time, but extensive shearing of the polymer by the rotating screws may provoke mechanical degradation. Crowley and coworkers reported that the degradation of polyethylene oxide during extrusion at low screw speeds could be diminished by reducing the temperature, suggesting a thermal degradation mechanism. Increasing the screw speed initially decreased polymer degradation due to shorter residence times, before mechanical fracture occurred at very high screw speeds. Low-molecular weight polyethylene oxide functioned as a plasticizer and enhanced the chemical stability of the parent polymer during extrusion [13].

1.3 IMPLICATIONS OF PLASTICIZATION OF HOT-MELT EXTRUDED DELIVERY SYSTEMS

1.3.1 Definition and effects of plasticizers in polymeric systems

Traditional plasticizers are compounds that are added to formulations to modify the properties of the polymer. When used in hot-melt extruded blends, the plasticizer will decrease the polymer's glass transition temperature and melt viscosity. The blend can be processed applying lower temperatures and reduced mechanical work. The significance

of efficient plasticization increases when polymers with high glass transition temperatures are used, or if any blend component is susceptible to thermally induced degradation. Low melt viscosities are pivotal to maximize the output and yield of the extrusion process, and to minimize the residence time of the material inside the heated barrel. When added to coating formulations, plasticizers improve the film coalescence at reduced temperatures during the coating process and make the film more flexible.

Plasticizers can be classified regarding their state being liquid or solid, their hydrophobicity, molecular weight, chemical structure or whether they are externally added to the blend or grafted into the polymer during polymerization. Solid-state plasticizers yield numerous advantages over liquid plasticizers in terms of handling and processing. Powdered plasticizers can be easily dry-blended with the drug and the polymer without forming tacky pastes with poor flow properties. The produced blends are of high homogeneity, and feeding into the extruder is facilitated due to superior powder flow. Solid plasticizers are generally less volatile, so that evaporate loss during extrusion is minimized.

1.3.2 Mechanisms of plasticizer action

The most important theories on mechanisms of plasticizer action were developed in the 40's and 50's including the lubricity theory, gel theory and free volume theory [27].

According to the lubricity theory, the plasticizer positions itself between the polymer chains so that attractive forces between the macromolecules are lowered and the gliding of the planes is facilitated during plastic flow. The gel theory describes a polymer as a three-dimensional network structure that is stabilized by temporary points of attachment between the polymeric chains similarly to a physically cross-linked gel.

Plasticizers reduce the number of contacts by solvation of the chains, resulting in a less rigid network of higher elasticity.

The free volume theory was established by Fox and Flory and is based on thermodynamic principles. It defines the volume of a polymer as the sum of the occupied and the free volume. The free volume is created by the movement of polymeric chain ends, side chains and the main chain, and is impacted by the polymer molecular weight, structure and the temperature. The mobility of the polymer chains and hence the free volume increase greatly above the glass transition temperature or in the presence of plasticizers. Mathematical models to predict the glass transition temperature of a polymer blend including the Fox equation or Gordon-Taylor equation are based on the free volume theory.

1.3.3 Polymer-plasticizer compatibility

Polymer-plasticizer compatibility is defined as the ability of the plasticizer to form a homogeneous phase with the polymer without exudation of liquid-state plasticizers or crystallization of solid-state plasticizers. Thermodynamic concepts have been developed to explain or predict the compatibility between a polymer and a plasticizer. The compatibility during hot-melt extrusion is generally enhanced since plasticizer-polymer miscibility is thermodynamically favored. The entropy gain by mixing at elevated temperatures contributes to the negative free energy of the process. However, the plasticizer needs to remain solubilized in the polymer on the molecular level during storage at room temperature, which is only the case for highly compatible polymer-plasticizer combinations.

Early on, it was observed that like dissolves like, concluding that plasticizer and polymer should exhibit similar polarities to maximize compatibility. Interaction

parameters including the Flory-Huggins interaction parameter χ were introduced to predict the compatibility of a polymer with solvents, but can also be applied for other low molecular weight compounds including plasticizers or drugs. Interaction parameters are based on enthalpic and entropic principles, and obtained from the calculation of the free energy of mixing. Polymer-plasticizer combinations exhibiting interaction parameters below 0.5 are likely to produce miscible, one-phase systems when extruded, but may not necessarily remain stable one-phase systems during storage [28].

Cohesive density energy or solubility parameters have been developed to predict the long-term stability of solid solutions during storage. These concepts consider only enthalpic aspects, since the entropy gain due to mixing is expected to be similar for most systems. Intermolecular forces between the polymer and low-molecular weight compounds are treated as a sum of dispersive, polar and hydrogen-bonding interactions. Solubility parameters can either be determined experimentally from evaporation enthalpies, equilibrium swelling or surface tensions, or be calculated from the chemical structure of the components. Highly compatible plasticizer-polymer systems should exhibit very similar solubility parameters with a difference of less than 2 [28].

1.3.4 Plasticizer effects on polymers and plasticization efficiency

Plasticizers are added to hot-melt extrusion formulations for several reasons:

1. Hot-melt extrusion of polymers with high glass transition temperatures may become feasible by the addition of a plasticizer. A decrease in glass transition temperature below the onset temperature of thermal degradation reactions will open a temperature window within which thermal processing will be possible.
2. A plasticizer-induced decrease in melt viscosity of the polymeric carrier during extrusion will enhance the process output rate, increase the yield, minimize the

residence time of the material inside the extruder and hence reduce heat exposure. Low melt viscosities are further pivotal for the extrusion of multiparticulates due to the small orifice diameters of the applied dies.

3. Plasticizers minimize the shear stress acting on the material during hot-melt extrusion by reducing the melt viscosity of the formulation. This is important for high-molecular weight components including polymeric excipients or biological compounds which may be sensitive to shearing.
4. The finishing and visual appearance of the extruded dosage form will be enhanced by adding a plasticizer.

Since plasticizers modify the physico-chemical properties of the polymer, a quantification of the plasticizer effects on the polymer provides a tool to evaluate their plasticization efficiency. Based on the nature of hot-melt extrusion as a thermal and mechanical process, an analysis of plasticization efficiency should encompass the polymer properties most relevant for the extrusion process: glass transition temperature and melt viscosity.

Amorphous polymers undergo a transition from the brittle, glassy to a rubbery, deformable state characterized by a sharp increase in chain mobility and free volume at their glass transition temperature or Tg. The measurement of a polymer's Tg in the presence of increasing levels of plasticizers requires monitoring of characteristic polymer properties that change at the Tg while heating the specimen. A popular and versatile tool represents differential or modulated differential scanning calorimetry (DSC or MDSC) which detects the characteristic change in heat capacity occurring at the Tg. A plot of the plasticizer concentration versus the Tg may yield a straight relationship within the compatibility limit of the system, with the slope of the line being characteristic of the plasticization efficiency. When exceeding the compatibility limit, the plasticizer will

form a separate phase, and the Tg of the polymer will remain constant. The Tg of the plasticized polymer will be intermediate to the Tg of the polymer and the plasticizer, and may be predicted using mathematical models as discussed by Marcilla and Beltran [27]. These models are based on the free volume theory and examples include the Gordon-Taylor equation, Fox equation and expressions proposed by Kelly and Bueche or by Couchman. Alternatively to changes in heat capacity, the Tg can be determined as changes in the thermal expansion coefficient using thermo-mechanical analysis (TMA), changes in viscoelastic properties employing differential mechanical analysis (DMA), altered dielectric properties or changes in magnetic properties applying magnetic resonance spectrometry [29].

Rheology studies characterize the deformation and flow behavior of polymers and can also be employed to characterize the efficiency of plasticizers. Plasticizers have been shown to decrease the melt viscosity as well as the process torque in a concentration dependent manner [30, 31]. Most polymeric melts show non-Newtonian flow with pseudoplastic and viscoelastic elements attributed to the chain entanglement of the macromolecules [32]. Besides the presence of plasticizers, the melt viscosity of extrusion blends is influenced by many other factors including the molecular structure and molecular weight of the polymeric carrier, the content of non-melting solids in the blend, the processing temperature and the shear rate. In most experimental set-ups, the viscosity or the torque is monitored either as a function of increasing temperature, screw speed or time while keeping the other parameters constant. Different analytical instruments may be employed to study the effect of plasticizers on the polymer melt viscosity including capillary viscometers, rotational viscometers (also referred to as cone-plate/ parallel-plate or cylinder-cup type rheometers) or Brabender torque rheometers. Most rotational viscometers may be operated at oscillatory frequencies to minimize sample disturbance

during testing. This allows the monitoring of viscoelastic properties including elastic and viscous modulus and complex viscosity during the temperature scan, which were demonstrated to decrease with increasing plasticizer concentrations [33]. Torque rheometers or hot-melt extruders may be used to investigate torque/ temperature or torque/ rotation speed relationships. The obtained data may be converted into viscosity units when calibrated versus a traditional viscometer [34].

Besides Tg determinations and rheology studies, the effects of plasticizers on the mechanical properties of the polymer can be employed to evaluate plasticization efficiencies. The most frequently used mechanical parameter is the tensile strength, which generally decreases with increasing plasticizer concentrations in a linear manner [35]. More efficient plasticizers and increasing plasticizer concentrations further increase the elongation or strain and decrease the hardness and elastic modulus of polymeric specimens.

1.3.5 Potential pitfalls encountered with plasticized systems

It is important to be aware of the problems and challenges one may encounter when employing plasticizers in pharmaceutical dosage forms. Unwanted effects of plasticizers in hot-melt extruded delivery systems include:

1. An increased extrudate flexibility or tackiness may compromise downstream-processing including milling or strand cutting.
2. High plasticizer levels may be physiologically incompatible and/ or be toxic.
3. Plasticizers increase the free volume of the polymer, which can be studied using positron annihilation lifetime spectroscopy (PALS) [36]. As a consequence, physical instabilities may be promoted in the presence of plasticizers. The increased mobility of the polymeric chains will promote aging processes of the

polymer itself including continuing matrix coalescence or crystallization during storage, both processes resulting in slower drug release rates. Second, the molecular mobility of drug molecules that are dispersed in the amorphous state will be increased. If the amorphous system is thermodynamically instable, solid-state changes including phase separation and drug recrystallization will occur at accelerated rates and reduce the shelf-life of the product.

4. Plasticizers may compromise the ability of the matrix to control the drug release since water-soluble plasticizers can leach from the system and increase the matrix porosity.
5. When using a plasticizer in pharmaceutical formulations, one must be aware that the plasticizer itself exhibits a certain molecular mobility within the polymer matrix and may migrate into contacting materials during storage. This material in contact with the plasticized dosage form may be a gas, for example when volatile plasticizers evaporate, a liquid as during dissolution studies or a second polymer. Common primary packaging materials contain polymers and plasticizers, and plasticizer migration can occur in both directions.

These examples demonstrate that a careful consideration of the benefits and drawbacks of plasticization and an extensive characterization of the multi-component system are pivotal in the development of formulations for hot-melt extrusion.

1.4 MODIFIED RELEASE MATRIX SYSTEMS PREPARED BY HOT-MELT EXTRUSION

1.4.1 Factors influencing the drug release from matrix systems

The drug release rate and mechanisms from matrix-type delivery systems are influenced by a multitude of factors including matrix porosity, permeability, swelling

behavior and solubility of the polymer, loading of soluble compounds in the formulation, drug solubility, drug solid-state and particle size, plasticizer type and level and dosage form geometry and surface area. The drug release from insoluble carrier materials including polymers and lipids is mainly governed by diffusion, which can be understood as a three-step process: water ingression into the matrix, drug dissolution and drug diffusion through the matrix into the dissolution medium. Each of the steps can be rate-controlling, depending on the properties of the matrix. If the polymer swells or dissolves in the dissolution medium, further release mechanisms come into play. The matrix permeability to the penetrating water or diffusing drug is a function of the initial porosity, the number and size of pores formed by leaching of soluble components, and also by the thickness and viscosity of polymeric gel layers on the surface. For a complete drug release, the polymer needs to either dissolve, or the loading of soluble formulation components needs to be above a characteristic threshold value to eliminate finite drug clusters in the interior and allow a percolation of the entire matrix. The initial porosity of hot-melt extruded matrices is generally low and can be minimized using elevated processing temperatures or including plasticizers to enhance polymer coalescence. In addition to drug diffusion through water-filled pores, diffusion though the polymer network has also been discussed as release mechanism for poorly water-soluble drugs [37]. In this case, the diffusion rate will also depend on the degree of polymer crystallinity, since diffusion is only possible in amorphous regions as the permeability of crystalline regions is very low due to dense chain packing. The solid state and the particle size of the drug further impact the dissolution rate of the drug inside the matrix. Most matrix-type systems undergo burst release during the initial period of dissolution testing which is attributed to the release of unprotected drug at the surface. Burst release effects

are more pronounced for dosage forms exhibiting large surface-area-to-volume ratios including multiparticulates, and at elevated drug loadings.

1.4.2 Applications and downstream processing of hot-melt extruded dosage forms

The pioneering work in the adaption of hot-melt extrusion for pharmaceutical applications was conducted by Speiser and Huettenrauch in the 60's and 70's. Over the past 20 years, tremendous research efforts have been directed towards the bioavailability enhancement of poorly soluble drugs using solid dispersion technology. Hot-melt extrusion has been demonstrated to be an efficient and highly accepted technology for the preparation of amorphous solid solutions or fine crystalline suspensions exhibiting enhanced solubility and dissolution rates [7]. The formulation of soluble compounds for extended or delayed delivery provides a further important application field for hot-melt extrusion.

The utilization of differently shaped dies and appropriate downstream processing makes hot-melt extrusion a highly versatile technology for the manufacture of a vast number of different dosage forms. Films can be produced by extruding the material through slit-shaped dies onto cooled rolls which stretch the film to the targeted thickness. Extruded strands may be cut into tablets or pelletized into short cylinders, which can then be spheronized to obtain spherical particles. Cutting may be performed after cooling of the strand on conveyer belts (strand pelletizers), or directly upon extruder exit in the soft state (die-face pelletizers). In addition to cutting operations, monolithic matrices may be obtained by injection molding into tablet-shaped cavities [38, 39] or by calendaring in the soft state between two counter-rotating calendar rolls [40]. Grinding of hot-melt extrudates yields powders which may be filled into capsules, directly compressed into tablets or used for dry powder coating applications [41].

1.4.3 Monolithic, hot-melt extruded dosage forms providing modified drug release

1.4.3.1 Water-soluble, swellable polymers as carriers

Hydrophilic swellable polymers are popular materials for directly compressed matrix tablets due to their ability to provide zero-order release profiles [42]. However, most of these polymers including hydroxypropyl methylcellulose and other polysaccharides exhibit very high glass transition temperatures, making their hot-melt extrusion challenging. A review of the scientific literature showed that polyethylene oxide (PEO) in varying molecular weights is the most widely used matrix material for hot-melt extruded, hydrophilic systems for sustained drug delivery attributed to its low melting range and good thermal processibility. Zhang and McGinity demonstrated that the release of chlorpheniramine maleate from PEO 1000K and 7000K melt extruded matrices was controlled by the erosion kinetics of the polymer and by drug diffusion though the swollen gel layer [43]. The drug release from melt extruded tablets was further found to be more sustained than from directly compressed tablets of the same composition due to the reduced porosity of the hot-melt extruded matrix [9]. Plasticization of PEO with supercritical carbon dioxide increased the polymer crystallinity, but also the drug release rate due to the increased porosity of the produced extrudate [44]. Elevated amounts of hydrophilic or amphiphilic additives including PEG 3350 [43] and vitamin E TPGS [13] accelerated the drug release from PEO matrices, while hydrophobic polycaprolactone [45] or viscous agar [46] prolonged the release. The drug release was neither influenced by the extrusion screw speed nor by the extrusion temperature within the investigated ranges [45]. Mixtures of PEO and chitosan or xanthan gum could be successfully extruded and provided pH-dependent dissolution

profiles, while the combination of both polymers in PEO sustained the release and made it pH-independent attributed to intermolecular hydrogel formation [47].

1.4.3.2 Insoluble polymers as carriers

Drug release from insoluble polymeric matrices is primarily governed by diffusion processes, which are a function of the porosity of the system. Applying the percolation theory, the major pathway of drug release from an insoluble matrix is by diffusion through water-filled pores, and to a lesser extent, by diffusion through the polymer [48]. Only drug particles that are in contact with the dissolution medium (infinite clusters) will dissolve and be released by diffusion. The critical drug load or total soluble fraction that is necessary to form a continuous network of pores during the dissolution process is referred to as percolation threshold [49]. Below the percolation threshold, only drug at the surface in contact with the medium will be released, while significant amounts of drug remain trapped as finite clusters inside the insoluble polymer matrix. Attributed to the high degree of matrix coalescence during hot-melt extrusion, the initial porosity of hot-melt extruded dosage forms prior to dissolution of soluble components is very low when compared to compressed tablets [9]. The contribution of initially present pores to drug diffusion is hence minor, and drug release rates are dependent on diffusion through channels created by leaching of soluble formulation components including the drug, hydrophilic plasticizers or polymers during the dissolution process. This circumstance makes hot-melt extrusion a valuable technology for the preparation of sustained release matrices containing high loadings of water-soluble drugs. Common strategies to tailor the release profile or achieve a complete drug release over the dissolution period include the addition of soluble low-molecular weight excipients or polymers, increasing the drug

load or modifying the dosage form geometry and hence surface area that is available for diffusion processes.

Sprockel incorporated 50 or 70% theophylline into polymeric disks by hot-melt extrusion using polyethylene, polycaprolactone, polyvinyl acetate or cellulose acetate butyrate as the release-controlling carrier. Higher drug amounts could not be loaded since the processibility of higher percentages of non-melting drug in the formulation was compromised. The nature of the polymer influenced the diffusion rates from the disk surfaces at constant drug loadings. Increasing the soluble fraction in the matrix by using higher drug levels or soluble additives increased the drug diffusion rates attributed to a higher number of infinite clusters. The drug release was also found to be influenced by the solubility and true density of the drug since the occupied drug volume is higher for low-density drugs at equal mass percentages in the formulation [50]. The drug release from polyvinyl acetate based tablets prepared by either cutting of the extruded strands or by compression of the milled extrudates was mainly governed by diffusion and could also be accelerated by higher drug loadings or water-soluble polymers as additives in the formulation [51].

Crowley and coworkers prepared ethylcellulose-based matrix tablets containing 30% guaifenesin by either direct compression or hot-melt extrusion to investigate the influence of the processing method on the drug release. Further studied parameters included ethylcellulose particle size, the compaction force used for tablet compression and the processing temperature for melt-extruded systems. The drug release rate could be correlated to the porosity of the prepared tablets and was diffusion-controlled for hot-melt extruded products. Processing by hot-melt extrusion, a higher extrusion temperature and small particle size ethylcellulose decreased the porosity and increased the tortuosity of the matrices, resulting in slower drug diffusion and release rates [9].

Further popular polymers for the melt extrusion of sustained release dosage forms include Eudragit® RS PO and Eudragit® RL PO attributed to their low glass transition temperatures and melt viscosities. Zhu and coworkers demonstrated that the effect of the TEC level in melt extruded tablets was different from the film coated systems. While higher plasticizer levels promoted the film coalescence and decreased the drug release from the coated dosage form, the drug release increased at higher TEC levels for hot-melt extruded tablets due to pore formation in the matrix after TEC dissolution [52]. An increase in drug amount also increased the diffusion controlled release rate of a soluble model drug, while the release of poorly soluble indomethacin remained unchanged at a higher drug level [37]. The indomethacin release from a Eudragit® RL based matrix could be enhanced by adding polymers that were soluble and/ or decreased the adsorption of the drug to the quaternary ammonium groups of the polymer during dissolution [53]. Fukuda and coworkers incorporated sodium bicarbonate into Eudragit® RS PO matrices to prepare porous, buoyant tablets since carbon dioxide was generated during the extrusion process. Hot-melt extruded formulations of low density were demonstrated to float for 24 hours und provided a sustained drug release for one of the two investigated model drugs. The release rate could be tailored by increasing the drug load, adding acid-soluble Eudragit® EPO or by modifying the matrix geometry [54].

More recently, Kollidon® SR, a copolymer of polyvinyl acetate and polyvinylpyrrolidone (8:2) with a low glass transition temperature, has been explored as sustained release carrier for melt extruded tablets. The diffusion controlled drug release increased at higher drug loadings and when water-soluble hydroxypropyl cellulose was added [55]. Tablets compressed from milled extrudates exhibited a lower tensile strength but a better control of the drug release by diffusion processes compared to directly

compressed compacts. The release rate could be tailored by adding soluble Kollidon® VA (polyvinylpyrrolidone-co-vinyl acetate) at a 10 or 20% level to the composition [56].

1.4.3.3 Lipids and waxes as carriers

Lipid or wax carriers are popular matrix materials for sustained release formulations due to their low costs, high physiological compatibility and low melting ranges. The most common preparation methods for lipids require their complete melting to exploit their binding properties as in melt granulation and spray-congealing. Liu and coworkers prepared wax granules containing 15% drug and 30% glyceryl palmitostearate (Precirol® ATO 5) by either hot-melt extrusion or melt granulation at temperatures above the melting point, and compared the properties of the granules and of compressed tablets. Both methods produced sustained release granules, and the tablets prepared from these granules released the drug at a slower rate than directly compressed compacts of the same composition. Hot-melt extruded granules provided a more uniform drug content over different particle size fractions and produced harder tablets [57].

A frequently encountered problem with thermally processed wax carriers is their physical instability during storage, resulting in unstable drug release profiles. Lipids are complex polymorphic compounds, and storage ususally leads to re-crystallization of amorphous regions and conversions of metastable modifications. It has been shown that the polymorphic composition of recrystallized lipids after hot-melt extrusion is dependent on the extrusion temperature [58] and on the presence of partial glycerides in the formulation [59]. Solid lipid extrusion in a twin-screw extruder allows processing of lipids below their melting point to minimize physical instabilities and produce extrudates of low porosity. Reitz and Kleinebudde demonstrated that the melt extrusion of glyceryl trimyristate (Dynasan® 114) at low temperature produced matrices of very low porosity

(1.5%), exhibiting a stable and sustained theophylline release at high drug loadings (50 and 75%). The processing temperature was optimized so that the lipid only softened instead of melted, and the solid lipid fraction was high at 80-90% during thermal processing. The solid state of the lipid remained unchanged after extrusion below the melting point and during accelerated storage [60]. Using solid lipid extrusion, stable extrudates with tailored drug release profiles could be obtained by extruding mixtures of tripalmitin (Dynasan® 116) and polyethylene glycol [61].

1.4.3.4 Enteric polymers as carriers

Hot-melt extrusion of enteric polymers produces matrix systems with delayed release properties. Andrews and coworkers demonstrated that melt extruded tablets containing 15% 5-aminosalicylic acid and Eudragit® L100-55 released less than 5% drug over 2 hours in acid [62], while hot-melt extruded Acryl-EZE® tablets containing 20% theophylline yielded 10% drug release [63]. Yang and coworkers prepared enteric Eudragit® L100 tablets releasing less than 3% drug by either cutting of the extruded strands into tablets or by direct compression of comminuted extrudates [64]. Melt extruded Eudragit® S100 tablets for the colonic delivery of 5-aminosalicylic acid also showed excellent gastric protection [21]. When compared to directly compressed matrix tablets which failed to efficiently delay the drug release in acidic media, hot-melt extruded matrices provided reduced drug diffusion rates in acid due to their low porosity.

1.4.4 Multiparticulate, hot-melt extruded dosage forms providing modified drug release

1.4.4.1 Methods of pellet preparation and general properties of hot-melt extruded pellets

Traditional methods of pellet preparation require multiple steps and the use of water or organic solvents. Popular techniques including wet-mass extrusion/ spheronization, granulation or balling utilize binder solutions or dispersions in combination with kneading and compaction forces to generate spherical or semi-spherical particles. Alternatively, pellets may be prepared by layering of core seeds or by spray drying. Modified release properties are mainly achieved by the subsequent application of a functional coat in case of reservoir-type pellets, or may be provided by the dissolution properties of the matrix material itself (matrix pellets). Although film-coating is well established and widely used, this procedure is labor intensive and costly since it requires the careful optimization of multiple steps including coating, drying and curing. The preparation of matrix pellets instead reduces the number of production steps and may overcome challenges associated with film-coating. Wet-mass extruded matrix pellets may provide sustained release profiles for poorly soluble compounds whose release is controlled by the erosion kinetics of the matrix material [65]. Thermal methods such as melt granulation or spray congealing may be used to sustain the release of soluble drugs in lipophilic matrices based on triglycerides, waxes or fatty acids [66, 67].

Alternatively, hot-melt extrusion can be used for the preparation of modified release pellets containing a highly soluble drug dispersed in a release-controlling polymer. The diameter and cross sectional geometry of the extruded pellets are mainly controlled by the design and orifice size of the product-shaping die. The produced pellets show a narrow particle size distribution and tight particle size fractions may be obtained

at high yields compared to traditional wet-mass extrusion methods [8]. The release of water-soluble drugs from hot-melt extruded pellets is mainly controlled by the permeability and dissolution behavior of the carrier and by the amount of soluble components in the formulation. As opposed to pellets prepared by traditional wet-massing techniques, the initial porosity of melt extruded matrix pellets is low, minimizing drug diffusion through water-filled pores [9]. Pellets with high drug loads may be successfully prepared under preservation of the controlled release properties. As demonstrated for a formulation containing 30% theophylline, pellets providing sustained drug release could be prepared by hot-melt extrusion, while wet-massed pellets failed to prolong the drug release [8]. Electron microscopic images of pellet cross-sections showed that melt extruded matrices were highly coalesced and void of pores, while wet-massed pellets remained porous agglomerates of distinct particles.

1.4.4.2 Hot-melt extruded pellets with sustained release properties

Follonier and coworkers investigated four polymers (ethylcellulose, cellulose acetate butyrate poly(ethylene-co-vinyl acetate) and Eudragit® RS PM) as thermoplastic carriers for the melt extrusion of sustained release diltiazem hydrochloride matrix pellets containing drug amounts of 30-70% [14, 68]. The rate and extent of drug release was dependent on the carrier polymer, the pellet particle size and the drug load. All formulations yielded sustained release profiles with biphasic dissolution characteristics: an initial burst release due to dissolution of drug at the pellet surface, followed by a slow, diffusion-controlled phase. Hydrophilic polymers and swelling superdisintegrants were added to the formulation to suppress the initial burst by gel formation and promote a complete drug release by increasing the matrix porosity in the second phase. Miyagawa and coworkers demonstrated that a twin-screw extruder may be used for the preparation

of cylindrical sustained release pellets based on carnauba wax [69]. The generation of high pressures in the melting zone enabled processing at temperatures below the wax melting point. Soluble and swellable polymers increased the drug release rates in a concentration dependent manner by promoting crack and pore formation in the matrix. Granules based on glyceryl palmitostearate could be successfully prepared with a single-screw extruder when the ratio between melting wax and non-meltable filler was optimized [57]. Brabender et al. developed mini-matrices containing ethylcellulose as the thermoplastic carrier for the sustained release of ibuprofen [11]. Although high drug loads of 60% were used, the release from the ethylcellulose matrices was very slow with only 20% drug released in 24 hours. Hydrophilic polymers were added to increase the drug release rate. In contrast to hydroxypropyl methylcellulose compacts, higher viscosity grades increased the dissolution rate to a larger extent attributed to their higher swelling capability which promoted water penetration into the matrix. When xanthan gum was used instead of hydroxypropyl methylcellulose, the initial burst release was eliminated and drug release profiles approaching zero-order kinetics could be produced.

1.4.4.3 Hot-melt extruded pellets with delayed release properties

According to the current USP, the drug release from delayed release articles is limited to no more than 10% in acidic medium pH 1.2 over 2 hours. As previously pointed out for sustained release pellets, drug at the particle surface is exposed to the release medium and undergoes burst release during the initial acidic stage of the dissolution test. High drug loads and small pellet particle size increase the fraction of drug that is devoid of the control by the enteric polymer, resulting in failure of the USP requirement for the maximum release in acid. As previously demonstrated for hot-melt extruded matrix systems based on Eudragit® L100-55, pellets extruded through a 1.2 mm

die and containing 20% theophylline released more than 25% drug in 2 hours at pH 1.2, compared to 10% drug release from melt-extruded tablets with a diameter of 6 mm [63]. As disclosed in patent application WO 2008/101743, the permeability of enteric polymers may be reduced by utilizing blends with an insoluble polymer [70]. It could be demonstrated that matrix pellets containing 50% drug exhibited enhanced gastric resistance when anionic Eudragit® FS 30D in the spray-dried form was extruded in a physical mixture with insoluble Eudragit® RS PO [71]. Additional challenges arise from the thermal properties of most enteric polymers. The temperature window between glass transition and thermal degradation is oftentimes small, so that the use of plasticizers becomes indispensable. Efficient plasticization is further required to lower the melt viscosity and reduce the elastic recovery or die swelling of the polymer as the preparation of small pellets involves an extrusion of the softened material through die orifices with diameters of 1 mm or less. Plasticizers exhibiting aqueous solubility may leach from the pellet or promote water penetration into the matrix, resulting in increased drug release rates by diffusion through the porous network during the acidic stage.

1.4.4.4 Advantageous downstream processing of hot-melt extruded pellets

Hot-melt extruded matrix pellets potentially exhibit a higher robustness than coated particles towards downstream processing procedures which is attributed to their high mechanical strength, low friability and the circumstance that the release performance is independent of the intactness of a functional coat. Since wet-massed pellets are porous agglomerates of distinct particles, they mainly fail by adhesive or cohesive fracture, or by crack propagation of flaws when subjected to compression forces [72]. On the other hand, hot-melt extruded dosage forms are highly coalesced matrices exhibiting low porosity and being held together by intermolecular forces and physical

entanglement between polymeric chains. These strong cohesive forces and the lack of pores are responsible for the high mechanical strength of melt extruded pellets. As demonstrated by Young and coworkers, multi-particulate tablets of acceptable hardness and low friability could be prepared by direct compression of 50% hot-melt extruded pellets with tableting excipients [73]. Furthermore, the release properties of the unprocessed pellets could be reproduced after tableting independent of the compaction force, pellet-to-filler ratio and tableting excipient when a rapid disintegration of the tablets was ensured.

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Chapter 2: Research Outline

2.1 OVERALL OBJECTIVE

The overall objective was to investigate the influence of formulation factors and processing parameters on the properties of hot-melt extruded, controlled release dosage forms for the oral delivery of water-soluble active compounds. The impact of polymer plasticization on the processibility, solid-state properties and release characteristics of the active compound was studied. The applicability of hot-melt extrusion technology for the preparation of a variety of solid dosage forms including tablets, pellets and multiparticulate matrices was investigated.

2.2 SUPPORTING OBJECTIVES

2.2.1 Investigation of Citric Acid as a Solid-State Plasticizer for the Hot-Melt Extrusion of Eudragit® RS PO Matrix Tablets

Plasticization of pharmaceutical polymers by solid compounds has been previously reported. Efficient plasticization requires the melting of the plasticizer and its miscibility with the polymer during extrusion. The utilization of solid-state plasticizers yields advantages over traditional liquid plasticizers in terms of material handling and processing, product content uniformity and stability. The capability of citric acid to interact with polymers by hydrogen bonding and its high physiological acceptance make it an ideal candidate for the plasticization of pharmaceutical formulations for hot-melt extrusion applications. The compatibility of citric acid monohydrate with Eudragit® RS PO, a methacrylic polymer providing sustained drug release, was studied by modulated differential scanning calorimetry (MDSC) and powder X-ray diffraction analysis

(PXRD). The plasticization efficiency was examined by mechanical testing of plasticized films and by monitoring the extrusion process parameters.

2.2.2 Study of the Effects of Citric Acid Monohydrate on the Solid-State and Drug Release Properties of Diltiazem Hydrochloride in Melt Extruded Eudragit® RS PO Matrix Tablets

The utilization of plasticizers in matrix systems potentially impacts their drug release performance by alteration of the matrix microstructure, polymer properties and solid-state characteristics of the drug itself. The miscibility between diltiazem hydrochloride with the polymer and with citric acid monohydrate during thermal processing was investigated by MDSC and PXRD. The influence of the citric acid monohydrate level and the diltiazem hydrochloride particle size on the drug dissolution rate was investigated at constant drug-to-polymer ratios. It was observed that the drug release rate increased and became independent of the drug particle size as a function of the citric acid monohydrate level. The mechanisms of dissolution rate enhancement in the presence of citric acid monohydrate were studied in comparison to alternative pore forming excipients at constant polymer levels. The matrix porosity and morphology were examined by scanning electron microscopy (SEM), and the degree of drug crystallinity was analyzed using PXRD.

2.2.3 Investigation of the Influence of Formulation Factors on the Properties of Enteric Hot-Melt Extruded Matrix Pellets

This study was driven by the objective to prepare multiparticulates by hot-melt extrusion that have diameters below one mm and provide delayed drug release. Traditional multiparticulates of the reservoir-type require an additional coating step to impart controlled release properties to the dosage form. The hypothesis was that enteric,

matrix-type multiparticulates can be prepared by hot-melt extrusion. Attributed to the low porosity of melt extruded systems, the drug release is controlled solely by the matrix, so that subsequent coating with release-controlling polymers is not necessary. Five anionic polymers that had been traditionally employed for enteric coating applications were investigated as matrix materials regarding their processibility by melt extrusion and their gastric resistance. Based on the results of this study, Eudragit® S100 was selected, and the effect of drug loading on the processibility and release properties of the matrix pellets was studied. The influence of five plasticizers differing in aqueous solubility, plasticization efficiency and molecular weight was examined with respect to the thermal properties of the polymer, solid-state of the drug, pellet microstructure and delayed release characteristics.

2.2.4 Investigation of the Influence of Plasticizer Type and Level on the Properties of Eudragit® S100 Matrix Pellets Prepared by Hot-Melt Extrusion

Based on the results obtained in the previous chapter, three efficient plasticizers for the hot-melt extrusion of Eudragit® S100 were selected for further studies. The viscosity-temperature behavior of polymeric melts was investigated at a constant shear rate as a function of the plasticizer type and level. In addition to the thermal behavior, the drug release properties and mechanical strength of the plasticized pellets were studied using dissolution experiments and diametral compression analysis.

2.2.5 Study of Formulation and Processing Factors that Impact the Applicability of Hot-Melt Extrusion for the Embedment of Enteric Coated Particles into Multiparticulate Monolithic Matrices

Although multiple-unit systems exhibit beneficial biopharmaceutical properties, monolithic dosage forms are preferred with regard to the final product to ensure patient

compliance and dosing accuracy. The most common post-processing technologies include the filling into hard-gelatin capsules and the compression into multiparticulate tablets. Tableting of functionally coated particles is challenging since the integrity of the film may be compromised during the compaction process. Differences in size, shape, density and flowability between coated particles and powdered tableting excipients further promote blend segregation, resulting in tablets with poor content uniformity. The objective was to investigate hot-melt extrusion as an alternative technology for the preparation of multiparticulate monolithic matrices without compromising the delayed-release properties of the enteric particles. Attributed to the absence of unidirectional compaction forces and vibrational movements during tableting, improved content uniformity and gastric protection of the final dosage form were expected. Particles of different mechanical strength (theophylline granules, pellets and layered microcrystalline cellulose spheres) were enteric coated with Eudragit® L30D-55 and characterized by diametral compression analysis and dissolution testing. Six hydrophilic, semi-crystalline polymers were studied as potential carriers for the enteric particles. The miscibility between the carrier polymer and the enteric polymer was investigated by differential scanning calorimetry to predict a potential solubilization and damage of the particle coating during the extrusion process. The influence of the carrier polymer, particle load and the particle strength on the preservation of the enteric properties during hot-melt extrusion was studied. The delayed-release characteristics of soft particles that were extruded in a poloxamer 407 matrix were examined after one year of storage and compared to a directly compressed formulation.

Chapter 3: Investigation of Citric Acid as a Solid-State Plasticizer for the Hot-Melt Extrusion of Eudragit® RS PO Matrix Tablets[1]

Abstract:

The use of solid-state plasticizers for the hot-melt extrusion of pharmaceutical dosage forms has been shown to be beneficial compared to liquid plasticizers. The purpose of this study was to determine the suitability of citric acid (CA) as a solid plasticizer for the preparation of Eudragit® RS PO extended release matrix systems by a melt extrusion technique. The influence of increasing levels of CA monohydrate (CA MH) or anhydrous CA in the powder blend on the extrusion process parameters (screw speed and motor load) was determined as a function of temperature. The solubility of CA MH in extruded tablets was studied by means of modulated differential scanning calorimetry (MDSC) and powder X-ray diffraction (PXRD). Films were cast from organic solutions to demonstrate the plasticizing effect of CA MH as a change in physico-mechanical properties (tensile strength, elastic modulus and elongation). The CA release from extruded tablets was studied over 12 hours. The monohydrate form was found to distinctly facilitate the extrusion of Eudragit® RS PO, whereas the addition of anhydrous CA to the polymer powder was less effective. This divergent behavior in plasticization of Eudragit® RS PO was attributed to the higher solubility of the monohydrate in the acrylic polymer. The plasticizing effect of the CA MH reached a plateau at 25% during hot-melt extrusion which coincided with the solubility limit of the organic acid in the polymer as shown by MDSC and PXRD results. The citric acid

[1] Significant portions of this chapter were taken from: Schilling, S.U., Shah, N.H., Malick, A.W., Infeld, M.H., Martin H. Infeld, and McGinity, J.W. Citric acid as a solid-state plasticizer for Eudragit® RS PO. Journal of Pharmacy and Pharmacology, 2007, 59, p: 1493-1500.

monohydrate increased the flexibility of Eudragit® RS PO films as demonstrated by a decrease in tensile strength and elastic modulus, and an increase in elongation as a function of CA MH concentration. The dissolution of CA from the matrix tablets followed an extended-release profile, with CA MH exhibiting a faster dissolution rate than the anhydrous form. In conclusion, CA MH was found to be an effective plasticizer for Eudragit® RS PO that facilitates the production of controlled release matrix systems by hot-melt extrusion.

3.1 INTRODUCTION

Hot-melt extrusion is a simple method to produce solid dispersions/ solutions of poorly water-soluble drugs to increase their release rate [1], and an alternative method to tablet compression or film coating to manufacture controlled-release dosage forms of highly soluble drugs [2, 3]. The large variety in die shapes allows the manufacture of various dosage forms such as tablets, pellets or films [4]. The extrudate can also be ground to a powder and compressed into tablets or used for dry powder coating [5]. Benefits of melt extrusion include efficient and continuous processing, the elimination of solvents and the absence of compressibility requirements for the excipients in the powder blend.

The inclusion of a plasticizer into the formulation is generally necessary since most pharmaceutical polymers exhibit high glass transition temperatures (Tg). Plasticized polymers soften at a lower temperature and yield a lower melt viscosity, and thus, can be melt processed at lower temperatures. Most pharmaceutical plasticizers employed today are in the liquid state, for example organic esters (citrates and phthalates) and polyols (glycerol, PEG's with low molecular weight). Several solid compounds such as lidocaine

hydrochloride [6], methylparaben [7], ibuprofen [8, 9], chlorpheniramine maleate [10], tartaric acid [11] and indomethacin [12] have been reported previously to exert plasticizing effects on polymers of pharmaceutical interest. Solid-state plasticization is thought to occur through distribution of the plasticizer in the molten polymer after being melted or dissolved during extrusion, and occupation of active binding sites following the same mechanisms as with liquid plasticizers. Therefore, the solid compound must be sufficiently soluble in the polymer, and an interaction between both materials is necessary to achieve plasticization [9].

The application of solid-state plasticizers is advantageous compared to liquid plasticizers. The mixing process prior to extrusion is more efficient, and the higher homogeneity of the obtained powder formulation yields an enhanced uniformity of the final product. Improved flow properties assure a stable and continuous powder flow through the extruder. Further important advantages are the higher thermal stability of most solid-state plasticizers and the decreased weight loss due to evaporation during the melt extrusion process. A lower tendency of plasticizer leaching or migration upon storage has also been discussed [13].

Citric acid (CA) is a widely used excipient in pharmaceutical formulations as an acidifying agent to decrease the microenvironmental pH in enteric coated dosage forms [14-16]. Researchers have further used CA as a hydrophilic carrier for poorly soluble drugs in solid dispersions produced by co-melting techniques to increase the dissolution rate and bioavailability [17, 18]. The CA molecule has a high capacity for hydrogen-bond formation and thus possesses a potential to interact with and plasticize certain pharmaceutical polymers. Bruce et al. reported a plasticizing effect of CA on Eudragit® L 30D-55 [16] and Eudragit® S100 [19] when incorporated into either enteric film coatings or matrix tablets, respectively. Wan et al. [20, 21] found CA to be beneficial for

wall formation in spray dried HPMC microcapsules. Chitosan films cast from aqueous CA solutions were reported to exhibit a high flexibility, demonstrating CA to be a good plasticizer for this polymer [22, 23].

The application of Eudragit® RS PO as carrier polymer in hot-melt extruded matrix systems has been previously reported [24]. The objective of the present study was to investigate the ability of citric acid to function as a solid-state plasticizer for the melt extrusion of Eudragit® RS PO. The properties of extruded tablets and cast films containing different levels of CA were determined. The solubility of the organic acid in the polymer was studied by modulated differential scanning calorimetry (MDSC) and powder X-ray diffraction (PXRD). The mechanical properties of cast films were investigated, and the CA release from extruded tablets was observed over 12 hours. Since the anhydrous form of CA exhibits different properties when compared to the monohydrate, both materials were processed separately with the acrylic polymer, and the properties of the resulting tablets were determined.

3.2 MATERIALS

CA MH (powder, U.S.P.) and anhydrous CA (powder, U.S.P.) were purchased from Spectrum Chemicals (Gardena, CA). The monohydrate was ground with a mortar and a pestle and passed through a 60 mesh sieve (250 μm) prior to use. Eudragit® RS PO was donated by Degussa Röhm America (Piscataway, NJ), while Cab-O-Sil® M-5P was provided by Cabot Corp. (Billerica, MA).

3.3 METHODS

3.3.1 Manufacture of hot-melt extruded tablets

The anhydrous citric acid (25% based on the total weight) or citric acid monohydrate (0 to 30% based on the total weight) was geometrically diluted with the polymer and blended. Cab-O-Sil® M-5P (0.5%) was included into the formulations to promote a constant powder flow during the extrusion process. The blends were manually fed through a hopper into an extruder (Randcastle single-screw extruder, model RCP 0750 Microtruder, Cedar Grave, NJ) and processed at temperatures between 90 and 140°C, depending on the processability of the formulation. The screw speed was set to a maximum of 20 rpm, while the motor load was limited to 0.700 drive amperes, and the pressure did not exceed 200 PSI (1.379 MPa). The molten polymer strand exited through a circular 6 mm die and was manually cut into 250 mg tablets.

3.3.2 Preparation of films

Eudragit® RS PO and CA MH (0 to 30%) were dissolved in 50 ml acetone so that 15% (w/v) solutions were obtained. The films were cast onto leveled 15 × 15 cm square teflon-coated plates and allowed to dry at room temperature for 24 hours, followed by an additional 24 hours in a 40°C oven to facilitate solvent removal. After the drying process, uniform rectangular specimens (15 mm × 70 mm × 300 μm) were cut and stored at 25±1°C and 50±5% relative humidity for at least 48 hours prior to analysis. Film thickness was measured at 6 different locations along the entire length of the film with a manual micrometer (Mituoyo, model ID C1012EBS, Aurora, IL). Only films with an average thickness of 280 to 320 μm and a variation of less than 30 μm (10%) were used for analysis.

3.3.3 Influence of CA concentration on extrusion process parameters

To determine the influence of CA on the processability of Eudragit® RS PO during hot-melt extrusion, the process parameters screw speed and motor load (current) were monitored as a function of CA content and the preset temperature in the die zone. The quotient of the maximal applicable screw speed divided by the measured load at a given temperature was calculated for each CA level.

3.3.4 Thermal analysis

The solubility of CA in the extrudates and the influence of CA on the glass transition temperature of Eudragit® RS PO were studied by modulated differential scanning calorimetry (MDSC) with a TA Instrument model 2920 (New Castle, DE). Extrudates containing 0 to 30% CA MH were ground to a fine powder, and 8 to 12 mg samples were accurately weighed into aluminum pans and sealed. The samples were heated from -30 to 170°C at a rate of 10°C/min with the modulation set to ±1°C every 60 seconds and a nitrogen flow of 40 ml/min. The maximal amount of CA MH that could be incorporated into the extrudate without exhibiting any melting peak for the organic acid during the first heating run was reported as the solubility limit.

3.3.5 X-ray diffraction analysis

The degree of CA crystallinity in ground extrudates was evaluated by powder X-ray diffraction (PXRD) using a Philips Electronic Instrument type 42273 (Mount Vernon, NY). Samples were analyzed in the 2-theta range from 5 - 50° with a step size of 0.05° every 4 seconds. They were exposed to a Cu-K alpha radiation under 40 kV and 40 mA. The crystallinity of extrudates containing increasing monohydrate levels or anhydrous

CA was compared to the physical mixtures, and the influence of the extrusion temperature on the crystallinity of CA MH was investigated.

3.3.6 Physico-mechanical properties of films

The mechanical properties of the cast films were investigated using an Instron Model 4201 equipped with Bluehill 2.5 material testing software (Instron, Norwood, MA). The procedure was based on the ASTM D 882 guideline for mechanical testing of thin films [25]. The rectangular strips were fixed between two hydraulic grips with an initial grip separation of 50 mm and stretched at a rate of 25 mm/min. The effect of the CA MH level on the tensile strength, elastic modulus and elongation of the films was studied. The tensile strength was calculated by dividing the maximal load by the initial cross-sectional area of the film, while the elastic modulus was determined as the slope of the initial linear part of the load-strain curve. The elongation was reported as the absolute increase in length of the film at the moment of break. All values were the average of at least 6 determinations.

3.3.7 Content of volatile components in films

The content of volatile components in films equilibrated at 25±1°C and 50±5% RH for 48 hours was determined to exclude large amounts of moisture or residual solvent as plasticizing agents. The technique was based on the USP loss on drying method and was carried out in a moisture analyzer AND MF-50 (A&D Engineering, Inc., Milpitas, CA). Approximately 1 g of film material was accurately weighed and spread as a single layer in a circular aluminum dish that was dried beforehand until weight constancy was reached. The sample was kept at a constant temperature of 110°C until the weight loss

per minute did not exceed 0.02%/ min. The content of volatiles was reported as the average percent weight loss from 3 tested specimens.

3.3.8 Citric acid release study

Release studies from melt extruded tablets containing 25% CA MH or anhydrous CA and processed at a die temperature of 120°C were carried out according to the USP 27 procedure for extended release dosage forms in a USP apparatus 2 (paddle method, Varian, Cary, NC). Phosphate buffer pH 6.0 (900 ml, 37°C) was used as the dissolution medium, and the paddle speed was set to 100 rpm. For each determination, 6 samples consisting of 2 tablets (500 mg) were analyzed over 12 hours. The actual CA content was determined after complete destruction of the tablets with a Polytron homogenizer (Kinematica Inc., Newark, NJ). The percent CA released from the tablets was calculated from the actual CA content of each sample as a function of dissolution time.

3.3.9 Citric acid assay

A Waters HPLC System (Milford, MA) equipped with a C_{18}-reversed phase column (Capcell PAK, 3 × 100 mm, Shiseido Co., Tokyo, Japan) and a UV-detector set to 212 nm (996-PDA detector, Waters Inc., Milford, MA) was utilized to determine the CA content in the dissolution samples. The method was based on the findings of Ding et al. [26]. The column temperature was held constant at 30°C during analysis, and the injection volume was 20 µl. Phosphate buffer (10 mM), which was adjusted to pH 2.4 with concentrated phosphoric acid, and methanol were used as the mobile phase (95:5) at a constant flow rate of 0.5 ml/min. The low pH of the mobile phase was necessary to prevent ionization of the trivalent organic acid during analysis. The relationship between

CA content and UV signal was found to be linear with a correlation coefficient of 0.99997 over the range between 2 and 200 µg/ml (corresponding to 1.44 – 144.00% of CA MH in tested samples). The reproducibility for multiple injections (n = 3) exhibited less than 2.0% relative standard deviation for each tested concentration.

3.3.10 Statistical analysis

Minitab Release 14 Statistical Software (Minitab Inc., State College, PA) was employed to carry out statistical analysis on the extrusion, physico-mechanical and dissolution data. All tests were based on the 95% confidence interval or on the closest provided value (Mann-Whitney), respectively. The effect of the CA MH concentration and the formulation type (anhydrous CA or CA MH) on the extrusion process parameters was analyzed by Kruskal-Wallis Test and pairwise Mann-Whitney median comparisons (nonparametric analysis, n = 3). The value for the screw speed/ motor load quotient obtained for an extrusion at 120°C die temperature was selected as the response parameter since all formulations could be processed at this temperature. The influence of the CA MH concentration on the film properties (elastic modulus, tensile strength and elongation) was evaluated using one-way ANOVA followed by post hoc Tukey's test (n = 6). A univariate two-factor ANOVA design with repeated measures on one factor (time) and Tukey's test were applied to determine the effect of the formulation type on the CA released at each sampling time point (n = 6). Also, the f2 similarity factor [27] was calculated from the means of % released at each time point to compare the entire dissolution profile of both investigated formulations.

3.4 RESULTS AND DISCUSSION

3.4.1 Influence of CA on extrusion parameters

Formulations containing Eudragit® RS PO with 0 to 30% CA MH or 25% anhydrous CA, based on the total formulation weight, were extruded at temperatures between 90 and 140°C, with a screw speed of 20 rpm or less, so that the motor load was maintained below 0.700 drive amperes. Improved processability of a powder blend by plasticization of the polymer yields a higher screw speed and a lower motor load for a predefined extrusion temperature. Plasticizers act by interposing themselves between polymer chains and disrupting cohesive interactions, thus resulting in a more malleable polymer with a lower melt viscosity. Since the resistance of the polymeric melt towards the rotating movement of the screw decreases, the load required of the motor is diminished. Consequently, the blend can be processed at higher screw rotation speeds without exceeding the safety motor load or screw pressure limits. To consider the influence of both parameters, the quotient of the highest applicable screw speed divided by the necessary motor load was investigated as a function of the CA content. This quotient can be interpreted as an index of processibility of the formulation at the preset die temperature, and improved processibility due to plasticization became noticeable as high quotients at lower temperatures.

Fig. 3.1 shows the screw speed/ load ratios for formulations with increasing CA MH levels at different extrusion temperatures (end zone). A relatively high temperature of 140°C was necessary to extrude the pure polymer at a screw speed of 20 rpm, while blends containing CA MH could be processed at lower temperatures (130-110°C). Statistical analysis using a Kruskal-Wallis test demonstrated a significant influence of the CA MH concentration on the response parameter at 120°C die temperature (P=0.003). A

pair-wise median comparison by Mann-Whitney test showed that the screw speed/ motor load quotient significantly increased when the CA MH concentration was changed from 0 over 10, 15 and 20 to 25% (significant difference in all medians). The improved processability of blends comprising higher CA MH level at increased screw speeds under a reduced motor load indicated a decrease in melt viscosity and made an extrusion at lower temperatures possible. The absence of a statistically significant difference between the 25 and 30% CA formulation suggested that the plasticizing effect of CA MH plateaued at these concentrations. This ceiling effect coincided with the solubility limit of CA MH in Eudragit® RS PO as determined by MDSC (Fig. 3.2), supporting the hypothesis that only dissolved CA functioned as a plasticizer. These results demonstrated that the CA MH acted as a plasticizer and/ or as a thermal lubricant on Eudragit® RS PO when the polymer was melt extruded.

The results in Fig. 3.1 further illustrate that CA MH facilitated the extrusion process more efficiently than the anhydrous form, since significantly higher screw speed/ motor load values were obtained for the 20 and 25% CA MH formulation when compared to the blend with 25% anhydrous CA at three temperature levels (110-130°C). This phenomenon can be explained by the lower melting point of the monohydrate and its higher tendency to interact with the polymer due to lower cohesive forces when compared to the anhydrous form; CA MH has a melting point of 135°C, while anhydrous CA melts at 155°C (determined by DSC, data not shown). It can be assumed that the melting point of the monohydrate was further depressed through interactions with the Eudragit® RS PO, so that at least a softening during extrusion, and consequently, an enhanced distribution of the organic acid in the polymer melt was facilitated. Recrystallization of CA MH after cooling of the extrudate to room temperature did not occur in tablets containing up to 20% CA, since the interactions between Eudragit® RS

PO and CA MH enabled the CA MH to dissolve in the extrudates. The anhydrous form, having a higher melting point and more stable lattice structure, did not melt or dissolve completely in the polymer during processing. These differences in solubility were supported by PXRD data. As only molecularly dispersed CA can function as a plasticizer, the monohydrate with its higher solubility in Eudragit® RS PO was more effective in reducing the polymer's melt viscosity and hence improving its processability for melt extrusion than the anhydrous form.

3.4.2 Solubility of CA in Eudragit® RS PO

Solubility of the solid plasticizer in a polymer is crucial since only molecularly distributed plasticizer is able to interact with the polymer chains and hence reduce cohesion forces. The CA molecule possesses a high capacity for hydrogen bonding, which was reported to be responsible for the stability of the amorphous state and prevents its recrystallization in solid dispersions [18]. Hydrogen-bond formation between the CA molecules and the Eudragit® RS PO chains should account for a sufficient solubility and a plasticizing effect of the organic acid in the polymer melt.

The solubility of CA in Eudragit® RS PO hot-melt extrudates was studied by MDSC and PXRD. Thermal analysis of extrudates containing 0 to 30% CA MH was carried out over a temperature range of -30 to 170°C. The MDSC method yielded sufficient sensitivity to detect a melt endotherm for 10% crystalline CA in a physical mixture with Eudragit® RS PO (Fig. 3.2). All thermograms exhibited a single glass transition for the acrylic polymer between 35 and 55°C. Extrudates with high CA levels (25 or 30%) displayed an additional endothermic event at either 144 or 152°C, respectively. This peak was attributed to the melting of anhydrous CA when the solubility of CA in the polymer was exceeded and excess CA re-crystallized from the solid solution

in the anhydrous form. Concentrations of up to 20% CA MH in extruded polymer resulted in one-phase amorphous systems with a single Tg and no melting endotherm. In these cases, the organic acid melted or dissolved in the polymer during the extrusion process and remained dispersed at a molecular level in the solidified polymer after cooling. The corresponding extrudates were transparent strands, supporting the existence of a molecular dispersion, while extrudates comprising 25% CA MH or higher levels were opaque.

The solubility of CA in Eudragit® RS PO was further investigated by PXRD. Extrudates processed at 110°C and containing 10, 20, 25 or 30% CA MH or 25% anhydrous CA were compared. Fig. 3.3 shows that extrudates with 10 and 20% CA MH were completely amorphous, while the 25% CA MH sample exhibited peaks of low intensity, suggesting a low degree of crystallinity for this formulation. The diffraction patterns of extrudates containing 25% anhydrous CA or 30% CA MH exhibited more distinct peaks and hence an increased degree of crystallinity. The results demonstrated that the solubility of the monohydrate form was exceeded at concentrations of 25% or higher. The excess of the CA MH solubility in the extrudates led to re-crystallization of CA in the anhydrous form. These findings were in agreement with the results from the MDSC experiments. The solubility of the anhydrous CA in the acrylic polymer was lower than that of the monohydrate; however, the peak intensity of anhydrous CA in the extrudate was reduced when compared to the physical mixture, which suggested that there was a partial dissolution of anhydrous CA in the polymer during extrusion. The lower solubility of the anhydrous form was attributed to the higher stability of the lattice due to stronger intermolecular forces, resulting in a higher melting point and a lower tendency to interact with the polymer. The monohydrate form softened or melted during the extrusion process which facilitated its molecular distribution between the polymeric

chains, while the anhydrous lattice remained intact to a higher degree. These findings support the previously reported differences in extrusion process parameters.

The extrusion temperature was found to influence the degree of CA crystallinity in the extrudates (Fig. 3.4). Extrudates containing 25% CA MH and processed at 100, 110 and 120°C die temperature were selected for further PXRD studies, since the CA solubility in the polymer was exceeded at this CA concentration. An increase in the processing temperature led to a decrease in CA crystallinity. The degree of crystallinity in samples extruded at 110°C was lower than for the 100°C samples, while extrudates processed at 120°C were amorphous. These findings demonstrated that a sufficiently high extrusion temperature either led to an increased miscibility between the components, or that the formation of a stable amorphous two-phase system was facilitated. Since similar tendencies were observed for samples with other CA levels, it can be concluded that the higher the content of CA MH in the formulation, the higher the required extrusion temperature for the formation of a non-crystalline extrudate.

3.4.3 Plasticizing effect of CA on Eudragit® RS PO

The mechanism of CA-induced facilitation of the Eudragit® RS PO extrusion process was expected to be due to plasticization. Since the interactions between the polymeric chains were reduced by the incorporation of a plasticizer, a shift in the polymer's glass transition to lower temperatures should be detectable as a function of an increasing CA concentration. The data obtained by MDSC (Fig. 3.2), however, showed only a very slight decrease in the Tg with increasing CA MH levels in the extrudates and hence did not convincingly demonstrate a plasticizing effect. This observation might be attributed to the fact that unplasticized Eudragit® RS PO possesses a low Tg around 60°C, and that the change in heat capacity was not distinct.

Plasticizers also decrease the stiffness and increase the flexibility of polymeric films. To demonstrate the plasticizing properties of CA MH on Eudragit® RS PO, films were produced applying a casting-solvent evaporation technique. Films containing 0 to 30% CA MH based on the total weight were cast from acetone solutions, and their physico-mechanical properties were investigated. The tensile strength and the elastic modulus characterize the stiffness of a film and are directly proportional to the force that is required for film-stretching, whereas the maximal elongation correlates with the film flexibility. The presence of a plasticizer in a film formulation generally results in a decreasing tensile strengths and moduli and increasing elongations. Films cast from solutions containing 20% CA or less were smooth and transparent, confirming the solubility of the organic acid in Eudragit® RS PO up to this concentration. Higher levels of CA such as 25 or 30%, however, led to films with macroscopically visible crystals on the film surface and exhibited dramatically altered mechanical properties. These films were very brittle and readily broke when being attached to the grips of the Instron, and thus they were not analyzed. The data in Fig. 3.5 demonstrates a reduction in the tensile strength from 4.46 to 2.30 MPa when the CA MH concentration was increased from 0 to 20%. According to the results of ANOVA and Tukey's test, the tensile strength values for the 0%, 10% and 20% level were significantly different. The decrease in the elastic modulus from 492 to 48 MPa with increasing CA concentrations was found to be significant for the 0, 5, 10 and 15% level, but not for the 20% level. The elongation increased only insignificantly at low CA concentrations (0.76 ± 0.21 mm to 1.65 ± 0.20 mm for 0% and 10%, respectively), while the 15 and 20% level exhibited significantly higher elongation values (7.59 ± 1.01 cm and 10.89 ± 1.07 cm). These findings for the physico-mechanical properties of the polymeric films support the hypothesis that CA functioned as a plasticizer for Eudragit® RS PO.

Adsorbed water and residual acetone are able to exert plasticizing effects in cast films. The high hygroscopicity of CA is well known [28]. To exclude adsorbed moisture and residual solvent as possible reasons for the observed changes in film properties at higher CA levels, the content of volatile components of the films was determined. The volatile content was low in all films (3.28 ± 0.08%-3.85 ± 0.18%, n = 3) and not dependent on the CA concentration, so that their influence on the mechanical properties was deemed negligible and the observed changes were attributed to the differences in the CA level.

3.4.4 CA release from extruded tablets

The dissolution profile of citric acid from the polymer matrix was investigated to evaluate the capability of the system to retard the release of water-soluble API's. Leaching of hydrophilic plasticizers such as TEC from insoluble matrix systems during the dissolution process was demonstrated to impact the drug release rate and mechanism [10]. Hot-melt extruded matrices are characterized by a low porosity and a high tortuosity when compared to direct compressed or granulated dosage forms. The addition of hydrophilic compounds such as citric acid to the formulation will lead to an increased channel formation in the insoluble matrix when the system is exposed to the dissolution medium, allowing incorporated drugs to diffuse through the water-filled pores at a faster rate.

Dissolution studies with Eudragit® RS PO matrix tablets containing 25% CA MH or anhydrous CA were carried out over 12 hours in a pH 6.0 phosphate buffer (apparatus 2, paddle method). Since the maximal extrusion temperature (130°C) was below the decomposition temperature of CA, which has been reported to be thermally stable up to 160°C [29], and the transition time through the extruder did not exceed four minutes,

thermal decomposition of CA was unlikely. The actual CA content of each tablet after complete destruction with a Polytron homogenizer was found to be between 98.0% and 101.0% by HPLC analysis, confirming the thermal stability and content uniformity of CA in the polymeric carrier after the extrusion process.

Although Eudragit® RS PO is insoluble at all pH values and consequently controls the release of highly water-soluble components, a rapid release profile of the CA from the extrudates was expected due to the high water solubility of the organic acid, allowing a quick diffusion through channels formed in the polymer matrix. The pore formation in HPMC matrix systems through rapid CA leaching has been previously reported [30]. However, dissolution testing revealed an extended release profile for CA with 42.05±0.76% and 36.55±1.45% released after 6 hours and 57.99±1.35% and 53.66±1.98% released after 12 hours for CA MH and anhydrous CA, respectively (Fig. 3.6). The small surface area of the studied monolithic dosage form and the high affinity between the polymer and the organic acid, which is essential for plasticization, are two possible explanations for the slow CA release. Furthermore, the incorporated level of CA (25%) might have been below the minimal concentration which is necessary for continuous channel formation to allow percolation throughout the polymer matrix.

For the release of the monohydrate and the anhydrous CA, an f2 value above 50 (f2 = 66.90) demonstrated the similarity of the dissolution profiles. The comparison of both profiles by repeated measures ANOVA and Tukey's test showed a significantly lower release for the anhydrous form at each sampling time point. The differences in release rates can be explained by the different degree of crystallinity of the CA in the samples with anhydrous CA being more crystalline in melt extruded Eudragit® RS PO. Since crystalline phases are more stable systems and possess a lower surface energy, they

usually have a lower dissolution tendency than amorphous phases, resulting in a decreased dissolution rate when compared to non-crystalline systems.

3.5 CONCLUSION

The present study demonstrated that citric acid functioned as an effective solid-state plasticizer in Eudragit® RS PO films and hot-melt extrudates. The extrusion process was found to be facilitated by increasing the concentration of citric acid, and plateaued at 25% based on the total formulation weight. Citric acid monohydrate (CA MH) was more effective in improving the processability than the anhydrous form, with the higher plasticization efficiency of the monohydrate being attributed to its higher solubility in the acrylic polymer. The solubility of CA MH in Eudragit® RS PO was limited and dependent on the extrusion temperature. Concentrations of up to 20% CA MH were found to be soluble in extrudates as well as in cast films, while extrudates with 25% CA MH required an extrusion temperature of at least 120°C to remain amorphous. A reduction in the glass transition temperature of Eudragit® RS PO extrudates by CA MH was not convincingly shown by MDSC data; however, the tensile strength and elastic modulus of polymeric films decreased as a function of CA level, while the elongation increased, indicating plasticization of the polymer. Dissolution studies demonstrated a slow and controlled release of CA from extruded tablets with the monohydrate form being released faster than the anhydrous form. In conclusion, citric acid monohydrate was shown to be sufficiently soluble in Eudragit® RS PO and was successfully used for the plasticization of Eudragit® RS PO when hot-melt extruded.

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3.7 FIGURES

Figure 3.1: Influence of citric acid monohydrate (CA MH) concentration and anhydrous citric acid on the extrusion parameters (screw speed divided by motor load) for the melt extrusion of Eudragit® RS PO as a function of die temperature. (◆) pure Eudragit® RS PO; Eudragit® RS PO with (■) 10% CA MH; (▲) 15% CA MH; (◇) 20% CA MH; (□) 25% CA MH; (△) 30% CA MH; (×) 25% anhydrous CA. (n = 3, error bars represent the standard deviation)

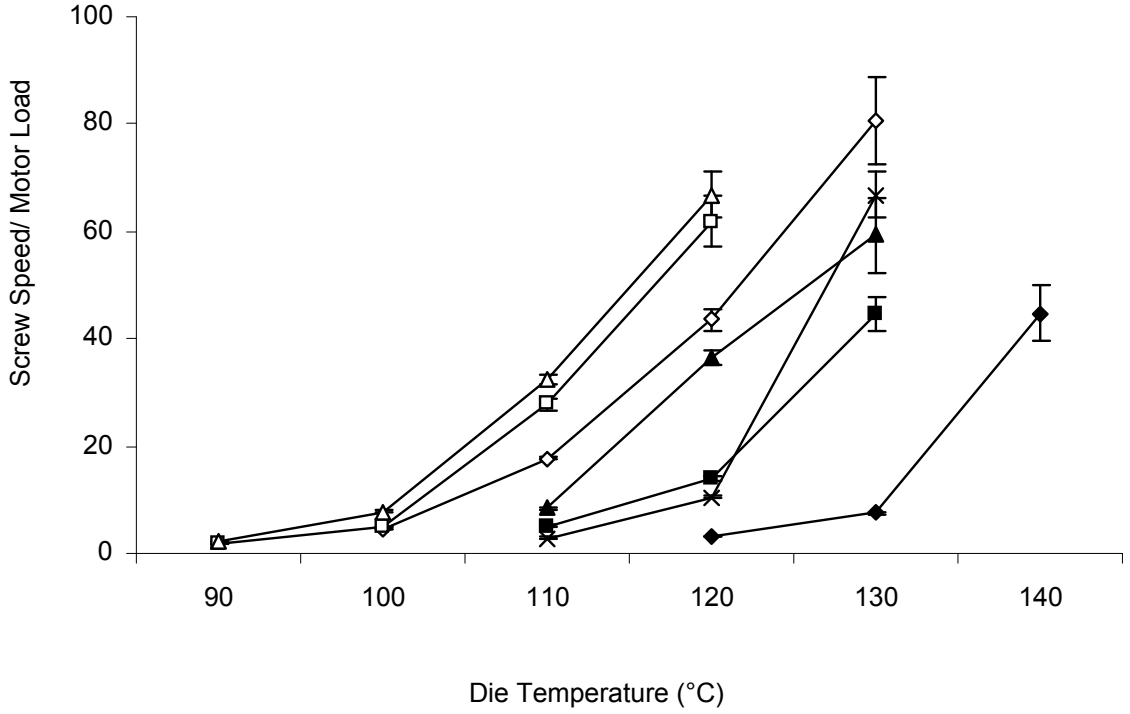


Figure 3.2: MDSC thermograms (1st runs) of hot-melt extrudates containing 0 – 30% citric acid monohydrate (CA MH). (a) physical mixture of 10% anhydrous CA in Eudragit® RS PO; Extrudate with (b) 0% CA MH; (c) 10% CA MH; (d) 15% CA MH; (e) 20% CA MH; (f) 25% CA MH*; (g) 30% CA MH*.
* An excess of CA MH solubility in the extrudates led to re-crystallization in the anhydrous form.

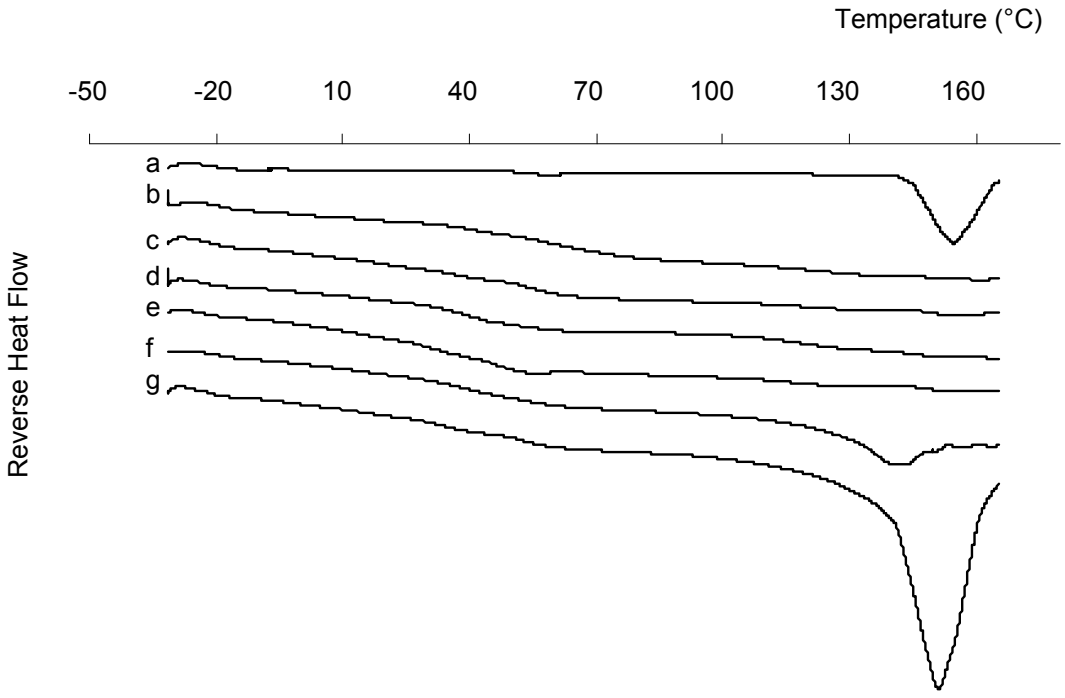


Figure 3.3: Influence of citric acid (CA) concentration and type (anhydrous form or monohydrate = MH) on the crystallinity of hot-melt extrudates obtained at 110°C. PXRD patterns of (a) anhydrous CA powder; (b) physical mixture of Eudragit® RS PO and 25% anhydrous CA; (c) Eudragit® RS PO powder; (d) extrudate with 10% CA MH; (e) extrudate with 20% CA MH; (f) extrudate with 25% CA MH*; (g) extrudate with 30% CA MH*; (h) extrudate with 25% anhydrous CA.
* An excess of CA MH solubility in the extrudates led to re-crystallization in the anhydrous form.

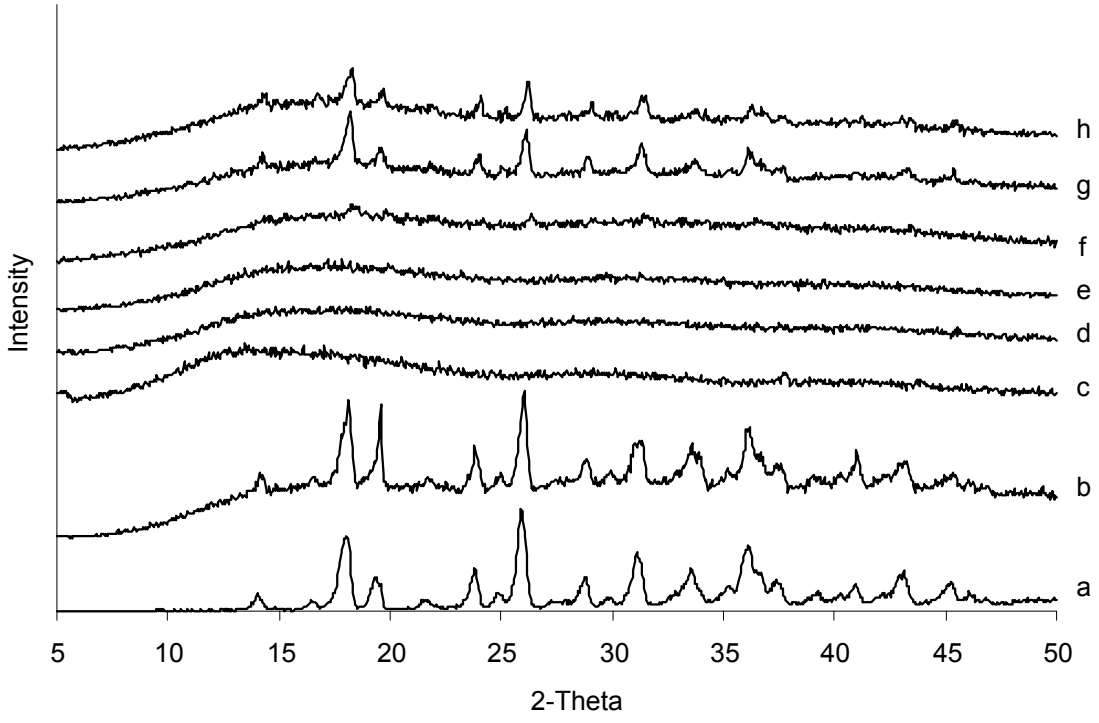


Figure 3.4: Influence of extrusion temperature on the crystallinity of hot-melt extrudates containing 25% citric acid monohydrate. PXRD patterns of (a) anhydrous citric acid powder; (b) extrudate obtained at 100°C*; (c) extrudate obtained at 110°C*; (d) extrudate obtained at 120°C; (e) Eudragit® RS PO powder.
* An excess of CA MH solubility in the extrudates led to re-crystallization in the anhydrous form.

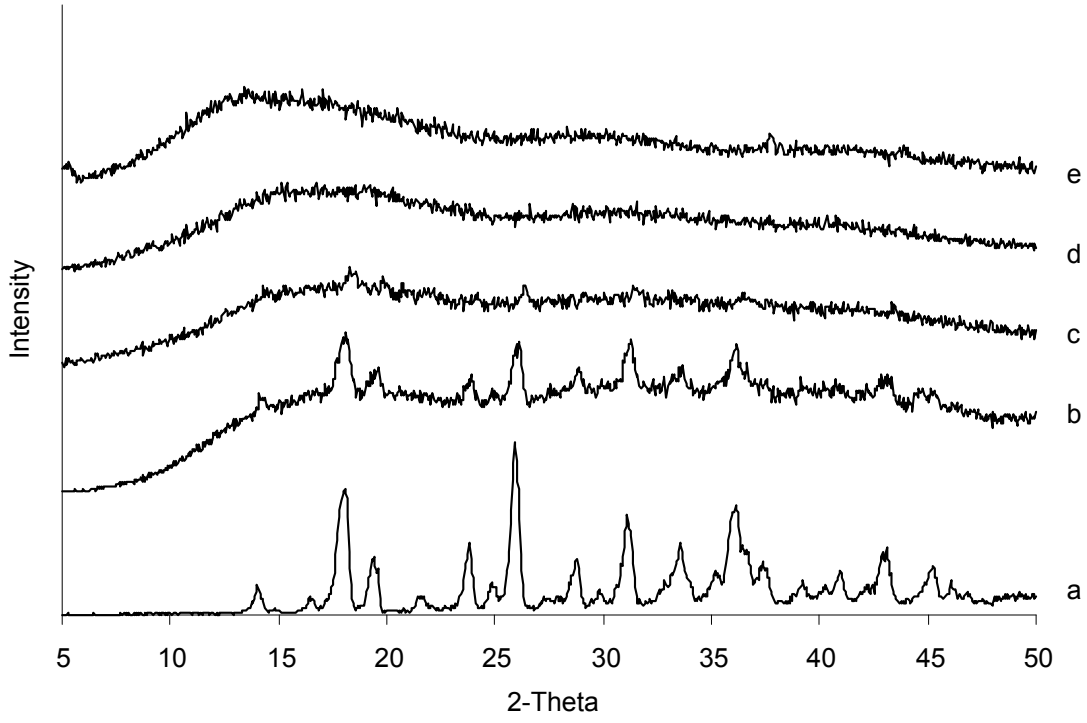


Figure 3.5: Influence of citric acid monohydrate (CA MH) concentration on the tensile strength and elastic modulus of films containing 0 – 20% CA MH (n = 6, error bars represent the standard deviation). Films were stored at 25±1°C/ 50±5% RH for 48 hours prior to analysis.

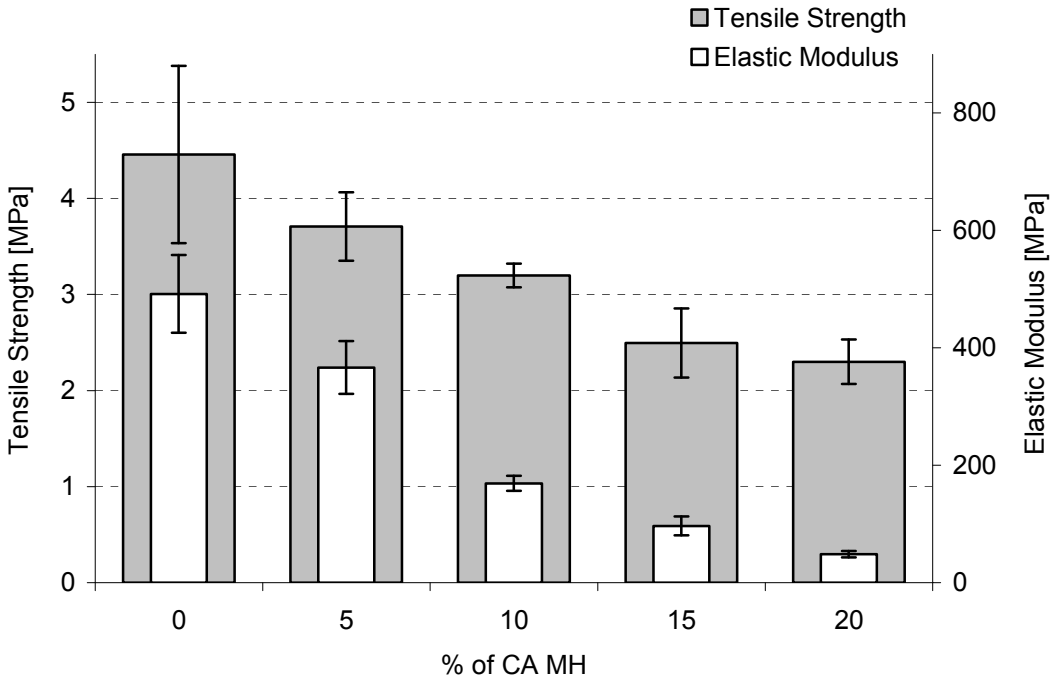
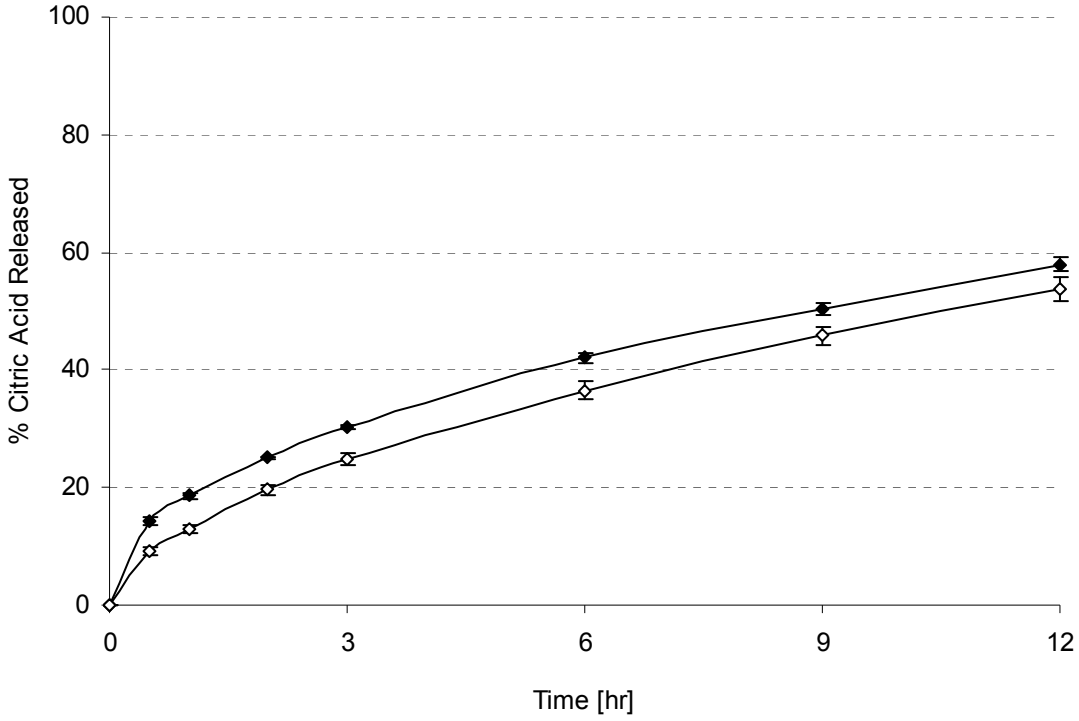


Figure 3.6: Release of citric acid monohydrate and anhydrous citric acid from Eudragit® RS PO tablets extruded at 120°C. (◆) formulation with 25% citric acid monohydrate; (◇) formulation with 25% anhydrous citric acid. Dissolution: USP paddle method, 900 ml phosphate buffer pH 6.0 as dissolution medium, 37°C, 100 rpm, n = 6.



Chapter 4: Study of the Effects of Citric Acid Monohydrate on the Solid-State and Drug Release Properties of Diltiazem Hydrochloride in Melt Extruded Eudragit® RS PO Matrix Tablets[2]

Abstract:

Incomplete drug release and particle size dependent dissolution performance can compromise the quality of controlled release matrix systems. The objective of the current study was to investigate the ability of citric acid monohydrate (CA MH) to enhance the release of diltiazem hydrochloride from melt extruded Eudragit® RS PO tablets and to eliminate drug particle size effects. Preformulation studies demonstrated the thermal stability of all components, drug insolubility in the polymer but miscibility with the CA MH. Tablets with either constant polymer levels or constant drug to polymer ratios and containing different drug particle size fractions and increasing amounts of CA MH were manufactured by melt extrusion and characterized by dissolution testing, powder X-ray diffraction and scanning electron microscopy. The addition of CA MH to the formulation promoted the thermal processibility and matrix integrity by plasticization of the polymer. The drug release from systems with constant drug-to-polymer ratio was significantly increased when CA MH was added as a result of enhanced pore formation. Particle size effects were eliminated when large amounts of CA MH were used due to the loss of drug crystallinity. Matrix tablets with CA MH furthermore showed a faster and more complete drug release compared to systems with drug only or alternative pore formers (sucrose, NaCl, or PEG 3350). The enhanced drug release was attributed to the amorphous

[2] Significant portions of this chapter were taken from: Schilling, S.U., Bruce, C.D., Shah, N.H., Malick, A.W., Infeld, M.H., and McGinity, J.W. Citric acid monohydrate as a release-modifying agent in melt extruded matrix tablets. International Journal of Pharmaceutics, 2008, 361, p: 158-168.

character of the soluble components, improved drug dispersion in the plasticized polymer along with increased polymer permeability. In summary, CA MH promoted the miscibility between the drug and Eudragit® RS PO during hot-melt extrusion, resulting in the extrusion of an amorphous system with improved dissolution characteristics.

4.1 INTRODUCTION

Hot-melt extrusion has been employed to manufacture matrix delivery systems exhibiting sustained or immediate drug release. Formulations to be processed by melt extrusion most commonly comprise the active drug together with one or several functional excipients [1]. Due to the poor thermoplastic properties of most drugs, the addition of a deformable carrier polymer or wax is required. The selection of the carrier material as well as the drug-to-carrier ratio greatly impacts the release properties of the dosage form [2]. Processing aids including plasticizers, glidants or thermal lubricants can be added to promote processibility and allow a reduction in extrusion temperature, making the process feasible for dosage forms containing drugs with compromised thermal stability.

A third group of excipients for melt extrusion can be characterized as drug release modifying agents. The mechanisms of release modification are varied and frequently linked to an alteration in the matrix properties, which can lead to an increase in the drug release rate by promoting either drug diffusion and/ or carrier erosion. A popular approach to increase the release of a poorly soluble active pharmaceutical ingredient (API) is the incorporation of hydrophilic polymers such as PVP and PVP-VA [3], PEO [4], HPMC [5] or Eudragit® EPO [6] into the matrix. Enhanced drug release from these systems can be attributed to a reduced drug particle size, increased API solubility in the

amorphous state and/ or the maintenance of drug supersaturation in the dissolution medium. Cyclodextrins [7] and surfactants [8, 9] have been successfully used to enhance the drug solubility in the dissolution medium and to improve powder wettability. Polymeric or low-molecular weight additives with high aqueous solubility can enhance drug dissolution due to leaching into the dissolution medium and formation of a porous network [2]. Water-soluble excipients of low molecular weight that are miscible with the polymer can simultaneously function as plasticizer and pore former. Zhu and coworkers reported increased drug release rates when high TEC levels were incorporated into diltiazem hydrochloride matrix tablets due to leaching of the plasticizer during dissolution [10].

Citric acid has been widely used as an acidifying agent in solid oral dosage forms [11, 12]. Solid dispersions of poorly soluble APIs in citric acid produced by co-melting techniques exhibited increased dissolution rates [13-15]. Furthermore, the plasticizing effects of citric acid monohydrate (CA MH) on certain acrylic polymers including Eudragit® L 30D-55 [16], Eudragit® S100 [17] and Eudragit® RS PO [18] have been previously demonstrated.

The objective of this study was to investigate the influence of CA MH on the release rate of a model API from a hot-melt extruded, extended release matrix system. Diltiazem hydrochloride (DIL HCl), a calcium channel blocker commonly used in the long-term treatment of hypertension, was selected as the model drug. The hydrochloride salt form is thermally stable below its melting point at 215°C and does not melt or dissolve when extruded in an Eudragit® RS PO matrix [10]. Drug release from extruded composites was investigated as a function of the drug particle size and the citric acid concentration, and compared to formulations containing alternative pore formers.

Characterization of the solid systems regarding true density, crystallinity and morphology was performed to explain the altered dissolution properties.

4.2 MATERIALS

Diltiazem hydrochloride (DIL HCl), citric acid monohydrate (powder, U.S.P.), anhydrous citric acid, sucrose and sodium chloride (NaCl) were purchased from Spectrum Chemicals (Gardena, CA). Polyethylene glycol 3350 (Carbowax Sentry™) was obtained from the Dow Chemical Company (Midland, MI). Citric acid monohydrate, sucrose and sodium chloride were ground in a mortar and pestle to obtain particles smaller than 250 μm. To investigate the influence of DIL HCl particle size on the dissolution rate, the obtained material was sieved into 3 different particle size fractions, and fine DIL particles (< 75 μm) and coarse DIL particles (150-250 μm) were used for the extrusion of the formulations 8-15 (Table 1). Eudragit® RS PO was kindly donated by Evonik Degussa (Piscataway, NJ).

4.3 METHODS

4.3.1 Thermogravimetric analysis (TGA)

The thermal stability of DIL HCl, CA MH, anhydrous citric acid, and Eudragit® RS PO was evaluated by thermogravimetric analysis (TGA). A powder sample of approximately 10 mg was accurately weighed into an aluminum pan and placed into the furnace of a Perkin-Elmer thermogravimetrical analyzer (7-series, Norwalk, CT). The percentage weight loss of the samples was monitored from 50 to 500°C employing a heating rate of 10°C/min. A compound was considered thermally stable when the percent

weight loss was smaller than 1% during heating to the highest employed extrusion temperature (150°C).

4.3.2 Drug-polymer binding study

A stock solution of DIL HCL in phosphate buffer pH 6.0 (0.1mg/ml) was prepared, and aliquots of 50 ml were filled into Erlenmeyer beakers. Increasing increments of Eudragit® RS PO (0, 10, 20, 40, 60 mg) were added to the beakers, and the suspensions were incubated at 37°C in an Innova 4300 Incubator Shaker (New Brunswick Scientific Co., Edison, NJ) at 200 rpm. After 24 hours, 1 ml of the suspension was removed from each beaker, centrifuged, filtered and analyzed for DIL HCl content using a UV spectrophotometer (μQuant 96-Well Plate Reader, Bio-Tek Instruments Inc., Winooski, VT) at 237 nm. Analysis was performed in triplicate.

4.3.3 Differential scanning calorimetry (DSC)

Physical mixtures composed of different drug to anhydrous citric acid ratios (7:1, 3:1, 1:1, 1:3, 1:7) were prepared to evaluate the miscibility between DIL HCl and the organic acid. An accurately weighed amount of powder (8-12 mg) was placed in aluminum pans, which were crimp sealed and heated from 0 – 250°C using a TA Instrument model 2920 (New Castle, DE). The heating rate was set to 10°C/min, and all thermograms show the heat flow versus temperature as monitored during the first run.

4.3.4 Processibility

Powder blends comprising a constant level of Eudragit® RS PO (60%, formulations 1-4) were extruded at different temperature settings to study the

processibility as a function of the DIL HCl to CA MH ratio. The preset temperature values were increased from zone 1-3 by 10°C, while the die temperature was equal to the temperature in zone 3. Temperature profiles between 60/70/80/80°C and 130/140/150/150°C were investigated. The processibility of a formulation by hot-melt extrusion can be characterized by process parameters such as screw speed, torque or motor load and melt pressure. The application of elevated screw speeds is advantages due to shorter residence times of the drug inside the barrel and hence a reduced exposure to high temperatures and in terms of process output rates and efficiency. The motor load was kept constant at 0.650±0.010 drive amperes, and the dependence of the applicable screw speed on the DIL HCl to CA MH ratio was investigated. Furthermore, the influence of the formulation on the motor load was determined at a constant screw speed of 20 rpm as a function of temperature. Low motor loads implicate a reduced work input of the engine due to the lower resistance of the moving screw against softened material with reduced melt viscosity.

4.3.5 Helium pycnometry

The true density of extruded tablets was evaluated by means of helium pycnometry using an AccuPyc 1330 Pycnometer, (Micromeritics Instrument Corporation, Norcross, GA). For each formulation, six specimens were analyzed by placing a 250 mg tablet into the chamber (cell volume of 12 cm^3) and purging with helium for 4 times at 20 PSI, followed by 3 analytical runs at the same pressure. The equilibration rate was set to 0.0050 PSI/min.

4.3.6 Manufacture of melt-extruded tablets

Fifteen formulations (Table 4.1) were processed using a vertical single screw extruder (Randcastle, model RCP 0750 Microtruder, Cedar Grove, NJ). Powder blends (150-200g) comprising either a constant percentage of Eudragit® RS PO (60%, formulations 1-7) or a constant API to polymer ratio (1:4) and employing either fine or coarse DIL HCl particles with increasing levels of CA MH (formulations 8-15) were premixed and manually fed into the extruder. The organic acid plasticized the polymer, which influenced the choice of extruder temperature settings. For all formulations, the temperature did not exceed 150°C in any of the 4 heating zones and the transition time through the barrel was less than 4 minutes. The screw speed was set to a maximum of 20 rpm, while the motor load was limited to 0.700 drive amperes, and the pressure did not exceed 200 PSI. The molten polymer strand exited through a circular die (6 mm diameter) and was manually cut into tablets.

4.3.7 Dissolution Experiments

Diltiazem HCl dissolution testing from extruded matrix tablets was carried out in 900 ml of 50 mM phosphate buffer pH 6.0 using a USP paddle apparatus (Varian, Cary, NC) over 12 hours. The paddle speed was set to 50 rpm, and the bath temperature was kept constant at 37.0±0.5°C. All experiments were run with 6 replicates. The percent DIL HCl released from the tablets at each time point was calculated as the percentage of the actual DIL HCl content of each tablet, which was determined in a sample of the final media after complete destruction of the tablet with a Polytron homogenizer (Kinematica Inc., Newark, NJ).

4.3.8 Diltiazem HCl assay

The DIL HCL concentration in the dissolution medium at each sampled time point was analyzed by means of HPLC (Waters Inc., Milford, MA). An aliquot of 10 µl was injected onto a C_{18}-reversed phase column (Capcell PAK, 3 × 100 mm, Shiseido Co., Tokyo, Japan) and analyzed at a flow rate of 0.5 ml/min using a mixture of 50 mmol phosphate buffer pH 6.0/ acetonitrile/ methanol at a 5:4:1 ratio and adjusted to pH 4.2 with phosphoric acid as mobile phase. The drug content was measured at 237 nm with a UV detector (996-PDA detector, Waters Inc., Milford, MA), and peaks were integrated using Empower Version 5.0 software (Waters Inc.). The analytical method yielded linearity (R2 < 0.999) for 0.5 - 60 µg/ml DIL HCl (corresponding to 0.9-108.0% of DIL HCl in tested samples) and was reproducible (RSD < 2.4% at each tested concentration, n = 6).

4.3.9 Powder X-ray diffraction (PXRD)

The degree of drug crystallinity in physical mixtures and extruded formulations was investigated by PXRD. Extrudates were ground with a mortar and pestle, and the powder was passed through a 60 mesh sieve (250 µm) prior to analysis. Physical mixtures were prepared in accordance with the extrudates by co-grinding of the components with a mortar and pestle. The samples were spread in a thin powder bed and subjected to X-ray in the 2-Theta range employing a Philips Electronic Instrument (Type 42273) with Cu K alpha radiation operating at 45 kV and 40 mA. The samples were scanned between 5-50° at a step size of 0.03° and a dwelling time of 1 sec (scanning rate of 1.8°/min).

4.3.10 Scanning electron microscopy (SEM)

The morphology of extruded tablets comprising 60% Eudragit® RS PO, DIL HCl and a soluble excipient was studied before and after 12 hours of dissolution in phosphate buffer pH 6.0 with a Zeiss Supra 40VP SEM (Carl Zeiss AG, Germany) equipped with a Gemini column in field emission mode. Cut tablets were placed onto mounts with carbon tape and coated with Pt/Pd (80:20) under argon atmosphere at 2.5 kV and 20mA to a thickness of 15 nm in a Cressington Sputter Coater 208 HR equipped with a Thickness Controller MTM 20 (Cressington Scientific Instruments Ltd., Watford, UK). The samples were exposed to an electron beam of 5 kV and an emission current of 300 μA, and pictures were taken employing Smart SEM V05.02.03 software.

4.3.11 Statistical analysis

Minitab Release 14 Statistical Software (Minitab Inc., State College, PA) was used to carry out statistical analysis (one-way ANOVA and post hoc Tukey's test). All tests were based on the 95% confidence level. Furthermore, the f2 similarity factor was calculated for the dissolution profiles using the means of % released at each time point [19].

4.4 RESULTS AND DISCUSSION

4.4.1 Thermal stability

The TGA experiments (Fig. 4.1) confirmed the thermal stability of Eudragit® RS PO and DIL HCl at the temperatures employed for the extrusion process as reported previously by Zhu et al. [10]. The weight loss for the polymer was less than 0.33% up to 150°C. The drug was stable with a loss in weight of 0.05% up to 150°C, and 0.55%

below its melting point at 215°C, respectively. The weight loss observed for CA MH below the extrusion temperatures was attributed to the loss of water bound in the lattice structure. Prior to its melting at 158°C, the percentage decrease in weight for CA MH was approximately 6%, a value below the percentage of lattice water in the MH (8.5% based on the chemical structure). The anhydrous form of citric acid exhibited a weight loss of less than 0.07% below its melting point, demonstrating the thermal stability at the extrusion temperatures.

4.4.2 Binding of DIL HCl to Eudragit® RS PO

Drug adsorption to the polymeric carrier may account for incomplete drug release from matrix dosage forms. Khalil and coworkers reported the complex formation between ammoniomethacrylates and salts of acidic drugs in phosphate buffer solutions, which was mainly attributed to electrostatic interaction [20]. In addition, nonelectrostatic binding due to hydrogen bonding or van der Waals forces may lead to adsorption of basic or neutral APIs, as has been shown for indomethacin and Eudragit® RL PO [8]. Due to the lower content of quaternary ammonium groups compared to Eudragit® RL PO, drug binding was expected to be less pronounced for Eudragit® RS PO. An overnight adsorption study with increasing increments of Eudragit® RS PO suspended in DIL HCl phosphate buffer pH 6.0 solutions showed only a small reduction in the concentration of free drug in solution (less than 3% at all investigated ratios) which was not statistically significant (Fig. 4.2). These results were consistent with the findings reported previously by Follonier and coworkers [21].

4.4.3 Solid-state miscibility between the formulation components

Binary physical mixtures were prepared to characterize the interactions between DIL HCl, CA MH and Eudragit® RS PO. The binary system of CA MH and Eudragit® RS PO has been previously investigated by our group [18]. The organic acid was miscible with the polymer at concentrations up to 20% and functioned as a solid-state plasticizer during the melt extrusion process. Due to the strong interactions between the functional groups of both components, the cohesive forces between the polymeric chains were reduced and the melt viscosity decreased, promoting the processibility of the polymer at lower extrusion temperatures.

Zhu and coworkers studied physical mixtures and extruded systems of DIL HCl and Eudragit® RS PO [10]. The drug did not exert plasticizing effects on the acrylic polymer and maintained a high degree of crystallinity during the extrusion process. We conducted extrusion experiments of binary drug-polymer blends comprising three different drug loadings (5, 10 and 20%) to determine the solubility of DIL HCl in the acrylic polymer and evaluate the limit of detection (LOD) for the PXRD method. Fig. 4.3 displays the diffraction patterns that were obtained for the extrudates in comparison to the corresponding physical mixtures. The physical mixtures were prepared by co-grinding the drug with the polymer applying the same procedure as for the extrudates comminution to avoid differences in crystallinity due to amorphization during grinding. The peaks of crystalline DIL HCl that were found in the extrudates were of similar intensity as in the physical blends at all three drug levels. A DIL HCl concentration as low as 5% was still detectable as a separate crystalline phase in the extruded systems, demonstrating that DIL HCl was virtually insoluble in Eudragit® RS PO.

The affinity between DIL HCl and citric acid was evaluated by thermal analysis (DSC, Fig. 4.4) and by a comparison of the solubility parameters. The pure materials and

physical mixtures containing varying ratios of both components were heated to 250°C. The pure drug as well as citric acid exhibited a high degree of crystallinity as can be seen by the sharp melting peaks at 215 and 158°C, respectively. Decomposition of the organic acid started immediately after the melting event since the signal did not return to the baseline level, but continued its downward shift. This thermal instability of citric acid at temperatures above its melting point was consistent with the TGA findings and was detectable in all the physical blends as a broad peak around 190°C exhibiting concentration dependent intensity. The thermogram obtained at a high DIL HCl to citric acid ratio (7:1, curve a) shows that drug melting occurred below this temperature. A broad endothermic event between 100 and 150°C exhibiting low enthalpy values was found for the 7:1, 3:1 and 1:1 mixtures of drug and citric acid. This peak represented the simultaneous melting of DIL HCl and citric acid, indicating their presence as a single inseparable phase at this temperature. The observed loss in melting enthalpy can be interpreted as non-ideal mixing behavior due to an intensive interaction and a high degree of miscibility between the two components. The addition of citric acid to the extrusion formulation depressed the melting point of DIL HCl below the extrusion temperature (110-120°C versus 215°C). Increasing the amount of citric acid to ratios of 1:4 or 1:7 led to the appearance of an additional citric acid melting peak at 143 and 151°C, respectively, indicating that a separate citric acid rich phase was present at high concentrations.

Comparison of the solubility parameters that were calculated for DIL HCl and citric acid according to Hansen (21.80 versus 25.52 $MPa^{1/2}$) or Hoy (20.85 versus 24.52 $J^{1/2}/ cm^{3/2}$) supported the high miscibility that was experimentally found for the two components. A difference of less than 7 between the solubility parameters of 2 components has been associated with a high degree of miscibility [22].

4.4.4 Influence of the DIL HCl to CA MH ratio on the processibility

Powder blends with a constant polymer level of 60% (formulations 1 – 4) were investigated for their suitability for hot-melt extrusion. The influence of the DIL HCl to CA MH ratio (1:0, 3:1, 1:1, 1:3) was studied over a temperature range between 80 and 150°C (zone 3 and die). The highest applicable screw speed under borderline motor load (0.640 – 0.660 drive amperage) was selected as the primary response parameter. When the target screw speed of 20 rpm was feasible, the motor load was monitored as a secondary response (values reported in parentheses in Fig. 4.5). Since hot-melt extrusion exerts a combination of melting and mechanical processes [23], the processibility of a formulation depends on its thermal as well as mechanical properties and the combination thereof. The thermoplastic behavior of the carrier polymer represents the dominating factor, but can be modulated by the incorporated API or additional excipients.

Fig. 4.5 shows that pure Eudragit® RS PO could be extruded at 20 rpm when the extrusion temperature was 140°C or higher. The viscosity of the softened polymer was a function of the temperature and decreased when the temperature was increased. Consequently, at higher temperatures, the resistance of the material inside the extruder barrel to the screw rotation decreased and the required motor load diminished. A substitution of 40% polymer by DIL HCl resulted in a blend with decreased thermoplastic deformability, necessitating an increase in the processing temperature. The temperature was limited to 150°C, although the target extrusion speed was not reached under the tested conditions. Eudragit® RS PO is susceptible to thermal degradation of the side chains at temperatures above 140°C [24], and the occurrence of die swell compromised the quality of the extrudate at higher temperatures. These results demonstrated that DIL HCl is poorly thermoplastic and neither melted at extrusion temperatures nor plasticized the polymer.

Blends containing 10-30% CA MH in Eudragit® RS PO, however, could be processed at lower temperatures (130-100°C, zone 3 and die). This improvement in processibility was attributed to the plasticizing effect of CA MH on the acrylic polymer and was investigated in a previous study [18]. The inclusion of 20% CA MH (with 20% DIL HCl) improved the processibility to a higher extent when compared to blends containing 10% of the organic acid (with 30% DIL HCl) as extrusion at 20 rpm became feasible at only 100°C. Increasing the CA MH level to 30% based on the total formulation weight did not result in further improvements. A comparison of the motor load values obtained for the extrusion at 20 rpm showed that there was no significant difference between the 20% and 30% CA MH formulation at any of the three investigated temperature levels (100, 110, and 120°C). This observation was due to the limited solubility of CA MH in Eudragit® RS PO, impeding further plasticization of the polymer at the higher CA MH concentration.

The plasticizing effect of CA MH on the acrylic polymer was supported by the results of helium pycnometry (Fig. 4.6). The increase in true density with increasing CA MH amounts was statistically significant up to 20% CA MH based on the total formulation weight, and demonstrated the formation of a denser matrix of higher integrity due to plasticization of the polymer.

4.4.5 Influence of CA MH level and drug particle size on the dissolution of DIL HCl from extruded matrix tablets containing constant drug-to-polymer ratios

The drug release rate from extruded matrices can be influenced by the raw material particle size of the API [25] or functional excipients [26]. Particle size independence of the drug dissolution profile is considered beneficial in terms of

robustness of the delivery system. Powder blends containing one of two different particle size fractions of DIL HCl (fine or coarse) and increasing increments of CA MH were extruded while maintaining a constant API-to-polymer ratio (1:4, formulations 8 – 15). Tablets containing 100 mg drug were cut manually and subjected to 12 hours dissolution in phosphate buffer pH 6.0 (Fig. 4.7).

Drug particle size can impact the release rate in several ways. Smaller particles possess a larger surface area that is exposed to the release medium, and commonly exhibit faster dissolution rates (Noyes-Whitney relationship). Applying the percolation theory [27], the major pathway of API release from an insoluble matrix is by diffusion through water filled pores, and to a lesser extent, by diffusion through the polymer. Only drug particles that are in contact with the dissolution medium, so called infinite clusters, will dissolve and be released by diffusion. The critical drug load or total soluble fraction (TSF) that is necessary to form a continuous network of pores during the dissolution process is referred to as percolation threshold [28]. Below the percolation threshold, only drug located at the surface in contact with the medium will be released, while significant amounts of API remain trapped as finite clusters inside the insoluble matrix. This behavior was observed for tablets without CA MH (DIL75/RS-0 and DIL200/RS-0) with an incomplete drug release of 21.87% (DIL75/RS-0) and 29.82% (DIL200/RS-0) after 12 hours. Both formulations further exhibited an initial burst effect that was attributed to the fast dissolution of API that was located at the surface of the tablet.

The number of pores and the degree of pore network coherence are a function of TSF and, if the water-soluble material is insoluble in the matrix polymer, pore formation is dependent on the particle sizes of the soluble materials in the formulation [2]. The addition of CA MH to the formulation while maintaining a constant ratio of DIL HCl and Eudragit® RS PO represented an increase in TSF. The matrix fraction accessible by the

dissolution medium became larger, while the number of isolated API clusters diminished. Increasing the amount of CA MH to a DIL HCl / CA MH ratio of 2:1, 1:1 and 2:3 resulted in faster drug release with 60.30, 69.95 and 75.69% being released after 12 hours from formulations containing fine API (DIL75/RS-10, DIL75/RS-20 and DIL75/RS-30). The same tendencies were found for the large particle size formulations (65.54, 72.37 and 77.10% for DIL200/RS-10, DIL200/RS-20 and DIL200/RS-30, respectively).

The influence of the DIL HCl particle size in the extrusion blend on the dissolution properties was further analyzed. Caraballo and coworkers reported a linear increase in percolation threshold with increasing drug particle size, implying that drugs of larger particle sizes required higher drug loadings to percolate an inert matrix [29]. For smaller particles, the formation of a coherent network of pores is statistically more probable due to the higher particle number at constant weight fraction when compared to coarse particles. For this reason and due to an increase in surface area, a faster DIL HCl release was expected for the fine particle size formulations. However, the results in Fig. 4.7 indicated that formulations with larger API particles yielded a higher release rate at all tested CA MH levels. This observation implied that the dissolution of drug particles prior to diffusion was not the rate-limiting step for the release of DIL HCl from Eudragit® RS PO matrices. Furthermore, higher pore network coherence and increased accessible volume fractions as expected for smaller particle formulations did not yield improved drug dissolution. It must be concluded that other matrix properties impacted the drug dissolution to a larger extent than the previously discussed factors. One possible explanation is the theoretical increase in tortuosity and thus diffusion path length in networks created by leaching of small particle size compounds when compared to larger particles. A second aspect might be the formation of a more homogeneous and denser

matrix when powders of small particle size were extruded, resulting in decreased drug release rates.

Interestingly, at high CA MH concentrations, the drug release became independent of the API particle size that was used for the extrusion. The release of DIL HCl from tablets of the formulation DIL75/RS-30 was very similar to the dissolution from DIL200/RS-30 (f2 = 79). Tablets including less CA MH yielded lower similarity factors (f2 = 61 or 59, respectively). These discrepancies in dissolution behavior were attributed to the elimination of DIL HCl crystallinity and the enhanced dispersion of the drug when large amounts CA MH were present.

4.4.6 Influence of CA MH level and DIL HCl particle size on the crystallinity of extruded matrix tablets containing constant drug-to-polymer ratios

Powder X-ray diffraction is a convenient method to investigate the physical state of solid dosage forms in terms of crystallinity. The previous experiments demonstrated that the LOD of this method for crystalline DIL HCl in Eudragit® RS PO extrudates was below 5%. The PXRD pattern of the formulations 8 – 15 are shown in Fig. 4.8. Extrudates without CA MH (DIL75/RS-0 and DIL200/RS-0) yielded a high degree of DIL HCl crystallinity with several characteristic peaks being present (2-Theta = 10.7, 15.4, 18.2, 19.5, 20.7, 27.7). These findings were due to the high melting point and insolubility of the drug in the polymer. The addition of increasing amounts of CA MH led to a decrease in DIL HCl crystallinity as seen for formulations DIL75/RS-10, DIL200/RS-10, and DIL200/RS-20. Formulations containing drug and CA MH at a ratio of 2:3 (DIL75/RS-30 and DIL200/RS-30) were completely amorphous, and so was DIL75/RS-20. The loss of drug crystallinity was attributed to the strong interaction with CA MH as previously demonstrated by DSC. The depression of the DIL HCl melting

point below the extrusion temperature and the decrease in melting enthalpy by interaction with CA MH promoted in-situ melting of the drug during processing. The high shear forces that were exerted by the rotating screw facilitated the dispersion of the melted API in the softened polymer matrix. The high degree of dispersibility and the amorphous character of DIL HCl were maintained in the final product due to rapid cooling after extrusion. The high degree of dispersion and the amorphous state of the drug accounted for the high dissolution rates that were observed for tablets containing CA MH.

A comparison of the extrudates prepared with either fine or coarse drug particles demonstrated a lower drug crystallinity in tablets prepared with fine DIL HCl. Formulation DIL75/RS-20 was completely amorphous, while DIL200/RS-20 exhibited small peaks at 10.7, 15.4 and 27.7 (2-Theta). Due to the short residence time of the powder material in the heated barrel, complete drug melting was more likely to occur if small particle sizes were used, whereas the melting of larger DIL HCl particles was incomplete. Surprisingly, the higher degree of crystallinity in extrudates manufactured with coarse API was correlated with faster drug dissolution. The employment of small particle size material for melt extrusion promoted the formation of a denser matrix with higher true density and tortuosity, but decreased porosity. Helium pycnometry showed the higher true density of matrices extruded with fine DIL HCl compared to their coarse DIL HCl equivalents, but the difference was only statistically significant for the formulations comprising DIL HCl and CA MH at a ratio of 2:1 (data not shown). Crowley and coworkers observed a decrease in drug release rate due to reduced porosity and increased tortuosity when small ethyl cellulose particles were used as the carrier material for hot-melt extrusion [26]. It can be concluded that differences in true density and porosity of extruded tablets with DIL HCl of different particle size compensated for the effects attributed to API crystallinity and surface area.

4.4.7 Dissolution of DIL HCl from extruded matrix tablets containing constant polymer levels

Tablets containing either varying DIL HCl to CA MH ratios (formulations 1 – 4) or an alternative soluble excipient (sucrose, NaCl or PEG 3350, formulations 5 – 7) were prepared, and their drug release properties were analyzed. Dissolution experiments were carried out in phosphate buffer pH 6.0 with 250 mg tablets over 12 hours. The polymer level was maintained constant for all formulations (60% of the total powder weight), as was the total soluble fraction (TSF = 40%), consisting of DIL HCl and either CA MH or a different soluble excipient. The release profiles in Fig. 4.9 demonstrated that a partial replacement of DIL HCl by CA MH resulted in an accelerated drug release rate. Formulation RS60-40/0 (TSF consisting of drug only) released 54.54% DIL HCl during the 12-hour experiment, whereas tablets containing CA MH yielded 76.50% (RS60-10/30), 83.09% (RS60-20/20) and 83.38% (RS60-30/10) after 12 hours. The difference in the amount of API released between the three tablet formulations containing drug and CA MH in varying ratios was small with f2 similarity factors of 77 (RS60-20/20 versus RS60-30/10), 70 (RS60-30/10 versus RS60-10/30) and 60 (RS60-20/20 versus RS60-10/30), respectively. According to Shah and coworkers [19], release profiles with a f2 similarity factor higher than 50 can be regarded as similar since the average variation at each sampling time point is less than 10% (less than 5% for $f2 \geq 65$).

Reviewing the scientific literature, the effect of citric acid on the drug release rate from sustained release matrix systems is mainly attributed to two properties: For weakly basic drugs with pH dependent solubility, the enhanced drug release has been attributed to the acidic character of citric acid. In buffered dissolution media, the acidity of citric acid is sufficient to maintain a low pH in the microenvironment of the API. Hence, a higher ratio of the API will be present in the more soluble ionized form, resulting in a

faster drug release. This phenomenon has been reported for the release of vinpocetine [30], trimethoprim [12] and dipyridamole [11] from HPMC matrices. An alternative mechanism explaining the higher drug dissolution from citric acid-containing systems is based on the high aqueous solubility of this compound (Table 4.2). Due to rapid dissolution of citric acid from the matrix, the porosity will increase, and drug diffusion through the water-filled porous network will be facilitated. This mechanism was reported to dominate the release of pelanserin hydrochloride from HPMC tablets [31]. Both mechanisms impose different requirements for the residence time of citric acid within the polymeric matrix. For the first effect, a delayed citric acid release is beneficial to prolong the acidic pH in the API environment, whereas the activity as a pore former requires a rather rapid citric acid release from the system. Drug solubility represents an additional factor that needs to be considered when evaluating the impact of both mechanisms. Only poorly soluble drugs will benefit from a solubility increase attributed to pH modification, while the effect will be negligible for compounds with high aqueous solubility over the entire physiologic pH range.

An increase in DIL HCl release induced by microenvironmental acidification due to CA addition can be excluded for three reasons: First, although the solubility of DIL HCl decreases with increasing pH values, it is still sufficiently soluble to maintain sink conditions during dissolution studies at pH 6.0. Second, Fig. 4.9 provides evidence that the release of DIL HCl was not influenced by the pH of the dissolution medium. Formulation RS60-40/0 exhibited highly similar dissolution curves in two different media, phosphate buffer pH 6.0 and simulated gastric fluid pH 1.2 (without pepsin, USP 29) with a f2 similarity factor of 90, corresponding to 1.43% average variation. Third, the release of CA MH from RS60-20/20 tablets was relatively rapid (Fig. 4.10), with 56.92% being released after 3 hours in phosphate buffer pH 6.0 (HPLC assay described in [18]).

These results suggest that the retention time of CA MH inside the matrix was too short to provide an acidic microenvironmental pH during dissolution.

To further investigate the capability of CA MH to act as a pore forming agent and to evaluate the contribution of this effect to the increased DIL HCl release rate, three additional formulations (no. 5-7) containing 20% drug and alternative pore formers at a 20% level were extruded. The TSF was held constant at 40% to eliminate modifications in drug release due to differences in Eudragit® RS PO level. All studied excipients showed high aqueous solubility, but differences in melting properties and plasticization effect on the polymer (Table 4.2). Sucrose was selected due to its high solubility and its similarities to citric acid concerning chemical structure and melting point. Sodium chloride is a salt with a very high melting point, making in-situ melting impossible. A medium molecular weight polyethylene glycol (PEG 3350) was chosen due to its plasticizing effect on Eudragit® RS PO similar to CA MH.

Fig. 4.11 demonstrates that formulations containing the alternative pore formers sucrose, PEG 3350 or NaCl yielded a slower drug release than RS60-40/0 tablets. Their ability to improve drug diffusion by pore formation did not exceed the pore forming capacity of the API itself at the same TSF. In contrast, tablets comprising CA MH (RS60-20/20) exhibited a significantly faster drug release than the formulation with drug only or additional alternative pore formers. The high aqueous solubility and rapid dissolution of CA MH during dissolution suggests a contribution of pore formation to the increased release rate. However, this property alone did not entirely account for the fast DIL HCL release that was observed for CA MH containing extrudates, since alternative pore formers failed to provide the same effect.

4.4.8 Morphology of extruded matrix tablets containing constant polymer levels

From the results of the dissolution experiments with alternative pore formers, it was assumed that the faster DIL HCl release from tablets with drug being partially replaced by CA MH could not only be explained by increased matrix porosities. Therefore, the influence of CA MH on the matrix morphology and on the solid state of the drug was investigated.

The morphology of cut tablets before and after 12 hours dissolution in phosphate buffer pH 6.0 was visualized with scanning electron microscopy (Fig. 4.12). The ratio of polymer to soluble fraction was 60:40 for the investigated formulations (nos. 1, 3 and 6). The SEM pictures of the tablets containing either 40% drug (RS60-40/0) or 20% drug with 20% NaCl (RS60-20/20N) yielded strong morphological similarities. Before dissolution, the surfaces were uneven and exhibited numerous large pores with diameters of 10-40 µm, both properties attributed to a lack of plasticization of the brittle polymer by the included additives. Following dissolution testing, the matrices were highly porous with rough surface structures due to the dissolution of drug and NaCl particles exposed to the release medium and the percolation of these soluble components through the inert matrix. Tablets containing CA MH as the soluble additive (RS60-20/20) yielded relatively even surfaces of high integrity and without pores before the dissolution experiment. This can be explained by the ability of the organic acid to plasticize the acrylic polymer during the extrusion process, promoting the formation of an intact matrix of higher apparent density. The exposure of the tablets to the dissolution medium over 12 hours resulted in the generation of cracks and few large pores, while the bulk of the surface remained relatively intact as opposed to the other two formulations. Large magnifications of 30,000x or higher indicated the existence of pores that were smaller

than 300 nm and were due to the leaching of soluble, fine dispersed compounds from the dosage form.

It can be concluded that the drug release from CA MH containing extrudates occurred through different mechanisms than from matrices with high drug loading or pore forming excipients. The DIL HCl release from formulations with 40% drug or alternative pore formers occurred primarily by diffusion through a network of pores in the micrometer range, which was generated by the leaching of soluble components. The pore formation was restricted to the exterior layers of the matrix, since the dissolution period was insufficient to allow water penetration though the whole tablet. This aspect was responsible for the incomplete drug release after 12 hours (27.88 – 54.54% depending on the additive) as demonstrated for these composites. Based on the findings from the binding study, DIL HCl adsorption to the polymer matrix during dissolution could be excluded as the explanation for the incomplete release.

Tablets with CA MH as a release modifying excipient exhibited a faster and more complete release of DIL HCl (83.09% after 12 hours). Two different mechanisms could account for this observation. The high miscibility between CA MH and DIL HCl and the decreased polymer melt viscosity due to plasticization promoted the melting and fine dispersion of the soluble compounds within the polymer during extrusion. Leaching of the highly dispersed API and CA MH from the matrix during dissolution testing may create an extensive and coherent pore network. The volume fraction of matrix material that is accessible for the dissolution medium was increased, resulting in a faster and more complete drug release. This process was less efficient for tablets containing alternative pore formers since their lack of miscibility with the API and the polymer impeded the melting and fine dispersion of the soluble material.

A second approach considers the modification of the polymer permeability by CA MH. The molecular dispersion of the organic acid between the polymeric chains resulted in an alteration of the polymer's properties in terms of processibility and aqueous permeability. Due to its hygroscopic nature [32] and high aqueous solubility, CA MH promoted the water penetration into the matrix by increasing the permeability of the polymer. Furthermore, when exposed to dissolution medium, chloride ions at the quaternary ammonium groups of Eudragit® RS PO can be exchanged by citrate counter ions. Wagner and coworkers [33] demonstrated that anions of mono- and diprotic acids present in the dissolution medium displayed a permeability enhancing effect after ion exchange. This was attributed to the larger hydration shell of these anions when compared to chloride, promoting water uptake and polymer swelling. The magnitude of permeability enhancement was dependent on the extent of ion exchange, anion valence and concentration, and on the properties of the hydration shell. Citric acid dissociates in water as a function of the pH into mono-, di- and trivalent ions that are capable of electrostatic interaction with the quaternary ammonium groups, resulting in an enhanced hydration and water permeability of the polymer.

4.4.9 Drug crystallinity in extruded matrix tablets containing constant polymer levels

Powder X-ray diffraction analysis was carried out with extrudate powders (formulations 3, 5 – 7) to assess the physical states of DIL HCl and of the soluble excipients in the Eudragit® RS PO matrices. The PXRD patterns obtained for the extruded materials were compared to the physical mixtures and the pure crystalline materials (Fig. 4.13). Patterns of crystalline DIL HCl exhibited numerous peaks in the 2-Theta range, and six characteristic peaks (10.7, 15.4, 18.2, 19.5, 20.7, 27.7) were selected

for the evaluation of the extrudate properties. The majority of these DIL HCl peaks could be identified in the extrudates comprising either sucrose (10.7, 15.4, 18.2, 27.7), NaCl (10.7, 15.4, 18.2, 19.5, 20.7, 27.7) or PEG 3350 (10.7, 15.4, 20.7, 27.7), while extruded material containing CA MH as the release modifying excipient was completely amorphous. Neither the drug nor CA MH itself was in the crystalline state, whereas the crystallinity of the other three excipients was evident from the presence of their characteristic peaks. The crystalline nature of sucrose and NaCl in the extrudates was expected since both compounds did not melt at extrusion temperatures, whereas PEG 3350 recrystallized after in-situ melting. The amorphous character of DIL HCl was a result of an enhanced miscibility with the polymer. Strong interactions between DIL HCl and CA MH promoted drug melting during extrusion and the stabilization of the amorphous state. Plasticization of the polymer by CA MH further encouraged the mixing process and improved the dispersion of DIL HCl and CA MH inside the Eudragit® RS PO matrix due to the reduced melt viscosity during extrusion.

4.5 CONCLUSION

The present study demonstrated the suitability of citric acid monohydrate (CA MH) to promote the release of a soluble model drug from hot-melt extruded Eudragit® RS PO matrices. Extrudates with drug only were crystalline due to the insolubility of DIL HCl in Eudragit® RS PO and yielded a slow and incomplete drug release attributed to the low porosity of the matrix. CA MH promoted the thermal processibility and matrix integrity by plasticization of the polymer. The addition of CA MH to formulations with constant drug-to-polymer ratios significantly increased the rate and extent of drug release as a more coherent porous network was formed during dissolution. Drug particle size effects on the dissolution rate were eliminated when large amounts of CA were added due

to complete drug melting and loss of drug crystallinity as a result of strong DIL HCl – CA MH interactions during extrusion. At constant polymer levels, the partial replacement of drug by alternative pore forming agents exhibiting high water solubility (sucrose, NaCl, PEG 3350) led to decreased drug release rates compared to formulations with only API, while CA MH greatly enhanced drug dissolution. We concluded that the mechanisms of the CA MH induced modification in drug release are complex and exceed pure pore formation. A promotion of the API dispersion in the polymer melt during extrusion, alterations in the solid state of the drug from crystalline to amorphous as well as a modification of the polymeric matrix were discussed as possible mechanisms of action.

In summary, the addition of CA MH as a release modifier and processing aid to an insoluble drug-polymer system enabled the extrusion of an amorphous matrix system exhibiting enhanced dissolution properties.

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4.7 TABLES

Table 4.1: Composition of tablets prepared by hot-melt extrusion.

Category	No	Experiments	Formulation Label	DIL HCl		CA MH	Eudragit® RS PO
				Amount [g]	Particle Size [µm]	Amount [g]	Amount [g]
Constant Polymer (60%)	1	Processibility	RS60-40/0	40	75 – 150	0	60
	2	Helium	RS60-30/10	30	75 – 150	10	60
	3	Pycnometry	RS60-20/20	20	75 – 150	20	60
	4	Dissolution	RS60-10/30	10	75 – 150	30	60
	5	Testing	RS60-20/20S	20	75 – 150	20 Sucrose	60
	6	SEM	RS60-20/20N	20	75 – 150	20 NaCl	60
	7	PXRD	RS60-20/20P	20	75 – 150	20 PEG	60
Constant API to Polymer Ratio (1:4)	8	Dissolution	DIL75/RS-0	20	< 75	0	80
	9	Testing	DIL200/RS-0	20	150 – 250	0	80
	10	PXRD	DIL75/RS-10	20	< 75	10	80
	11		DIL200/RS-10	20	150 – 250	10	80
	12		DIL75/RS-20	20	< 75	20	80
	13		DIL200/RS-20	20	150 – 250	20	80
	14		DIL75/RS-30	20	< 75	30	80
	15		DIL200/RS-30	20	150 – 250	30	80

Table 4.2: Physical properties of water-soluble excipients that were selected as release-modifying additives for the hot-melt extrusion of diltiazem hydrochloride / Eudragit® RS PO matrices.

Excipient	Water Solubility (at 20°C) [%]	Melting Point [°C]	In Situ Melting	Plasticization of the Polymer
Citric Acid Monohydrate	59	135	yes	yes
Sucrose	200	160	no	no
Sodium Chloride	36	804	no	no
PEG 3350	67	54-58	yes	yes

4.8 FIGURES

Figure 4.1: Thermal gravimetric analysis of (a) citric acid monohydrate, (b) anhydrous citric acid, (c) diltiazem hydrochloride, and (d) Eudragit® RS PO.

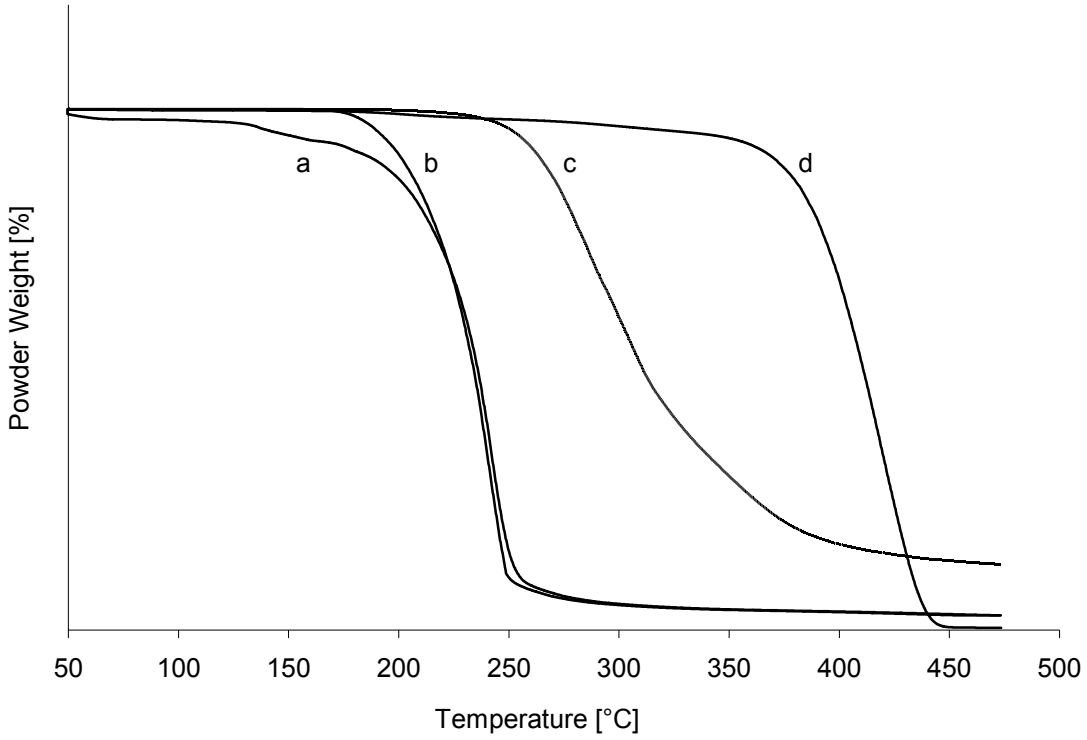


Figure 4.2: Binding of diltiazem hydrochloride to Eudragit® RS PO as a function of the drug-to-polymer ratio (n = 3, error bars represent the standard deviation).

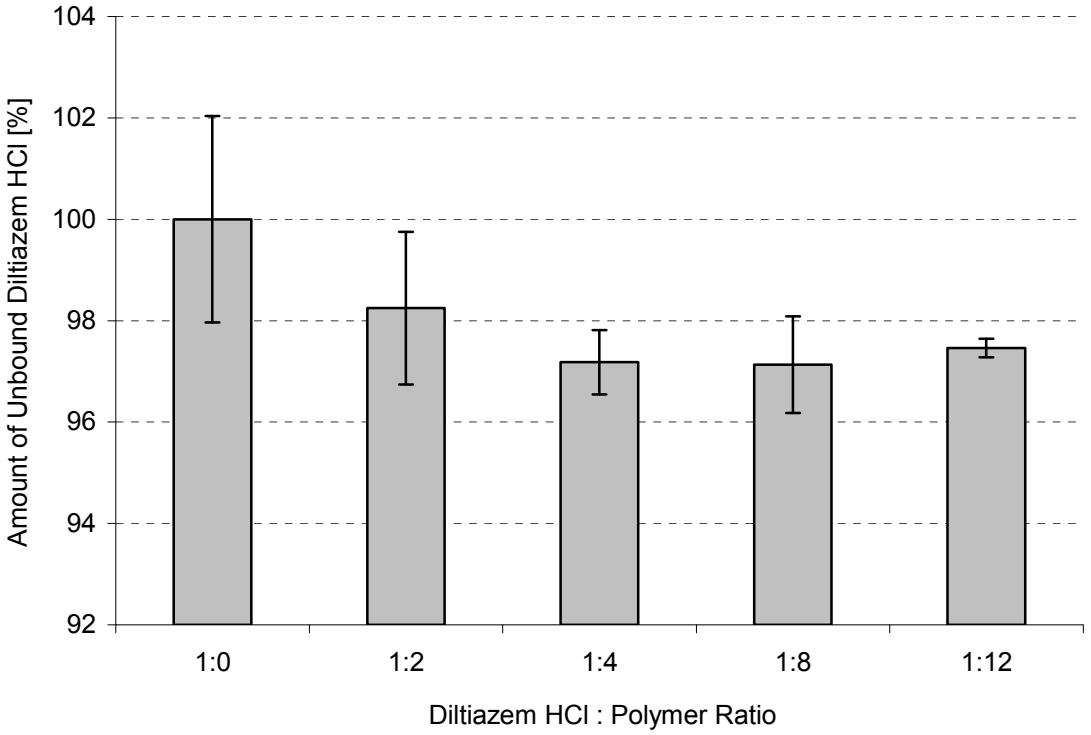


Figure 4.3: Powder X-ray diffraction patterns of physical mixtures (PMs) and hot-melt extrudates (HMEs) containing 5-20% diltiazem hydrochloride (DIL HCl) in Eudragit® RS PO. (a) HME with 20% DIL HCl, (b) PM with 20% DIL HCl, (c) HME with 10% DIL HCl, (d) PM with 10% DIL HCl, (e) HME with 5% DIL HCl, (f) PM with 5% DIL HCl.

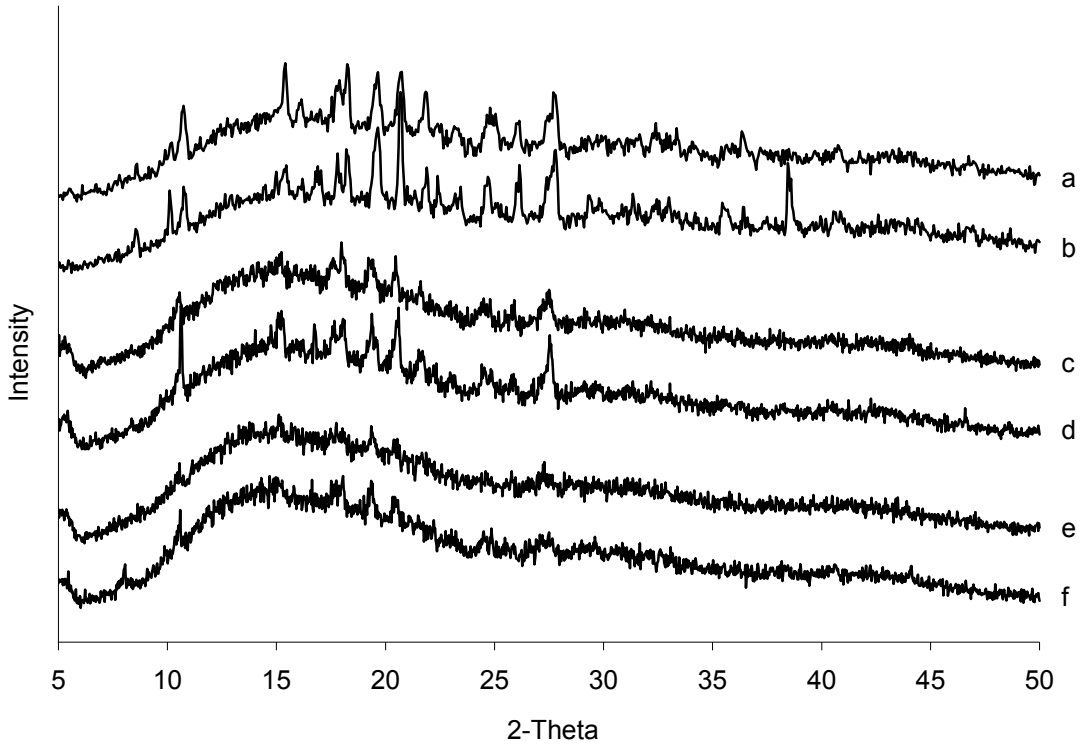


Figure 4.4: Differential scanning calorimetry profiles of diltiazem hydrochloride (DIL HCl) and anhydrous citric acid (CA) and physical mixtures thereof. (a) DIL HCl/ CA 7:1, (b) DIL HCl/ CA 3:1, (c) DIL HCl/ CA 1:1, (d) DIL HCl/ CA 1:3, (e) DIL HCl/ CA 1:7, (f) pure DIL HCl, and (g) pure anhydrous CA.

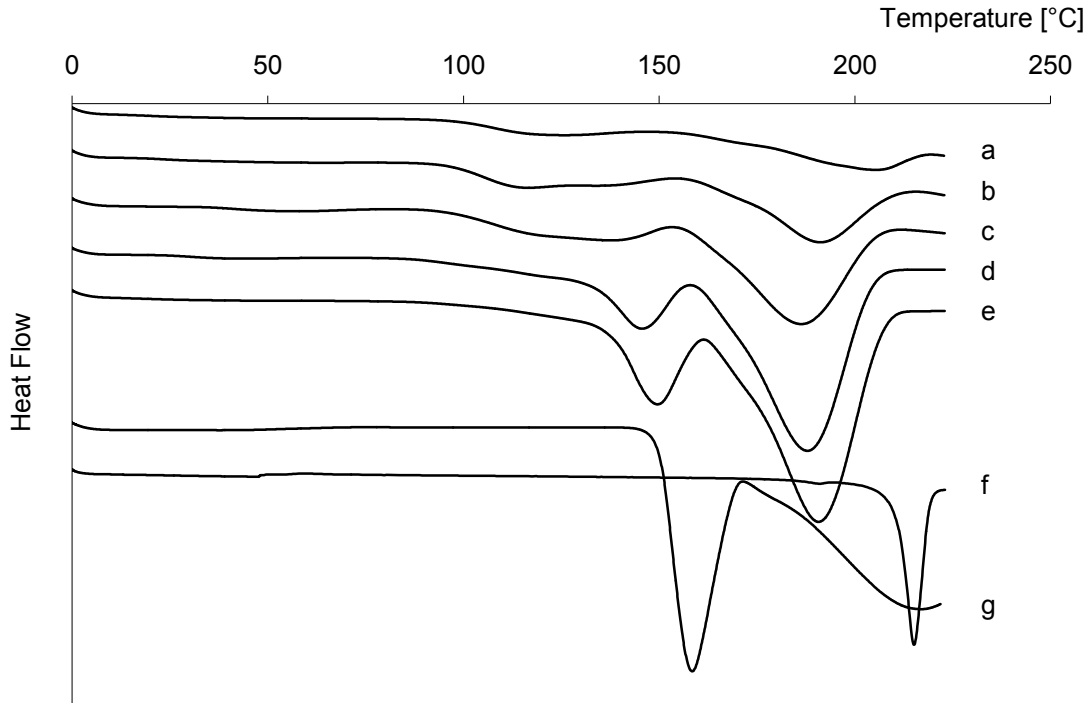


Figure 4.5: Influence of the diltiazem hydrochloride (DIL HCl) to citric acid monohydrate (CA MH) ratio on the screw speed applied for the melt extrusion of Eudragit® RS PO (constant level of 60%) as a function of temperature.
(×) Pure Eudragit® RS PO. Eudragit® RS PO with (◆) 40% DIL HCl, (■) 30% DIL HCl and 10% CA MH, (▲) 20% DIL HCl and 20% CA MH, (◇) 10% DIL HCl and 30% CA MH. (n = 3, error bars represent the standard deviation) The values in parentheses represent the motor load (drive amperage multiplied by 100) measured during extrusion at the target screw speed of 20 rpm.

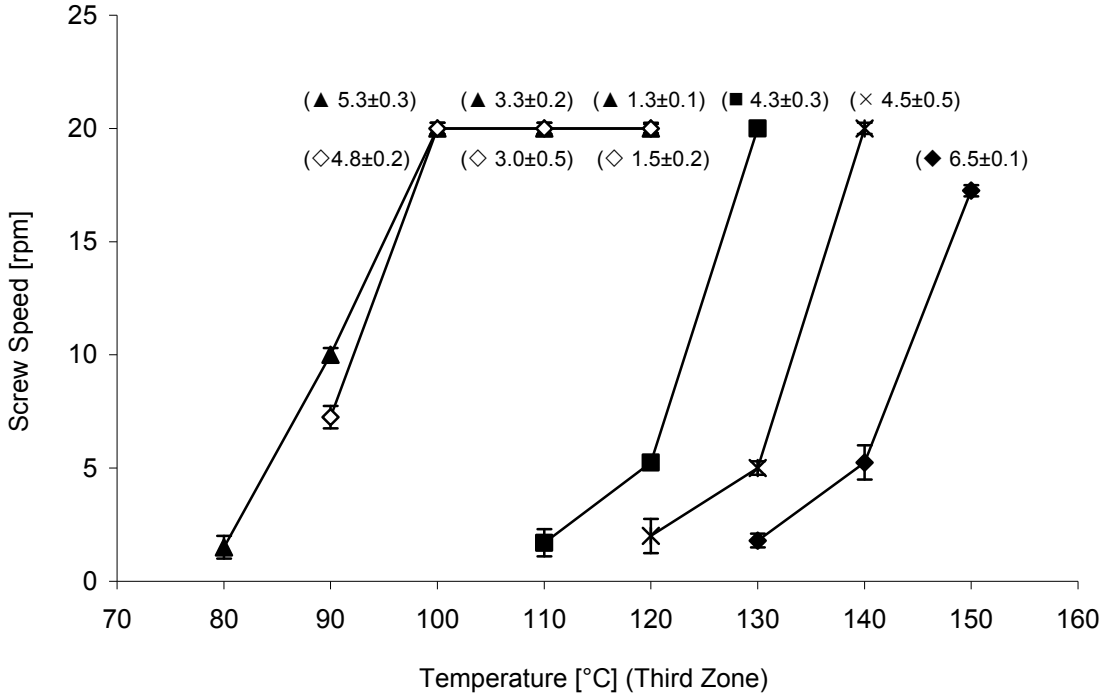


Figure 4.6: Influence of the diltiazem hydrochloride (DIL HCl) to citric acid monohydrate (CA MH) ratio on the true density of hot-melt extrudates containing Eudragit® RS PO at a 60% level. (n = 6, error bars represent the standard deviation).

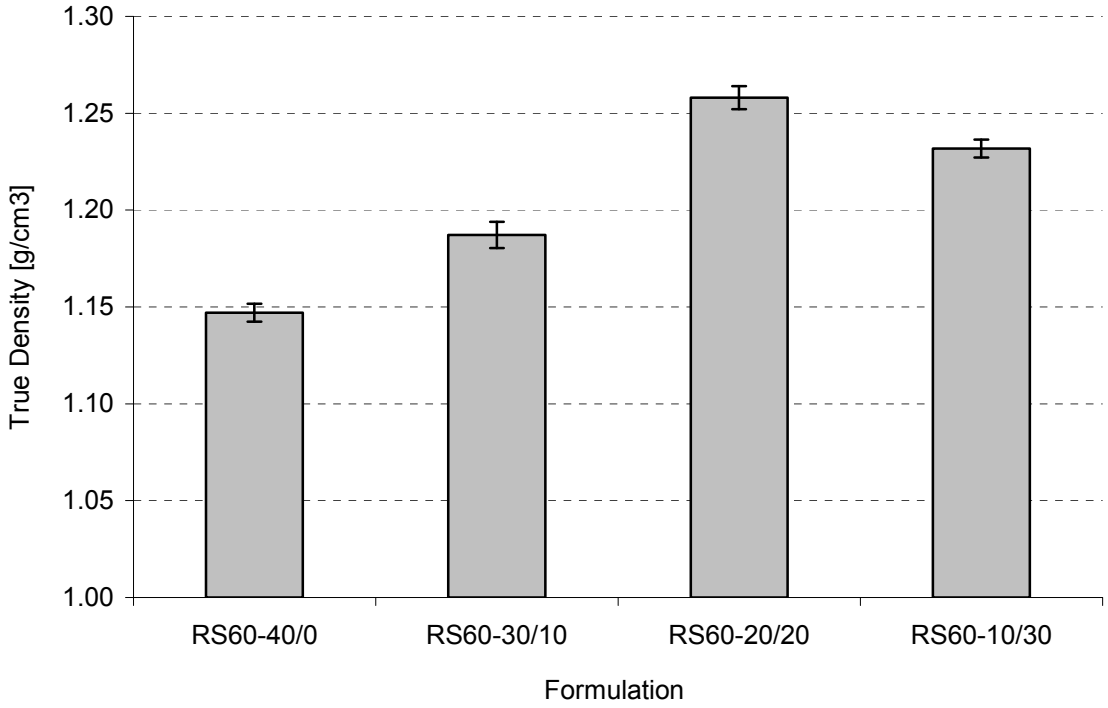


Figure 4.7: Influence of the diltiazem hydrochloride (DIL HCl) particle size in the extrusion blend and the addition of citric acid monohydrate (CA MH) on the drug release from extruded Eudragit® RS PO matrix tablets with constant DIL HCl to polymer ratio (1:4). (△) Small DIL HCl particle size (< 75 µm), and (■) large DIL HCl particle size (150-250 µm). (A) DIL HCl and no CA MH, (B) DIL HCl / CA MH 2:1, (C) DIL HCl / CA MH 1:1, and (D) DIL HCl / CA MH 2:3.
Dissolution: USP paddle method, 900 ml phosphate buffer pH 6.0 as dissolution medium, 37°C, 50 rpm, n = 6.

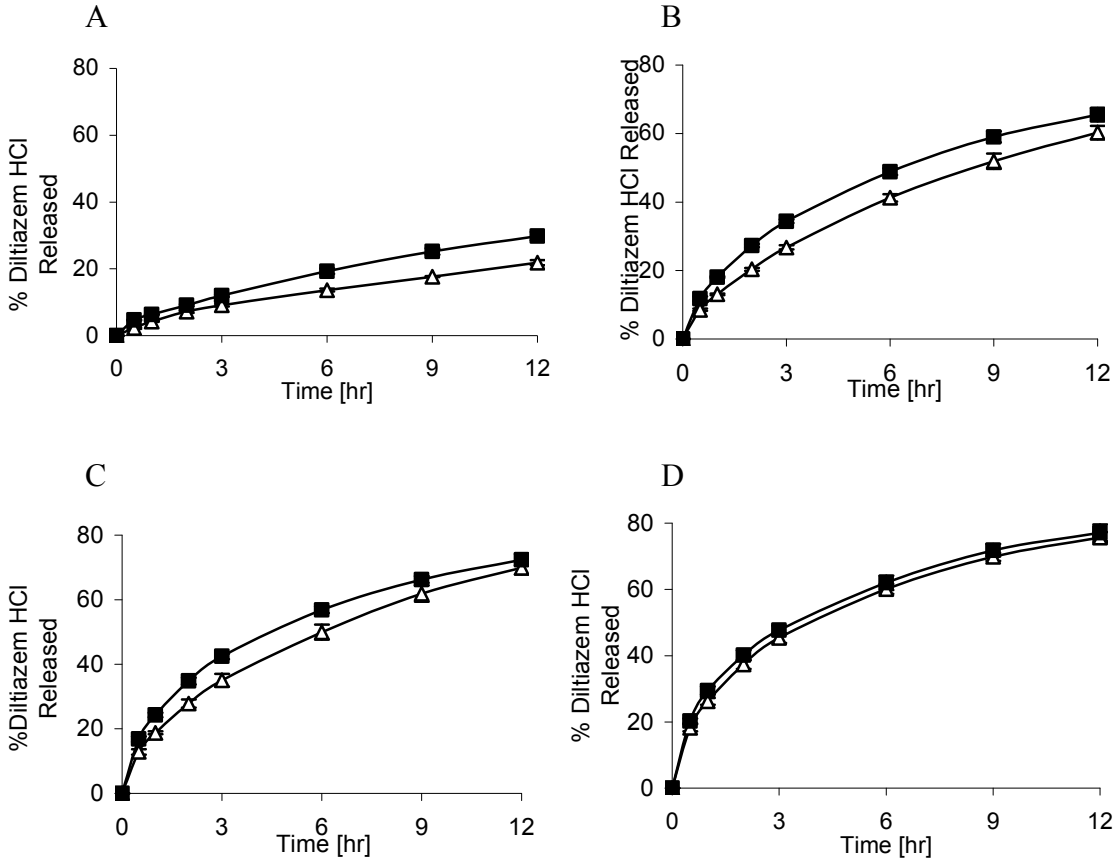


Figure 4.8: Influence of citric acid monohydrate (CA MH) concentration and diltiazem hydrochloride (DIL HCl) particle size on the crystallinity of hot-melt extrudates. PXRD patterns of extrudates with constant DIL HCl to Eudragit® RS PO ratio (1:4) and (a) DIL HCl (< 75 µm) / CA MH 2:3, (b) DIL HCl (150-250 µm) / CA MH 2:3, (c) DIL HCl (< 75 µm) / CA MH 1:1, (d) DIL HCl (150-250 µm) / CA MH 1:1, (e) DIL HCl (< 75 µm) / CA MH 2:1, (f) DIL HCl (150-250 µm) / CA MH 2:1, (g) DIL HCl (< 75 µm) and no CA MH, (h) DIL HCl (150-250 µm) and no CA MH.

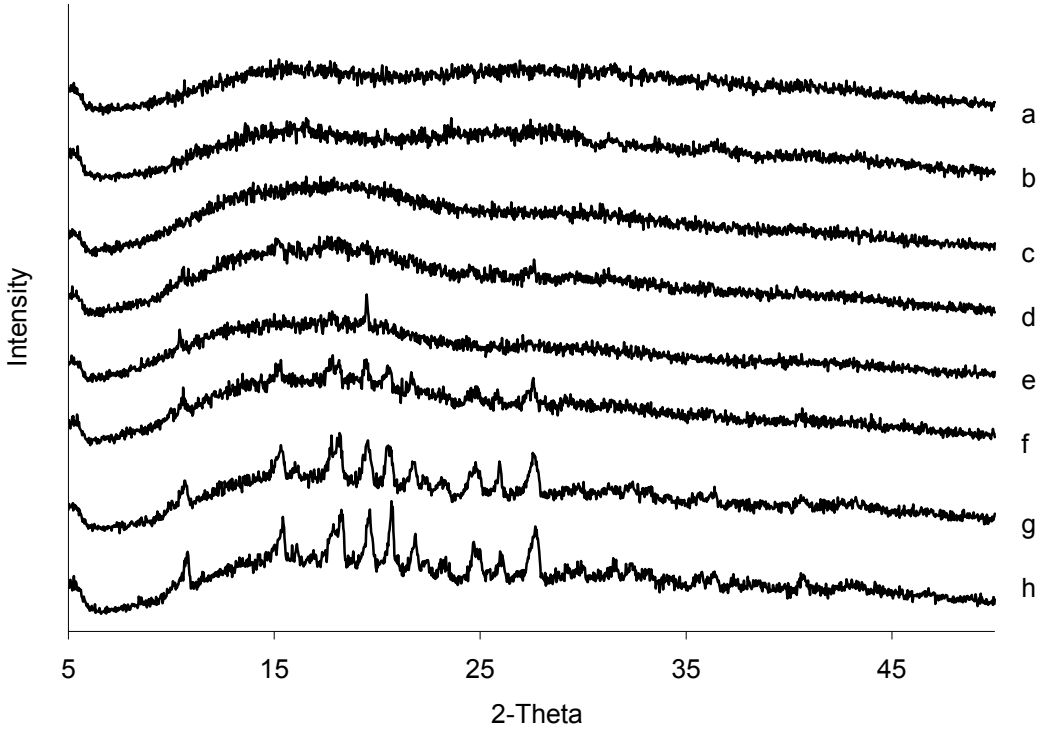


Figure 4.9: Influence of the diltiazem hydrochloride (DIL HCl) to citric acid monohydrate (CA MH) ratio and the pH of the dissolution medium on the drug release from extruded Eudragit® RS PO matrix tablets containing 60% polymer. (+) 10% DIL HCl and 30% CA MH, release in phosphate buffer pH 6.0, (◆) 20% DIL HCl and 20% CA MH, release in phosphate buffer pH 6.0, (△) 30% DIL HCl and 10% CA MH, release in phosphate buffer pH 6.0, (◇) 40% DIL HCl and no CA MH, release in phosphate buffer pH 6.0, (▲) 40% DIL HCl and no CA MH, release in simulated gastric fluid pH 1.2. Dissolution: USP paddle method, 900 ml dissolution medium, 37°C, 50 rpm, n = 6.

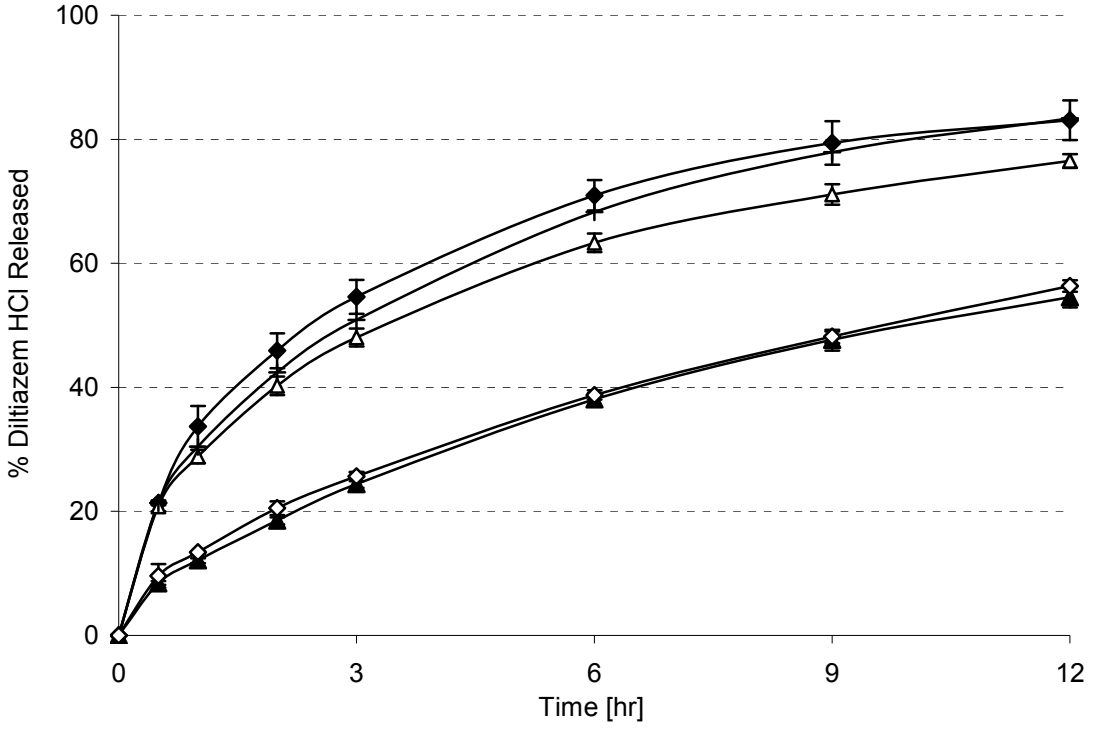


Figure 4.10: Release of citric acid monohydrate (CA MH) from extruded Eudragit® RS PO matrix tablets containing 60% polymer, 20% diltiazem hydrochloride and 20% CA MH.
Dissolution: USP paddle method, 900 ml phosphate buffer pH 6.0 as dissolution medium, 37°C, 50 rpm, n = 6.

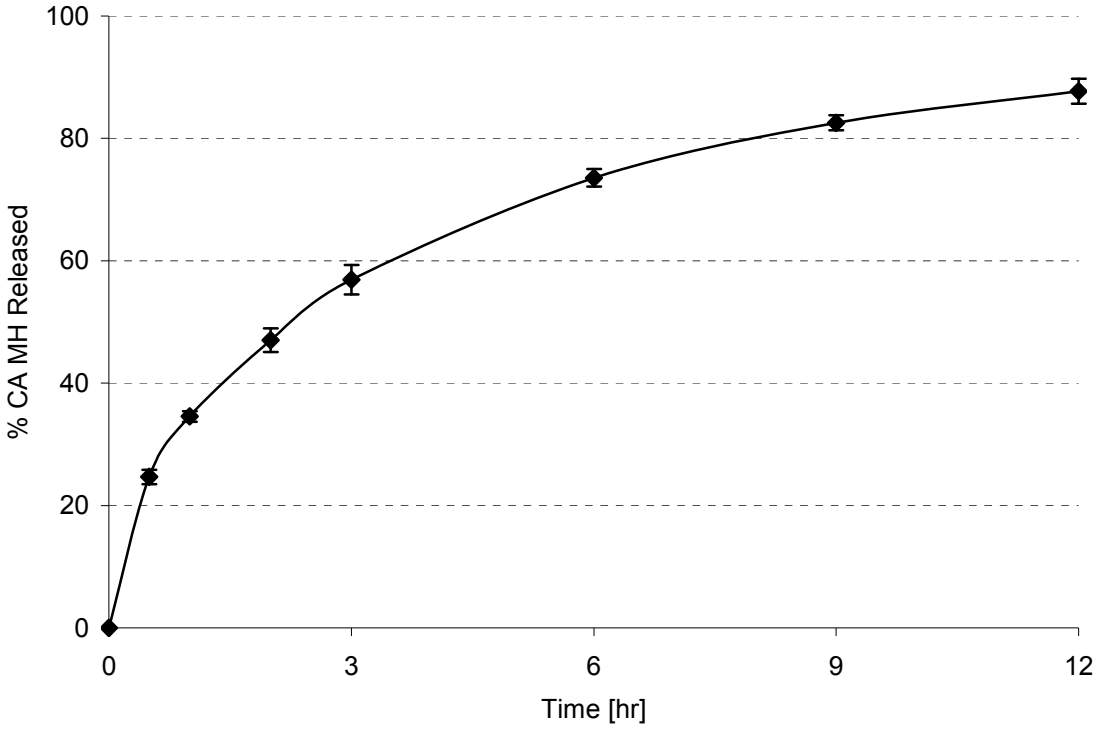


Figure 4.11: Effect of pore forming excipients on the diltiazem hydrochloride (DIL HCl) release from extruded Eudragit® RS PO matrix tablets containing 60% polymer, 20% DIL HCl and 20% of (◆) citric acid monohydrate, (▲) sucrose, (◇) PEG 3350, and (△) NaCl. (+) Extrudate with 40% DIL HCl and no pore forming excipient.
Dissolution: USP paddle method, 900 ml phosphate buffer pH 6.0 as dissolution medium, 37°C, 50 rpm, n = 6.

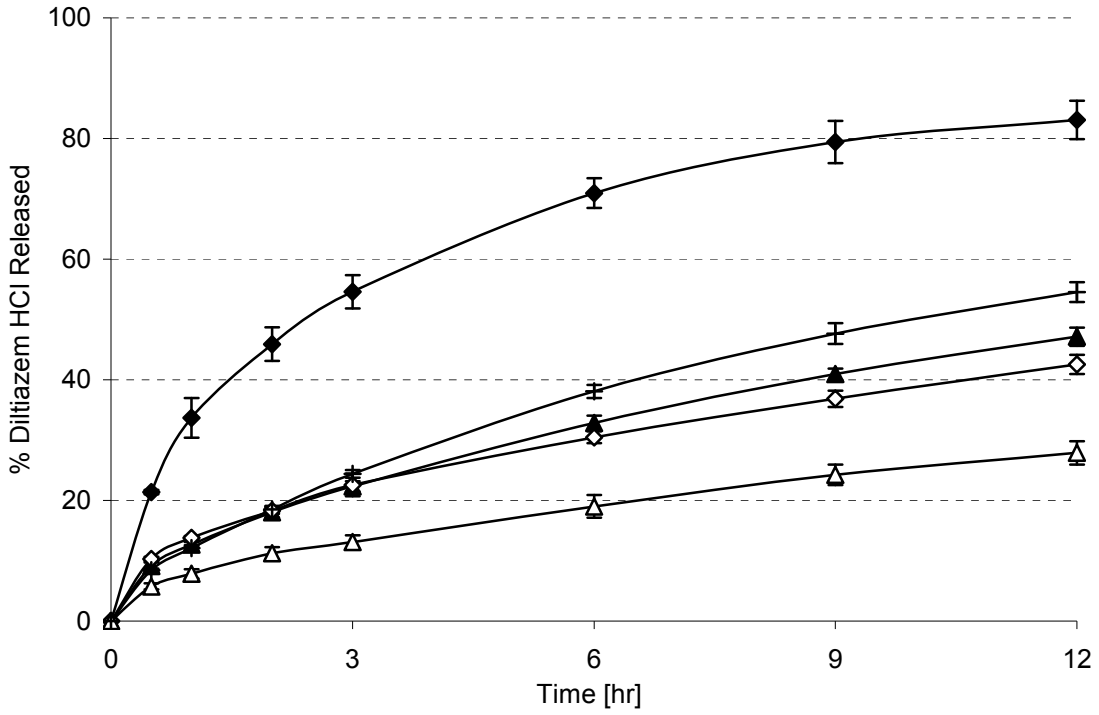


Figure 4.12: SEM of hot-melt extruded tablets composed of 60% Eudragit® RS PO, and (A) 40% diltiazem hydrochloride (DIL HCl), (B) 20% DIL HCl and 20% citric acid monohydrate, and (C) 20% DIL HCl and 20% NaCl. Pictures were taken before (X-1) and after (X-2) dissolution in phosphate buffer pH 6.0 over 12 hours.

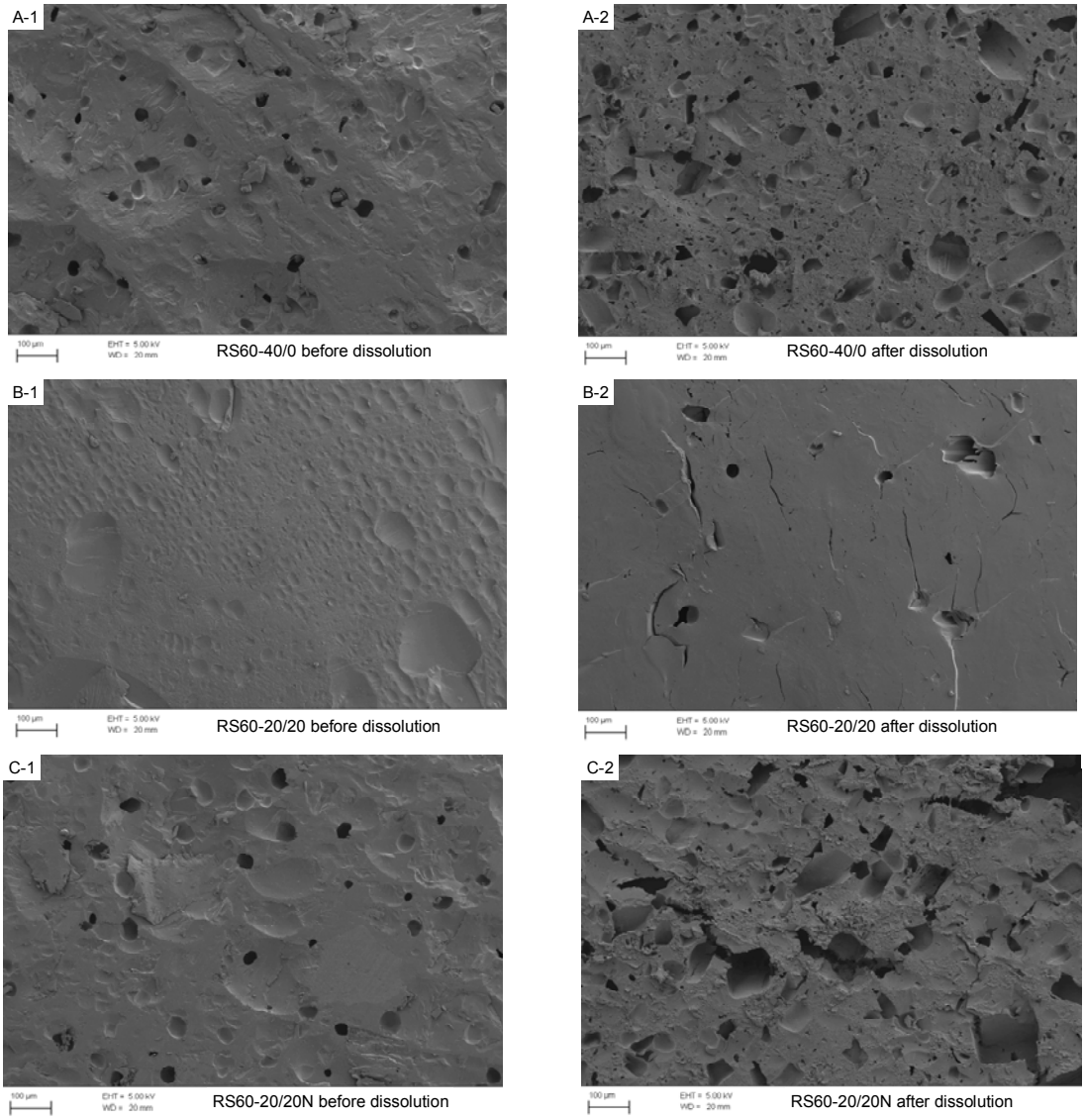
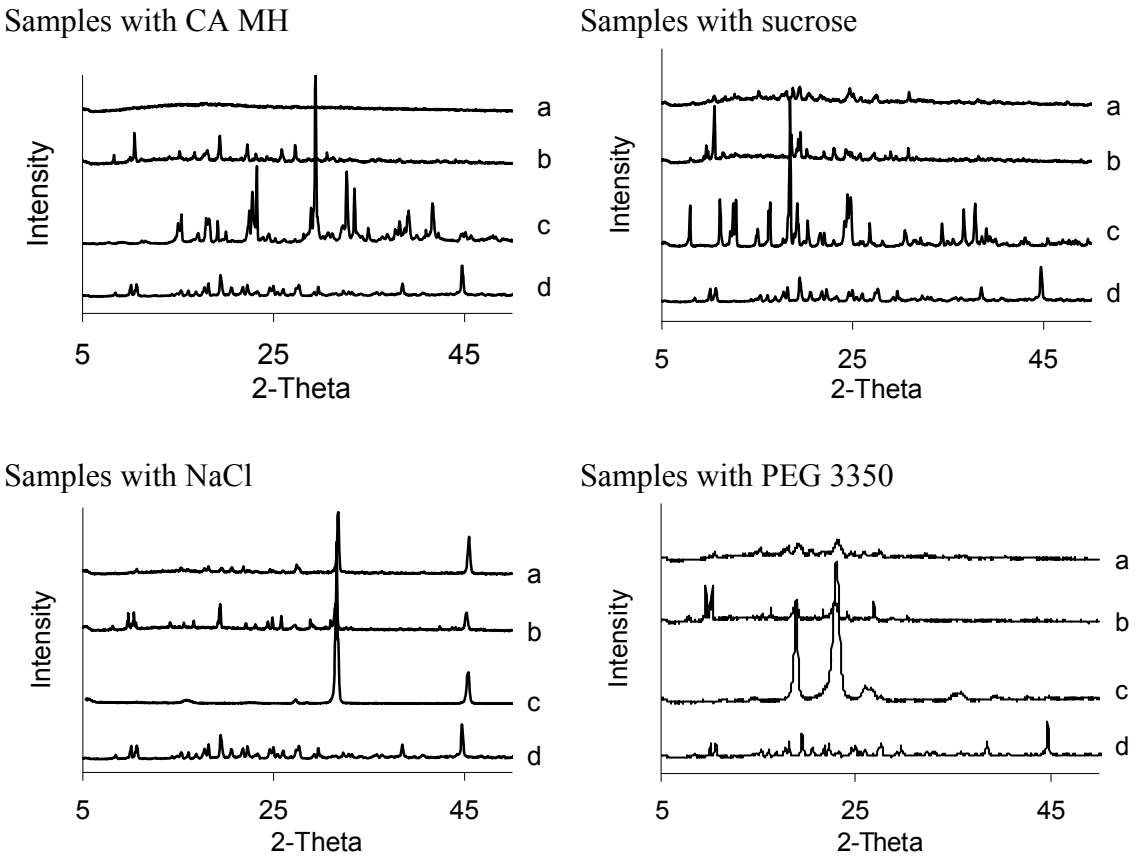


Figure 4.13: Effect of pore forming excipients on crystallinity of diltiazem hydrochloride (DIL HCl) in extruded Eudragit® RS PO matrix tablets containing 60% polymer, 20% DIL HCl and 20% of either citric acid monohydrate (CA MH), sucrose, sodium chloride (NaCl) or PEG 3350. PXRD patterns of (a) hot-melt extrudates, (b) physical mixtures, (c) pore forming excipient, (d) DIL HCl.



Chapter 5: Investigation of the Influence of Formulation Factors on the Properties of Enteric Hot-Melt Extruded Matrix Pellets[3]

Abstract:

The objective of this study was to investigate the properties of enteric matrix pellets that were prepared by hot-melt extrusion in a one-step, continuous process.

Five polymers (Eudragit® L100-55, L100 and S100, Aqoat® grades LF and HF) were investigated as matrix formers, and pellets prepared with Eudragit® S100 demonstrated superior gastric protection and acceptable processibility. Extruded pellets containing Eudragit® S100 and up to 40% theophylline released less than 10% drug over 2 hours in acid, however, the processibility and yields were compromised by the high amounts of the non-melting drug material in the formulation. Efficient plasticization of Eudragit® S100 was necessary to reduce the polymer's glass transition temperature and melt viscosity. Five compounds including triethyl citrate, methylparaben, polyethylene glycol 8000, citric acid monohydrate and acetyltributyl citrate, were investigated in terms of plasticization efficiency and preservation of the delayed drug release properties. The aqueous solubility of the plasticizer and its plasticization efficiency impacted the drug release rate from the matrix pellets. The use of water-soluble plasticizers resulted in a loss of gastric protection, whereas low drug release rates in acid were found for pellets containing insoluble plasticizers or no plasticizer, independent of the extent of Eudragit® S100 plasticization. The release rate of theophylline in buffer pH 7.4 was faster for pellets that were prepared with efficient plasticizers. The microstructure and solid-state

[3] Significant portions of this chapter were taken from: Schilling, S.U., Shah, N.H., Malick, A.W., and McGinity, J.W. Properties of melt extruded enteric matrix pellets. European Journal of Pharmaceutics and Biopharmaceutics, in press October 2009.

properties of plasticized pellets were further investigated by scanning electron microscopy and powder X-ray diffraction. Pellets prepared with efficient plasticizers (TEC, methylparaben, PEG 8000) exhibited matrices of low porosity, and the drug was homogeneously dispersed in its original polymorphic form. Pellets containing ATBC or citric acid monohydrate had to be extruded at elevated temperature and showed physical instabilities in the form of recrystallization at room temperature. Enteric matrix pellets with a diameter below one mm and containing 30% theophylline could be successfully prepared by hot-melt extrusion when Eudragit® S100 plasticized with either TEC or methylparaben was employed as the matrix material.

5.1 INTRODUCTION

Multiparticulate oral dosage forms offer several advantages over monolithic systems. The pellets disperse rapidly and more uniformly along the gastro-intestinal tract, reducing food effects on drug absorption and avoiding high local drug concentrations. The bioavailability of certain drugs can be enhanced in terms of increased absorption and minimized inter- and intra-subject variability [1]. Enteric or sustained release pellets can either be of the matrix type where the drug is embedded in the release controlling matrix, or of the reservoir type. The drug containing core of reservoir-type pellets is traditionally produced by wet-mass extrusion/ spheronization or by layering of the drug onto nonpareils. A functional coating is then applied to the pellets in a subsequent step. Matrix systems may be produced by wet-mass extrusion and spheronization, melt granulation or hot-melt extrusion using release-controlling carriers.

Hot melt extrusion has emerged as a recognized pharmaceutical manufacturing technology for the preparation of a variety of dosage forms including implants, tablets,

pellets and films [2]. The process has been successfully adapted for the preparation of sustained release matrix tablets [3-6] and pellets [7-9]. More recently, the preparation of enteric matrix systems by hot-melt extrusion has been reported. Andrews and coworkers demonstrated that melt extruded tablets containing 5-aminosalicylic acid and Eudragit® L100-55 released less than 5% drug over 2 hours in acid [10]. Yang and coworkers prepared enteric matrix tablets releasing less than 3% drug by cutting as well as direct compression of comminuted extrudates when using Eudragit® L100 as the matrix former [11]. Melt extruded Eudragit® S100 tablets for the colonic delivery of 5-aminosalicylic acid also showed excellent gastric protection [12]. The authors demonstrated that hot-melt extruded matrices exhibited reduced drug diffusion rates in acid due to their low porosity when compared to directly compressed matrix tablets which failed to delay the drug release in acidic media. The drug release from melt extruded pellets based on Eudragit® 4135 F was demonstrated to be slow with around 20% drug released within 2 hours at pH 1.2, while more than 85% theophylline were released from the corresponding wet-mass extruded systems [13]. In addition to prolonged drug release properties, melt extruded pellets are more robust when directly compressed into multiparticulate monolithic systems due to their high mechanical strength and the circumstance that the release performance is independent of the intactness of a functional coat. From a processing point of view, hot-melt extrusion is a continuous process abstaining from the use of solvents and involving fewer steps than traditional extrusion and coating procedures.

However, the manufacture of enteric pellets exhibiting particle sizes below 1 mm and releasing less than 10% of their drug content over 2 hours in acid remains challenging. Pharmaceutically acceptable enteric polymers generally exhibit high melt viscosities and glass transition temperatures above 120°C. The limited thermal stability

of most polymers and drugs and the use of dies smaller than 1 mm in diameter make efficient plasticization of the polymeric carrier necessary to reduce the glass transition temperature and melt viscosity during extrusion. Soluble plasticizers, however, can function as pore formers and increase diffusion controlled drug release [14, 15] which is undesirable for delayed release dosage forms. Furthermore, the incorporation of high drug loads into microparticulate pellets is challenging as a large fraction of the drug is located near the particle surface and will be exposed to burst release during the acidic stage. Beads based on Eudragit® L100-55 that were extruded through a 1.2 mm die and contained 20% theophylline as the model drug released more than 25% drug in 2 hours at pH 1.2, compared to 10% drug released for tablets with a diameter of 6 mm [16]. In patent application WO 2008/101743, a water-insoluble carrier (Eudragit® RL, RS or NE) was used in combination with an anionic polymer to reduce the permeability of the enteric matrix pellets during the acidic stage [17].

The objective of the present study was to investigate the properties of hot-melt extruded matrix pellets with a particle size below 1 mm and the ability to delay the release of theophylline as a water-soluble model drug. The thermal processibility and drug release characteristics of matrix pellets prepared with cellulosic polymers (Aqoat® LF and HF) and acrylic polymers (Eudragit® L100-55, S100 and L100) were studied. The effect of drug loading ranging from 10 to 40% on the processibility and release properties of pellets based on Eudragit® S100 was investigated. The compatibility and plasticization efficiency of five plasticizers including TEC, ATBC, PEG 8000, methylparaben and citric acid monohydrate with Eudragit® S100 were evaluated. Matrix pellets consisting of 30% theophylline and plasticized Eudragit® S100 were prepared by hot-melt extrusion, and the influence of the plasticizer on the release properties, solid-state properties of the drug and matrix microstructure was investigated.

5.2 MATERIALS

Anhydrous theophylline was selected as the water-soluble model drug and was purchased from Spectrum Chemicals (Gardena, CA). Hydroxypropyl methylcellulose acetate succinate (HPMC AS, Aqoat®) was used in two grades (LF and HF) and kindly provided by Shin-Etsu (New York, NY). Methacrylic acid copolymers of three different grades (Eudragit® L100-55, L100, S100) were donated by Evonik, (Piscataway, NJ). The plasticizers used for the study included triethyl citrate (TEC) and acetyltributyl citrate (ATBC, both donated by Vertellus, Greensboro, NC), citric acid monohydrate (CA MH, Fisher Scientific, Fair Lawn, NJ), polyethylene glycol 8000 (PEG, Carbowax Sentry, powder NF, Dow Chemical Company, Midland, MI) and methylparaben (MP, Spectrum Chemicals, Gardena, CA).

5.3 METHODS

5.3.1 Preparation of melt extruded pellets

Powder blends for extrusion (10g) were prepared by pre-mixing the polymer with the plasticizer and subsequent blending with the drug using a kitchen aid mixer (St. Joseph, MI). A mini extruder equipped with two co-rotating screws and a circular 500µm die (Haake Minilab, Rheomax CTW5, Thermo Electron, Germany) was used for the extrusion of drug loaded, polymeric strands, which were manually cut to obtain cylindrical pellets. Formulations and processing parameters are listed in Tables 5.1-5.3. The diameters of the extruded strands were measured with a manual micrometer (Mituoyo model C1012EBS, Aurora, IL) prior to cutting.

5.3.2 Plasticization efficiency: thermal analysis of physical mixtures

Eudragit® S100 and 30% plasticizer (based on the polymer weight) were blended with a mortar and pestle and analyzed by modulated differential scanning calorimetry (MDSC) to investigate plasticization efficiency. An accurately weighed amount of powder was sealed in an aluminum pan and heated using a TA Instrument model 2920 (New Castle, DE). The material was equilibrated at 0°C for 5 minutes and then ramped to 180°C at 10°C/min with a modulation of 0.5°C every 40 seconds. After quench cooling to 0°C at a rate of 20°C/min, a second run was performed. The glass transition temperature was measured in the second cycle as the midpoint of the step transition in the plot of reverse heat flow versus temperature.

5.3.3 Dissolution studies and theophylline assay

Dissolution testing was carried out in a USP paddle apparatus (Varian, Cary, NC) according to the method described for delayed release articles USP chapter <724>, method A. Pellets (100 mg, n = 3) were placed in 750 ml simulated gastric fluid pH 1.2 (SGF, without pepsin). After 2 hours, the pH was increased to pH 6.8 (HPMC AS LF and Eudragit® L100) or to pH 7.4 (HPMC AS HF, Eudragit® S100) by adding 250 ml 0.2M tribasic phosphate buffer and adjusting with diluted sodium hydroxide solution to the desired pH. The medium temperature and paddle speed were maintained at 37.0±0.5°C and 50 rpm, respectively. The theophylline content in withdrawn samples was quantified using a HPLC system (Waters Inc., Milford, MA) equipped with a C_{18}-reversed phase column (Capcell PAK 3 mm * 100 mm, Shiseido Co, Japan) and a UV detector (996-PDA, Waters Inc. Milford, MA). The mobile phase consisted of 20 mM phosphate buffer pH 5 and acetonitrile (9:1), the injection volume was 10µl and the flow rate was constant

at 0.5 ml/ min. Theophylline was eluted after 3.5 min, and the peak areas captured at 271.5 nm were integrated using Empower Version 5.0 software (Waters Inc.). Linear correlation was confirmed between 0.1 and 100.0µg/ ml (R^2 = 0.99997), and multiple injections yielded good reproducibility with RSD values between 0.08% (100.0µg/ ml) and 1.77% (0.1µg/ ml).

5.3.4 Scanning electron microscopy (SEM)

Cut pellets were mounted on carbon tape and coated with Pt/ Pd under an argon atmosphere at 2.5 kV and 20 mA to a thickness of 15 nm with a Cressington sputter coater 208 HR (Cressington Scientific Instruments Ltd., Watford, UK). The samples were analyzed with a Zeiss Supra 40VP SEM (Carl Zeiss AG, Germany) equipped with a Gemini column operating in field emission mode at an acceleration voltage of 5 kV and an emission current of 300 µA. Photographs were taken using Smart SEM V05.02.03 software.

5.3.5 Powder X-ray diffraction (PXRD)

The crystallinity of physical mixtures and ground extrudates was investigated with a Philips Electronic Instrument Type 42273 (Philips Electronic Instrument, Mount Vernon, NY). The generator operating voltage and current were 40 kV and 30 mA. Samples were spread in a powder bed and scanned in the 2-Theta range between 5-40° at a step size of 0.05° with a dwelling time of 2 seconds, corresponding to a scanning rate of 1.5°/ min.

5.4 RESULTS AND DISCUSSION

5.4.1 Selection of the enteric matrix polymer

The preparation of enteric pellets by hot-melt extrusion requires the use of a thermoplastic matrix polymer with acidic groups. Two cellulosic polymers, HPMC AS LF and HPMC AS HF (Aqoat® LF and HF) and three polymethacrylates (Eudragit® L100-55, L100 and S100) were investigated as potential carrier materials. The compositions of blends containing 10% theophylline in the different enteric polymers, the extrusion parameters (temperature and torque) and the average diameter of the extruded polymer strands are listed in Table 5.1. Unplasticized Eudragit® S100 and L100 exhibit high glass transition temperatures (Tg) of 172°C and 194°C (determined by MDSC), respectively, and undergo thermal degradation above 180°C [18]. High TEC levels (30% based on the polymer weight, 20.8% absolute) were necessary to sufficiently lower the Tg and the processing temperature of polymethacrylic blends below the threshold temperature of thermal degradation, while formulations with cellulosic polymers contained only 20% TEC based on the polymer weight (15% absolute). Yet, blends that were prepared with polymethacrylates had to be extruded at high temperatures (160 and 170°C) to efficiently reduce the torque and produce melt viscosities that were low enough to enable the exit of the polymer strand through the 500 µm die. Extrudates of Eudragit® L100-55 could not be produced as the melt was too viscous and produced torque values exceeding the alarm setting (368 Ncm). Pellets based on HPMC AS could be extruded at lower temperatures (120-130°C), faster output rates and exhibited less tendency to swell after die exit (strand diameters of 647±23µm and 598±8µm for Aqoat® LF and Aqoat® HF grade) compared to the polymethacrylates (diameters of 967±65µm and 883±12µm for Eudragit® L100 and S100). The advantageous processibility of the cellulosic

polymers could be explained by their lower molecular weights (approximate MW around 18,000) [19] compared to the methacrylic polymers (MW of 135,000 for Eudragit® L100 and S100, MW of 250,000 for Eudragit® L100-55) [20, 21] and their lower Tg (119°C, determined by MDSC), presumably resulting in lower melt viscosities and reduced elastic recovery after extrusion. The HPMC AS HF grade displayed slight advantages in processibility in comparison to the LF grade, as evidenced by lower and less variable torque values.

The drug release properties of extruded pellets at pH 1.2 (2 hours) and pH 6.8 (HPMC AS LF, Eudragit® L100) or pH 7.4, respectively (HPMC AS HF, Eudragit® S100) are shown in Fig. 5.1. All formulations showed an initial burst effect with a relatively high release after 15 min, followed by a sustained release over the remainder of the dissolution period in acid. A similar biphasic behavior has been reported for hot-melt extruded, insoluble matrix pellets [22]. The initial burst can be correlated with the release of drug from the surface of the pellets which were not protected by the enteric polymer and exposed to dissolution medium, while diffusion processes dominated at later time points. Cellulosic pellets plasticized with TEC exhibited a higher burst effect and faster drug diffusion rates in acid than the pellets made with polymethacrylates with more than 20% drug released after 2 hours. In an attempt to reduce the permeability of the matrix, TEC was replaced by the less soluble ATBC, and the amount of plasticizer was reduced in favor of the polymer content. The release in acid decreased to 14.84%, but still failed to meet the USP requirement of 10% or less after 2 hours. On the other hand, pellets extruded with the methacrylic polymers provided excellent gastric protection with 3.85% (Eudragit® L100) and 3.76% theophylline (Eudragit® S100) being released after 2 hours. Based on the manufacturing process by hot-melt extrusion, the initial porosity of the produced matrix pellets is expected to be low and not responsible for the differences in

release profiles observed in acidic medium. Cellulosic polymers are more hydrophilic than polymethacrylates and demonstrated faster water penetration into the matrix and more extensive hydration, presumably leading to increased matrix permeability and drug diffusion rates even in acidic medium. Similar results were reported for cured film-coated systems [23]. Pellets that were coated with Eudragit® S100 released the drug to a lesser extent over two hours in acid than pellets coated with Aqoat® HF.

In the buffer phase, theophylline was rapidly released from the HPMC AS based pellets (> 95% after 2 hours in buffer). The polymethacrylic pellets displayed a more sustained release profile with 61.15% (Eudragit® L100) and 66.56% released (Eudragit® S100), respectively, after 2 hours in the buffer. Similar extended release profiles in buffer were observed for hot-melt extruded matrix tablets based on Eudragit® S100 [12], Eudragit® L100-55 [10] and Eudragit® L100 [11]. This release behavior from Eudragit® pellets above dissolution pH was attributable to the larger MW and slower hydration and erosion characteristics of polymethacrylic copolymers. Siepmann and coworkers investigated the water uptake and dry mass loss of thin ethylcellulose films containing either HPMC AS or Eudragit® L as enteric polymer. The dry mass of TEC-plasticized ethylcellulose: HPMC AS films decreased faster and to a higher extent than that of ethylcellulose: Eudragit® L films in buffer pH 7.4, which was attributed to more rapid and more substantial dissolution of HPMC AS and leaching of the plasticizer. After 2 hours in the buffer, HPMC AS was completely released into the dissolution medium whereas 37% Eudragit® L remained within the film even after 8 hours [24].

Eudragit® S100 was selected as the matrix material for the preparation of pellets as it provided good gastric protection. This polymer further displayed acceptable processibility when high amounts of plasticizer were employed, and superior thermal stability compared to a polymer mixture. Pellets based on a 1:1 mixture of HPMC AS HF

and Eudragit® S100 were also investigated since an intermediate drug release profile was expected for this formulation. The extrusion temperature for this mixture was selected to be 140°C. Lower processing temperatures resulted in selective melting of Aqoat®, while the Eudragit® S100 remained as distinct powder particles without forming a coalesced matrix. These pellets were very friable and released high amounts of drug in acid, since non-molten Eudragit® S100 was less efficient in controlling the drug release. Extrusion at temperatures above 130°C, however, resulted in browning of the extrudate due to thermal degradation of the cellulose component. Pellets prepared with the mixture released 10.88% drug in acid which was lower than for HPMC AS pellets, but still above the 10% limit required by the USP.

5.4.2 Influence of drug loading

The formulation of controlled release matrix systems for high dose drugs poses challenges to the pharmaceutical scientist since the release rate is dependant on the integrity of the polymeric matrix. The maximum applicable drug loading is limited by the percolation threshold, defined as the critical load of soluble material that will form a percolating cluster when leaching from the matrix. Above this critical load, a continuous porous network will be formed during dissolution, resulting in a loss of the sustained or delayed release properties of the dosage form [25]. When multiparticulate matrix systems are utilized, the increase in surface area will lead to a higher fraction of drug at the surface and thus accessible by the dissolution medium, a circumstance that further impedes the incorporation of high drug loadings. Follonier and coworkers demonstrated that drug release rates from melt extruded, sustained release pellets correlated with the drug-to-polymer ratio, and that both phases, burst release and diffusion controlled release were accelerated when the amount of drug was increased [22].

To investigate the effects of drug load, enteric pellets were extruded with theophylline levels ranging from 10 to 40%, employing Eudragit® S100 as release-controlling matrix former and TEC as a processing aid at the 40% level based on the polymer content (Table 5.2). The increase in plasticizer content from 30 to 40% enabled extrusion at a lower temperature (140 instead of 160°C), but also increased the permeability of the polymeric matrix in both dissolution media. When comparing the drug release profiles of Eudragit® S100 pellets plasticized with 30% TEC (Fig. 5.1) to pellets plasticized with 40% TEC based on the polymer weight (Fig. 5.2), an increase in drug release from 3.76 to 6.10% was observed after 2 hours in acid, while the release after 2 hours in buffer increased from 66.56% (30% TEC) to 83.52% (40% TEC).

The strand diameter as an indicator for polymer swelling after die exit decreased only slightly from 883±12µm (30% TEC) to 870±23µm (40% TEC). However, as illustrated in Fig. 5.3, increasing the drug load resulted in reduced swelling as the extrudate diameter decreased significantly to 727±35µm (20% theophylline), 655±36µm (30% theophylline) and 537±21µm (40% theophylline) (one-way ANOVA, $\alpha = 0.05$, $p < 0.001$). The drug did not melt during extrusion (melting point = 277°C) and remained in the crystalline state. Higher amounts of non-melting material increased the resistance against the rotation of the screws resulting in higher torques and diminished process yields. The extrusion yield was determined as the percentage of the collected extruded material relative to the fed material (10 g). The obtained yield values were relatively low due to two reasons: The interior volume of the mini extruder holds approximately 5 g of material, which is difficult to disgorge and may remain inside the extruder, especially when small diameter dies are used. Second, insufficiently plasticized polymers or formulations with high solids content encounter a high resistance to exit through the die and tend to be pushed into the backflow channel which is part of the extruder design.

Possible strategies to optimize the yield include increasing the batch size, using larger diameter dies or dies with several orifices and extruding well plasticized blends to increase the material output. As can be seen in Fig. 5.2, pH-dependent biphasic dissolution profiles were obtained for all the investigated drug loadings. All compositions liberated the total amount of drug by matrix erosion after 4 hours in buffer at pH 7.4, with the 40% theophylline pellet formulation exhibiting a slightly faster release rate than pellets with lower drug content. The selection of the appropriate drug loading in matrix systems is generally based on dose requirements, controlled release characteristics and process yield as primary decision criteria. While the delayed release characteristics were preserved up to 40% theophylline in the formulation, the previous findings demonstrated that declining processibility by melt extrusion will limit the applicability to high drug loadings.

5.4.3 Plasticization efficiency of various plasticizers on Eudragit® S100

Plasticizers are traditionally low molecular weight compounds that are added to polymers to modify their physico-mechanical properties. Plasticizer-polymer compatibility is defined as the ability of the plasticizer to form a homogeneous phase with the polymer without exudation (liquid plasticizers) [26] or crystallization (solid-state plasticizers). When selecting an appropriate plasticizer, the compatibility with the polymer and plasticization efficiency are pivotal selection criteria. Efficient plasticizers for the melt extrusion of pellets need to lower the Tg of the plasticized polymer below the onset temperature of thermal degradation, and reduce the melt viscosity of the blend to enable material transport within the barrel and extrusion through the 500µm die orifice.

The extent of Tg reduction in the presence of a plasticizer can be used as a parameter to assess the plasticization efficiency [27]. Five compounds differing in

molecular weight, physical state, hydrophilicity and water solubility were investigated as possible plasticizing agents (Table 5.4). These properties were expected to impact plasticizer-polymer compatibility, plasticizing efficiency and drug release rates from extruded matrices. Citric acid monohydrate (CA MH), PEG 8000 and methylparaben (MP) are solid-state plasticizers that need to melt in order to plasticize the polymer. The citrates (TEC, ATBC) and PEG have been successfully employed for the plasticization of polymethacrylic polymers [28], while MP and CA MH are non-traditional plasticizers [29, 30]. The thermal properties of Eudragit® S100 and physical mixtures containing 30% plasticizer based on the polymer weight were studied by MDSC, and the Tg was determined in the second heating cycle (Fig. 5.4). The Tg of the pure polymer was recorded at 172°C, a value similar to those reported by other groups, (166°C [12] and 169°C [31]). Thermal degradation of the polymer starts at 180°C (onset) and accelerates above 188°C by formation of cyclic anhydrides between the carboxylic acid groups of the polymer [18]. The data in Fig. 5.4 demonstrates the differences in plasticization efficiency for the investigated plasticizers. Melting endotherms of MP, CA MH and PEG were not present in the second heating cycle, indicating good compatibility of these plasticizers with Eudragit® S100. Increasing the TEC concentration gradually from 10 to 20 and 30% resulted in a Tg decrease to 138, 121 and 101°C, respectively. When compared to TEC, CA MH and methylparaben showed similar plasticization efficiencies (Tg of 94°C), while ATBC was less suitable to lower the Tg of Eudragit® S100 (134°C). The reasons for the low plasticization efficiency of ATBC could be due to its high hydrophobicity caused by the butyl groups (low solubility and small hydrophilic fraction) and the lack of hydrogen bond donor groups in the molecule structure. All other plasticizers showed efficient Tg reduction and potential to be used as processing aids for the hot-melt extrusion of Eudragit® S100. When comparing the Tg of the plasticized

polymer with the processing temperature that was necessary to produce melt viscosities low enough for an extrusion through the 500μm die, it became apparent that an efficient plasticization of Eudragit® S100 for this application implied a reduction of the Tg to a temperature of 50°C or more below the extrusion temperature. These findings were in agreement with previous reports on melt extruded Eudragit® S100 matrices [12].

5.4.4 Selection of suitable plasticizers based on dissolution properties

As detailed in the previous sections, efficient plasticization of Eudragit® S100 was necessary to decrease the Tg and melt viscosity during hot-melt extrusion. However, plasticizers may also influence the drug release rate by modifying the matrix permeability. Soluble plasticizers can function as pore formers and increase the release of water-soluble drugs by enhancing matrix percolation [14, 15]. The formulation without plasticizer had to be extruded at 220°C, a temperature higher than the onset temperature for thermal degradation and, therefore, unacceptable. Blends containing CA MH or ATBC as plasticizers needed to be processed at 170°C and produced low extrudate yields. This behavior was expected for ATBC due to its low plasticization efficiency, but unexpected for CA MH which produced a Tg of 94°C in the MDSC experiments. Formulations with CA MH further showed excessive swelling and produced a porous extrudate exhibiting highly variable diameters. This observation could be due to moisture evaporation from the CA lattice or possibly thermal degradation of the organic acid and the polymer at the high extrusion temperature. Formulations plasticized with TEC, MP or PEG could be extruded at 140°C with MP-containing blends producing the lowest torque and largest yield. The diameters of extrudates with TEC and PEG were similar, but significantly higher for MP-plasticized extrudates (Table 3, One-way ANOVA, $\alpha = 0.05$, $p < 0.001$).

When evaluating the suitability of a plasticizer for the preparation of pharmaceutical products, its influence on the drug dissolution profile needs to be taken into consideration. The physical and chemical properties of the plasticizer and of the plasticized matrix impact the release characteristics of the dosage form. Fig. 5.5 illustrates the results of dissolution testing according to the USP method A for delayed release dosage forms. Pellets plasticized with 20% PEG or CA MH failed to provide gastric protection, exhibiting rapid drug release during the acid stage. This finding can partially be explained by the high aqueous solubility of these compounds. The porosity of the pellets increased during the dissolution experiment since soluble plasticizers can function as pore formers when they leach from the matrix. These results were in agreement with the findings of Zhu and coworkers who demonstrated faster drug release at higher TEC levels due to channel formation in melt extruded matrices [6, 14]. Moreover, Zhang et al. showed that the addition of PEG 3350 increased the drug release from melt extruded PEO matrix tablets by promoting matrix hydration, decreasing the viscosity of the hydrated layer and facilitating drug diffusion [3].

While the dissolution of theophylline from CA MH plasticized pellets still exhibited pH-dependency, the presence of 20% PEG resulted in the complete loss of the biphasic release profile, with more than 80% drug released within 2 hours in acid. This behavior was unexpected since CA MH exhibits higher water solubility and a lower MW than PEG, favoring faster diffusion from the matrix and enhanced pore formation. Several explanations for the more rapid release from PEG-containing systems might be responsible for these findings: Although both plasticizers were used at the same mass percentage (20%), their volume percentage is different since PEGs have a lower true density than CA MH. Calculations based on literature values for true densities of the employed materials (Eudragit® S100 = 1.20, theophylline = 1.49, CA MH = 1.54, PEG =

1.18) demonstrated that PEG was present at a higher volume percentage than CA MH (21.5% versus 17.4%) within the matrix. Consequently, the impact of the soluble PEG on the matrix permeability was more pronounced when compared to the CA matrix. Second, the acidic functional groups of CA MH likely lowered the microenvironmental pH and delayed polymer dissolution. Furthermore, PEG was shown to be a more efficient plasticizer for Eudragit® S100 than CA MH, thus presumably increased the polymer's free volume and permeability to a larger extent. Breitkreutz and coworkers demonstrated that strong interactions between Eudragit® L film coatings and PEG in acidic dissolution medium resulted in an increased penetration of PEG-associated water into the film and loss of enteric protection [32].

Pellets plasticized with either MP, ATBC or TEC yielded low drug release rates similar to the drug release form the unplasticized extrudate (5.91%) with 3.85, 5.84 and 7.14% theophylline released after 2 hours in acid. This finding suggests that leaching of plasticizer during dissolution and drug diffusion through pores were negligible. Furthermore, plasticized matrices extruded at lower temperature and non-plasticized systems produced at high temperatures exhibited similar drug release properties. It can be concluded that a lack of plasticization could be compensated by increasing the processing temperature in order to form an intact matrix of low porosity. In buffer, however, efficiently plasticized extrudates (MP and TEC) released theophylline at higher rates than extrudates with ATBC or without a plasticizer, presumably due to more rapid water penetration into the matrix and faster pellet dissolution.

5.4.5 Pellet characterization: microstructure and solid-state properties

The microstructures of the unprocessed theophylline particles and cut surfaces of extruded pellets were examined by SEM (Fig. 5.6). The drug itself was found to be of

irregular shape and crystalline, with a wide particle size distribution and agglomerates (Fig. 5.6A). Extruded pellets (B) without any plasticizer (C) or comprising MP (D), TEC (E) or PEG (F) as plasticizers showed crystalline theophylline particles dispersed in the smooth solidified melt. While the particles were still irregular in shape, the particle size was reduced and the size distribution more narrow compared to the unprocessed drug, presumably due to the effective mixing and high shear forces during processing. Miller and coworkers successfully applied hot-melt extrusion for the deaggregation and dispersion of engineered particles in a non-solubilizing carrier without altering the solid-state properties of the individual drug particles [33]. Regardless of the incorporated plasticizer, SEM photographs of the pellets showed a smooth matrix of high integrity and without pores. While the extrudate without plasticizer predominantly contained the theophylline crystals in clusters, the plasticized pellets exhibited a more homogeneous drug distribution throughout the entire matrix, favored by the reduced melt viscosity of the blend during extrusion. The surfaces of pellets without any plasticizer were further partially covered with needle-shaped nanocrystals that had recrystallized from the solidified matrix. Drug miscibility with the polymer was increased since this formulation was extruded at a higher temperature (220°C), promoting partial drug melting. Fig. 5.6G demonstrates that needle-shaped drug crystals had also grown on the entire surface of ATBC-plasticized pellets, which had been extruded at 170°C. Drug-polymer interactions may decrease the drug's melting point below the extrusion temperature and increase theophylline solubilization in the carrier. Amorphous systems exceeding the solubility limit at room temperature are thermodynamically instable and tend to recrystallize at storage temperature as previously reported for extrudates containing guaifenesin [34]. In addition to this thermodynamic instability, plasticized polymers further possess an increased molecular mobility attributed to their higher free volume, so that drug

recrystallization processes may occur at accelerated rates, as it has been reported for amorphous systems stored at increasing storage temperatures [35]. These findings demonstrated that high extrusion temperatures and the formation of partially amorphous systems promoted physical instabilities and should therefore be avoided. Pellets formulated with CA MH as a plasticizer were also extruded at 170°C and yielded a highly porous matrix (Fig. 5.6H). This foam-like microstructure may be caused by the evaporation of water liberated by the CA lattice or produced by condensation reactions between ionic carboxylic acid groups of the polymer and the plasticizer during thermal degradation. It has been reported that the formation of cyclic anhydrides is the main pathway of thermal degradation below 200°C for methacrylic acid polymers [18]. Citric acid might suppress the onset of polymer degradation below the extrusion temperature or directly react with the functional groups of the acrylic polymer. The presence of a coherent pore network throughout the pellets plasticized with CA MH enabled rapid water penetration and promoted fast drug dissolution during the acid stage.

The solid-state properties of the extruded pellets were analyzed by PXRD (Fig. 5.7). Unprocessed, anhydrous theophylline was highly crystalline and exhibited characteristic peaks at 2-Theta = 12.9 and 26.7 (highlighted squares in Fig. 5.7), while Eudragit® S100 was completely amorphous. The limit of detection for crystalline theophylline using this method was below 5% as demonstrated for a physical mixture of Eudragit® S100 containing 5% crystalline drug. In all extrudates (EX), the drug was present in the crystalline state and as the original polymorph since the diffraction patterns displayed the characteristic peaks of the unprocessed drug (Fig. 5.7). The peak intensities in extrudates containing PEG, TEC or MP were similar, while extrudates prepared at elevated temperatures (ATBC, CA MH, no plasticizer) produced patterns with reduced peak intensities attributed to partial drug melting and solubilization in the carrier. The

absence of characteristic peaks for crystalline PEG and MP demonstrated that both solid-state plasticizers completely melted during processing and were miscible with the methacrylic polymers at the employed ratio. Pellets prepared with CA MH, however, showed additional peaks in their diffraction pattern at 2-Theta = 18.0 and 27.4, which were attributed to recrystallized, anhydrous CA. This observation provided evidence that the compatibility limit was exceeded at the CA concentration used in this study. Recrystallized CA formed a separate phase in the polymer matrix and failed to exert a plasticizing effect on the polymer, resulting in poor processibility by melt extrusion.

5.5 CONCLUSION

Enteric matrix pellets with a diameter below 1 mm and containing up to 40% theophylline could be successfully prepared by hot-melt extrusion when plasticized Eudragit® S100 was employed as the matrix material. The manufacture of pellets using alternative enteric polymers was either compromised by a lack of thermal processibility (Eudragit® L100-55 and Eudragit® L100), or the pellets failed to provide gastric protection due to high matrix permeability in acid (Aqoat® LF and HF). The influence of five different plasticizers on the processibility and drug release kinetics was investigated. Methylparaben, PEG 8000 and TEC showed high compatibility with Eudragit® S100, plasticized the polymer efficiently and promoted a homogeneous dispersion of the crystalline drug within the matrix pellet at reduced particle sizes. Pellets containing ATBC, citric acid monohydrate or no plasticizer had to be extruded at high temperatures which promoted partial drug solubilization and drug recrystallization on the pellet surfaces. Plasticization with water-soluble compounds (PEG 8000 and CA MH) resulted in a loss of gastric protection due to plasticizer leaching and pore formation during the acidic stage. Pellets containing less soluble plasticizers (TEC, methylparaben, ATBC) or

no plasticizer exhibited low drug release rates in acid independently of the plasticization efficiency, while the release in buffer was higher for pellets prepared with efficient plasticizers (TEC or methylparaben). Methylparaben was superior to the other investigated plasticizers in terms of plasticization efficiency, product yield and pellet release properties.

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5.7 TABLES

Table 5.1: Compositions of blends, extrusion parameters and diameters of extruded strands containing 10% theophylline and different enteric polymers. (All extrusions were conducted using a screw speed of 100 rpm.)

Polymer	TEC [% based on polymer]	Temp. [°C]	Torque [Ncm]	Diameter ± SD [µm]
HPMC AS LF	20	120	85-120	647 ± 23
HPMC AS HF	20	120	80-100	598 ± 8
HPMC AS HF	10 (ATBC)	130	120-140	625 ± 8
Eudragit® L100-55	30	160	-	-
Eudragit® L100	30	170	145-160	967 ± 65
Eudragit® S100	30	160	125-135	883 ± 12
HPMC AS HF + Eudragit® S100 (1:1)	20	140	170-185	777 ± 140

Table 5.2: Formulations and process parameters for Eudragit® S100 based matrix pellets containing 10-40% theophylline (Theo) and 40% TEC based on polymer content. (All extrusions were conducted at 140°C and using a screw speed of 75 rpm.)

Theo [%]	Eudragit® S100 [%]	TEC [%]	Torque [Ncm]	Yield [%]	Diameter ± SD [µm]
10	64.3	25.7	170-190	28.0	870 ± 23
20	57.1	22.9	190-210	23.2	727 ± 35
30	50.0	20.0	200-220	18.3	655 ± 36
40	42.9	17.1	230-250	9.8	537 ± 21

Table 5.3: Compositions and process parameters of Eudragit® S100 matrix pellets containing 30% theophylline and different plasticizers. (All extrusions were conducted using a screw speed of 75 rpm.)

Eudragit® S100 [%]	Plasticizer [20 %]	Temperature [°C]	Torque [Ncm]	Yield [%]	Average ± SD [µm]
50	TEC	140	200-220	18.3	655 ± 36
50	ATBC	170	100-115	9.0	810 ± 149
50	PEG 8000	140	225-245	15.5	625 ± 21
50	CA MH	170	100-115	3.5	917 ± 297
50	MP	140	170-180	23.3	773 ± 32
70	none	220	60-80	6.4	598 ± 16

Table 5.4: Physicochemical properties of the compounds investigated as plasticizers for the hot-melt extrusion of Eudragit® S100 matrix pellets.

Plasticizer	State	T_m or T_b [°C]	MW [g/mol] formula	H-Bonds (D+A)	Hydrophilic Fraction [%]	Water Solubility [g/100 ml]
TEC	liquid	288 (T_b)	276 $C_{12}H_{20}O_7$	1+7	41	5.5
ATBC	liquid	326 (T_b)	402 $C_{20}H_{34}O_8$	0+8	32	< 0.1
PEG 8000	solid	65 (T_m)	≈ 8000	2+183	36.5	50
Citric acid monohydrate	solid	120 (T_m)	210 $C_6H_8O_7 \cdot H_2O$	4+7	55	163
Methyl-paraben	solid	126 (T_m)	152 $C_8H_8O_3$	1+3	32	0.3

5.8 FIGURES

Figure 5.1: Influence of the matrix polymer on the release properties of enteric matrix pellets. All formulations contained 10% theophylline. (◇) HPMC AS LF, 15% TEC, (◆) HPMC AS HF, 15% TEC, (×) HPMC AS HF, 9% ATBC, (△) Eudragit® L100, 20.8% TEC, (▲) Eudragit® S100, 20.8% TEC, (■) HPMC AS HF + Eudragit® S100 1:1, 15% TEC.
Dissolution: USP paddle apparatus, 50 rpm, 37.0±0.5°C, n = 3, 2 hours in 750 ml SGF pH 1.2 without pepsin, after 2 hours pH change to pH 6.8 (HPMC AS LF, Eudragit® L100) or pH 7.4 (HPMC AS HF, Eudragit® S100) by addition of 250 ml 0.2M tribasic phosphate buffer and NaOH solution.

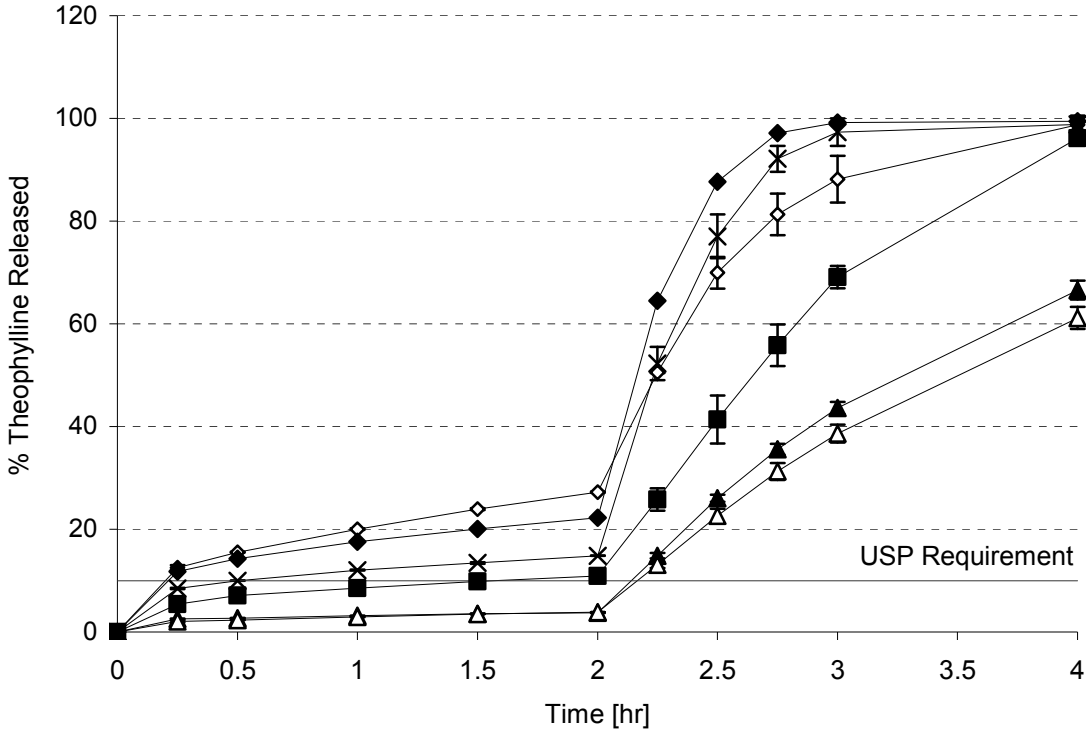


Figure 5.2: Influence of the theophylline loading on the release properties of Eudragit® S100 matrix pellets. (□) 10%, (▲) 20%, (×) 30%, and (◇) 40% theophylline.
Dissolution: USP paddle apparatus, 50 rpm, 37.0±0.5°C, n = 3, 2 hours in 750 ml SGF pH 1.2 without pepsin, after 2 hours pH change to pH 7.4 by addition of 250 ml 0.2M tribasic phosphate buffer and NaOH solution.

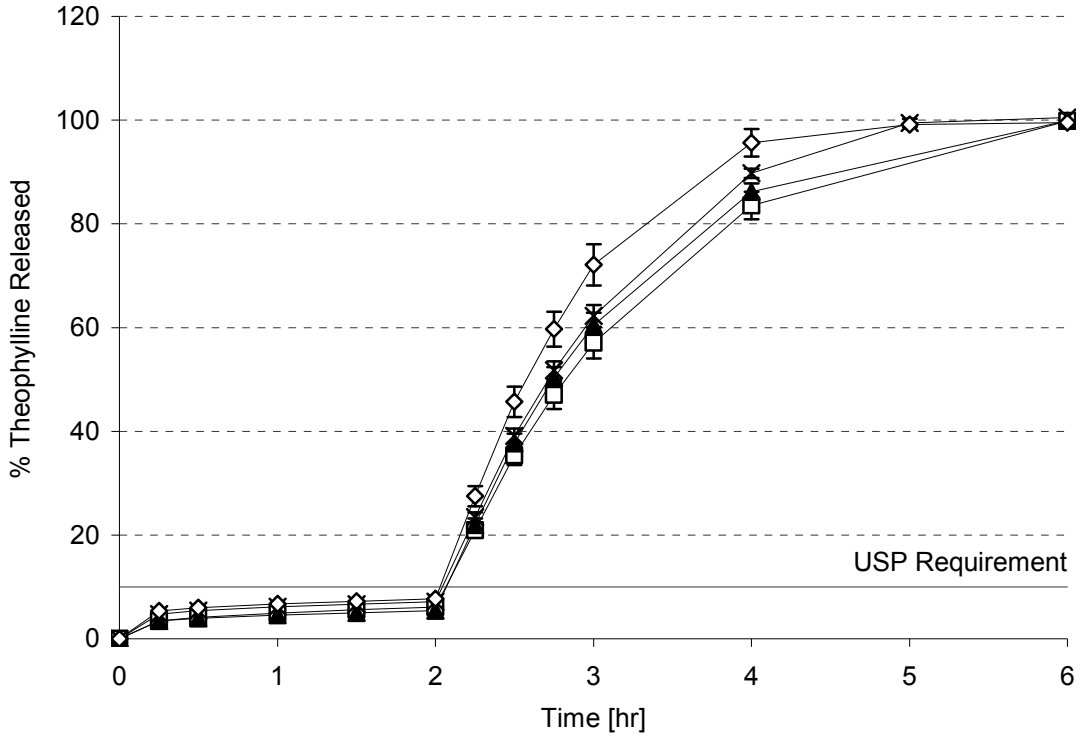


Figure 5.3: Influence of the theophylline content on the extrudate diameter and process yield for the extrusion of Eudragit® S100 matrix pellets.

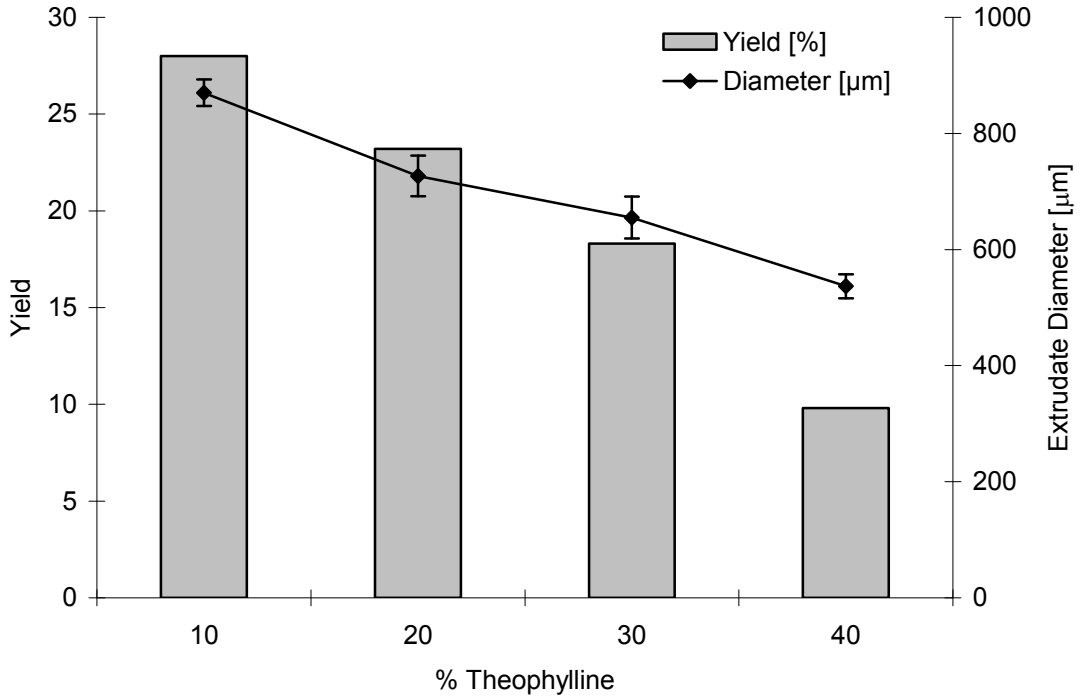


Figure 5.4: Influence of different compounds on the glass transition temperature of Eudragit® S100 as determined by MDSC.

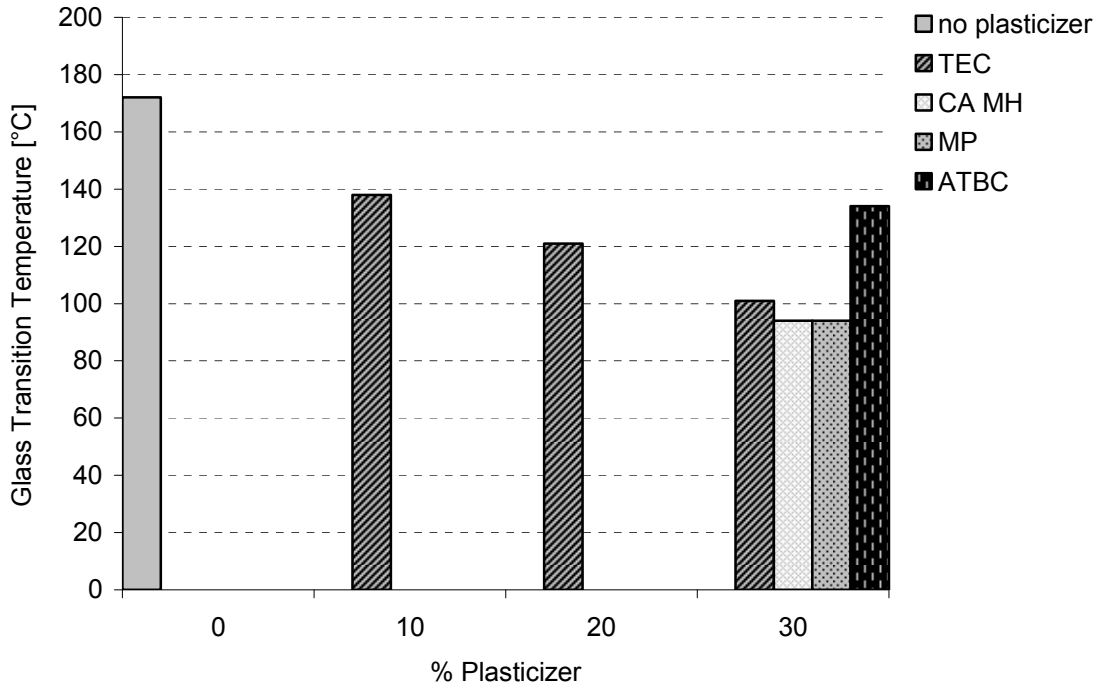


Figure 5.5: Influence of the type of plasticizer on the drug release from Eudragit® S100 matrix pellets. All formulations contain 30% theophylline and 20% plasticizer. (■) PEG 8000, (◇) CA MH, (□) MP, (◆) TEC, (△) ATBC, (×) no plasticizer.
Dissolution: USP paddle apparatus, 50 rpm, 37.0±0.5°C, n = 3, 2 hours in 750 ml SGF pH 1.2 without pepsin, after 2 hours pH change to pH 7.4 by addition of 250 ml 0.2M tribasic phosphate buffer and NaOH solution.

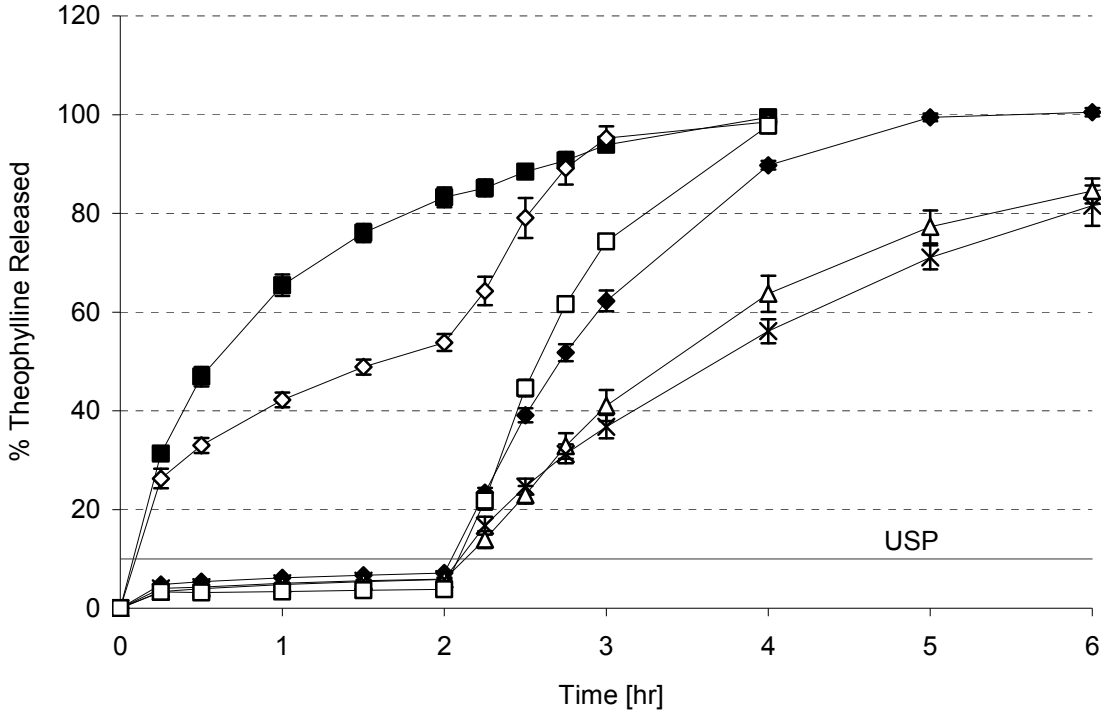


Figure 5.6: SEM pictures of A) theophylline powder; B and C) Extrudates without plasticizer; Extrudates with D) 20% methylparaben, E) 20% TEC, F) 20% PEG 8000, G) 20% ATBC, H) 20% CA MH.

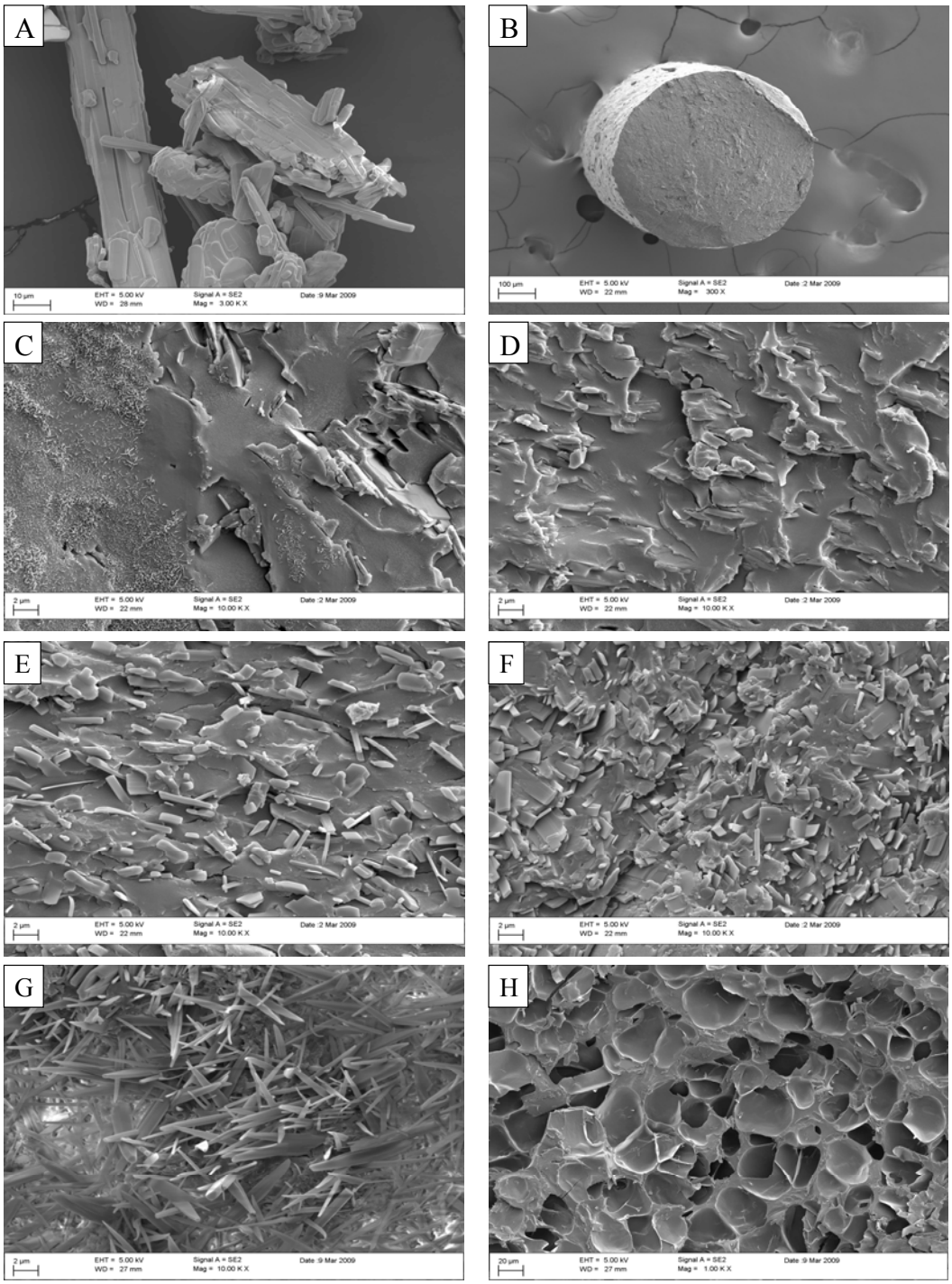
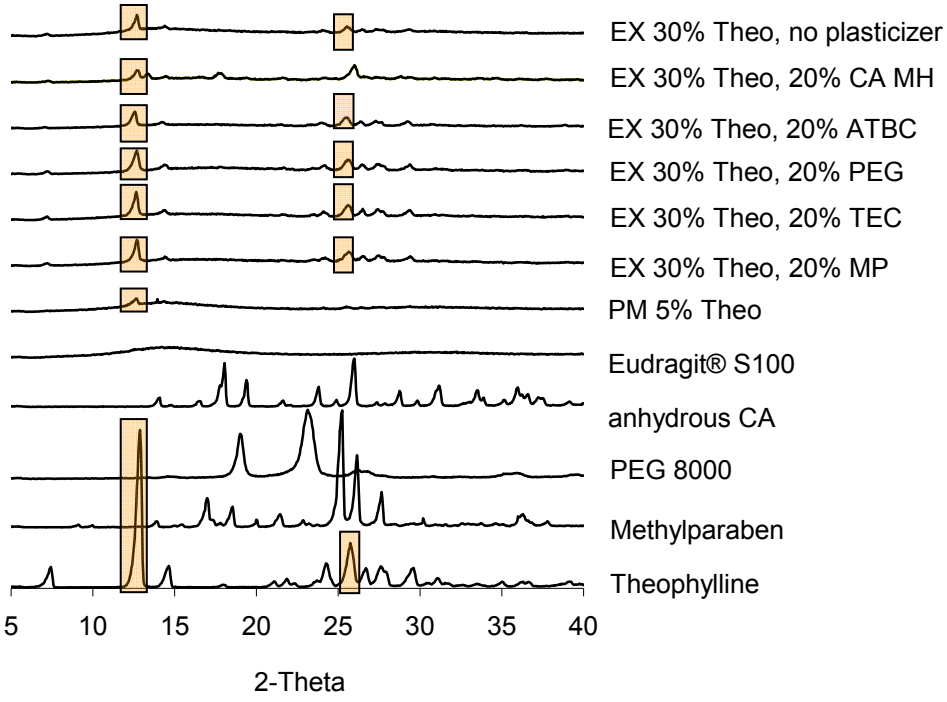


Figure 5.7: Influence of different plasticizers on the crystallinity of melt extruded Eudragit® S100 matrix pellets (EX) containing 30% theophylline (Theo). (PM: physical mixture, characteristic theophylline peaks are highlighted)



Chapter 6: Investigation of the Influence of Plasticizer Type and Level on the Properties of Eudragit® S100 Matrix Pellets Prepared by Hot-Melt Extrusion[4]

Abstract:

The objective was to investigate the influence of three plasticizers (TEC, methylparaben and PEG 8000) at two levels (10% or 20%) on the properties of hot-melt extruded Eudragit® S100 matrix pellets. Extrusion experiments showed that all plasticizers produced similar reductions in polymer melt viscosity. Differential scanning calorimetry and powder X-ray diffraction demonstrated that the solid-state plasticizers were present in the amorphous state. The drug release in acidic medium was influenced by the aqueous solubility of the plasticizer. Less than 10% drug was released after 2 hours at pH 1.2 when TEC or methylparaben was used, independent of the plasticizer level. Drug release at pH 7.4 resulted from polymer dissolution and was not influenced by low levels of plasticizer, but increased significantly at the 20% level. Mechanical testing by diametral compression demonstrated the high tensile strength of the hot-melt extruded pellets that decreased when plasticizers were present.

[4] Significant portions of this chapter were taken from: Schilling, S.U., Lirola, H.L., Shah, N.H., Malick, A.W., and McGinity, J.W. Influence of plasticizer type and level on the properties of Eudragit® S100 matrix pellets prepared by hot-melt extrusion. This paper is under review by the Journal of Microencapsulation.

6.1 INTRODUCTION

The interest in the development of multiparticulate systems for the controlled delivery of drugs stems from their beneficial pharmacokinetic properties. In contrast to monolithic systems, pellets spread into the digestive tract independent of the feeding state, avoiding high local drug concentrations and reducing inter-and intra-subject variabilities in drug absorption [1]. The drug release properties of pellets can be controlled by either a protective film coat (reservoir-type pellets) or by the permeability of the matrix material (matrix pellets).

The process of hot-melt extrusion allows the manufacture of controlled-release matrix pellets in a continuous manner avoiding subsequent film coating and the use of organic or aqueous solvents. A powder blend comprising the drug, a thermoplastic polymer and optional processing aids is mixed and transported inside a heated barrel by either one or two rotating screws. The softened material undergoes zones of increasing temperature and pressure before exiting through a product-shaping die. The diameter of the extruded strand is primarily governed by the diameter of the die orifice, but may also be influenced by the viscoelastic properties of the polymeric melt. Several technologies have been developed to accomplish a subsequent pelletization and spheronization of the extrudate in a continuous or semi-continuous manner [2-4]. Besides technological advantages, hot-melt extruded pellets allow the incorporation of higher drug loadings under preservation of the controlled release properties which is attributable to the low porosity of melt-extruded matrices when compared to pellets prepared by traditional wet-massing techniques [5]. Melt extruded matrix pellets further offer benefits during downstream processing such as direct compression into multiparticulate tablets which are related to their high mechanical strength and low friability [6].

The successful preparation of sustained release pellets by hot-melt extrusion has been reported in several publications [7-9] and patents [10, 11]. However, the manufacture of enteric pellets exhibiting a release of less than 10% after 2 hours in simulated gastric fluid remains challenging. Attributed to the larger surface area of small pellets, drug release in acid will be increased when compared to tablets as previously demonstrated for melt extruded Eudragit® L100-55 matrices containing 20% drug [12]. Another parameter to consider is the opposing trend between polymer permeability and thermal processibility. In a previously conducted study, we demonstrated that anionic cellulosic polymers (Aqoat® LF and HF) could be extruded at lower temperatures and higher yields than anionic methacrylic polymers (Eudragit® S100, L100) due to their lower glass transition temperature and melt viscosity [13]. However, only pellets prepared with Eudragit® S100 and L100 showed low release rates in acidic medium and were compliant with the USP requirement to release less than 10% drug after 2 hours at pH 1.2. Methylparaben, PEG 8000 and TEC were efficient plasticizers for Eudragit® S100 and enabled the extrusion of pellets at temperatures well below the onset of thermal degradation. Alternatively, anionic polymers with low glass transition temperature but too high permeability in acid (Eudragit® FS) may be blended with a water-insoluble polymer (Eudragit® RS, RL or NE) to reduce the drug release in simulated gastric fluid as disclosed in patent application WO 2008/101743 [14].

Based on the results that we obtained for Eudragit® S100 matrix pellets, the objective of the current study was to investigate the influence of three efficient plasticizers (TEC, methylparaben, PEG 8000) on the physical properties and drug release characteristics of melt extruded pellets. Employing a mixture design of experiments, pellets comprising one of the three plasticizers at a high level (20%) or low level (10%), theophylline at 30% and Eudragit® S100 as release controlling polymer were prepared

by hot-melt extrusion. The viscosity-temperature behavior of plasticized polymeric melts was studied by extrusion experiments conducted at different temperatures and constant shear rate. The pellet formulations were evaluated regarding the process yield, drug release after 2 hours in acid and release after 45 minutes in buffer pH 7.4, and the optimum plasticizer type and level were determined. The influence of plasticization on the solid-state properties of the drug and on the mechanical strength of the pellets was investigated by differential scanning calorimetry, powder X-ray diffraction and diametral compression analysis.

6.2 MATERIALS

Anhydrous theophylline and methylparaben (MP) were purchased from Spectrum Chemicals (Gardena, CA), and polyethylene glycol 8000 (PEG, Carbowax Sentry, powder NF) was obtained from Dow Chemical Company (Midland, MI). Triethyl citrate (TEC) was kindly provided by Vertellus (Greensboro, NC) and Eudragit® S100 was donated by Evonik (Piscataway, NJ).

6.3 METHODS

6.3.1 Preparation of melt extruded pellets

Powder blends for hot-melt extrusion consisted of a constant amount of theophylline (30%), 10 or 20% plasticizer (PEG 8000, TEC, methylparaben) and Eudragit® S100 as the thermoplastic matrix former (Table 6.1). The polymer and the plasticizer were premixed and then blended with the drug using a kitchen aid mixer (St. Joseph, MI). The powder blends (10 g) were manually fed into a twin screw mini extruder (Haake Minilab, Rheomax CTW5, Thermo Electron, Germany) operated in

flushing mode at a screw speed of 75 rpm. The processing temperatures depended on the plasticizer content (Table 6.1). After extrusion through a 500μm circular die, the strands were air-cooled to room temperature and manually cut into cylindrical pellets. The diameters of the extruded strands were measured with a manual micrometer (Mituoyo model C1012EBS, Aurora, IL) prior to cutting.

6.3.2 Plasticization efficiency – relative melt viscosity-temperature behavior of plasticized polymer melts

The processibility of blends containing 30% theophylline and different levels of plasticizer (0, 10 or 20%) was investigated using the Haake Minilab extruder described above. Five grams of material were manually fed into the extruder, operated in cycling mode at 75 rpm and at 3-5 different temperatures between 110 and 220°C. The torque values stabilized after approximately five minutes of cycling, and the equilibrium torque was monitored over two minutes and reported as the average of 24-32 readings. The extrusion speed (shear rate) was kept constant, and proportionality between viscosity and torque was assumed. The activation energies for the viscous flow of the polymer melts (E_a) were calculated from the slopes of the Arrhenius plots in Fig. 5.1 using the following relationships:

(1) $$\eta = \mathrm{A}e^{\frac{E_a}{RT}}$$

(2) $$\ln M = \frac{E_a}{RT} + C$$

where η is the absolute viscosity, M is the torque, R is the gas constant (8.314 J/mol/K) , A and C are constants and T is the absolute temperature.

6.3.3 Differential scanning calorimetry (DSC)

Differential scanning calorimetry was employed to investigate the crystallinity of the drug and the solid-state plasticizers after hot-melt extrusion. Physical mixtures or ground extrudates were accurately weighed into aluminum pans (10-15 mg) and crimp sealed. The samples were placed inside the furnace of a Thermal Advantage Model 2920 (TA Instruments, New Castle, DE), kept isothermally at 0°C for 5 min, and then ramped to 320°C using a heating rate of 20°C/min. The heat flow against a blank pan was reported as a function of the temperature during the first heating cycle.

6.3.4 Powder X-ray diffraction (PXRD)

The crystallinity of the unprocessed materials and ground extrudates was studied with a Philips Electronic Instrument Type 42273 (Philips Electronic Instrument, Mount Vernon, NY) at an operating voltage of 40 kV and a current of 30 mA. Samples were scanned in the 2-Theta range between 5-40° at a step size of 0.05° with a dwelling time of 2 seconds (1.5°/ min).

6.3.5 Dissolution studies and theophylline assay

The drug release properties of the hot-melt extruded pellets were studied in a paddle apparatus (Varian, Cary, NC) according to USP chapter <724> method A for delayed release articles. Pellets (100 mg, n = 3) were placed in 750 ml simulated gastric fluid pH 1.2 (SGF, without pepsin) at 37.0±0.5°C with a paddle rotation speed of 50 rpm. After two hours, the pH was adjusted to 7.4 by addition of 250 ml 0.2M tribasic phosphate buffer and diluted sodium hydroxide solution. The theophylline content in withdrawn samples was analyzed by HPLC (Waters Inc., Milford, MA) using a C_{18}-

reversed phase column (Capcell PAK 3 mm * 100 mm, Shiseido Co, Japan) and a UV detector (996-PDA, Waters Inc. Milford, MA) extracting at 271.5 nm. A mixture of 20 mM phosphate buffer pH 5 and acetonitrile (9:1) was used as the mobile phase at a flow rate of 0.5 ml/ min, and the theophylline peak areas (retention time 3.5 min) were determined with Empower version 5.0 software (Waters Inc.). Linear correlation was confirmed between 0.1 and 100.0µg/ ml (R^2 = 0.99997) and multiple injections yielded good reproducibility with RSD values between 0.08% (100.0µg/ ml) and 1.77% (0.1µg/ ml).

6.3.6 Mechanical strength of extruded pellets

The crushing strength of hot-melt extruded pellets was determined with a Chatillon Universal Tension / Compression Tester Model TCD-200 (Ametek, Largo, FL) as previously described [15]. A flat, circular steel plate was fitted onto a DFGS 50 digital force gauge and lowered in diametral direction towards the lateral surface of an individual pellet at a crosshead speed of 2.5 mm/ min. The load-deflection data was collected using Chatillon Nexygen TCD force testing software. The mechanical strength was reported as the tensile strength and calculated using equation (3) [16, 17].

$$\sigma = \frac{2P}{\pi dl} \quad (3)$$

Specimens with diameters (d) equaling the length (l) were selected for the experiments, and the maximum load (P) at which brittle fragmentation of the pellets occurred was used for the calculations.

6.3.7 Statistical analysis

The influence of the plasticizer type and level in hot-melt extruded Eudragit® S100 pellets was studied with a mixture design of experiments generated with JMP 7 software (SAS Institute Inc., Cary. NC). Three plasticizers were investigated at two levels (10 and 20%) with the theophylline concentration remaining constant at 30%. The product performance was evaluated regarding three response parameters: drug release in acid after 2 hours (minimum), release in buffer after 45 minutes (maximum) and extrusion yield (maximum). The JMP software was further utilized for one-way ANOVA ($\alpha = 0.05$) and post hoc Tukey Kramer analysis of the mechanical strength data and the dissolution rates in buffer.

6.4 RESULTS AND DISCUSSION

6.4.1 Plasticization efficiency – relative melt viscosity-temperature behavior of plasticized polymer melts

The flow of the blend inside an extruder is primarily controlled by the melt viscosity of the polymer. For the preparation of small pellets, the melt viscosity must be sufficiently low to enable extrusion through the 500µm die at acceptable output rates without exceeding the pressure and torque limits of the equipment. Most polymeric melts show non-Newtonian flow behavior with pseudoplastic and viscoelastic elements attributed to chain entanglement [18]. The melt viscosity is influenced by many factors including polymeric molecular structure, molecular weight, temperature, shear rate and degree of plasticization. The temperature dependence of the melt viscosity at a constant shear rate can be described by an Arrhenius type equation derived by Eyring (equation 1). A plot of the natural logarithm of the viscosity against the reciprocal of the absolute temperature produces a straight line with the slope yielding the flow activation energy

(E_a) divided by the gas constant when E_a is temperature independent [19]. The flow activation energy is dependent on the chemical structure of the polymer, and increasing E_a values were shown to correlate with decreasing volume expansion coefficients and increasing glass transition temperatures [19, 20]. Several research groups demonstrated that torque data can be used instead of viscosities to determine the E_a of polymeric melts, as long as the rotation speed remained constant and the time dependency of the measurement values was considered [21, 22]. Torque values obtained in the beginning were too high due to incomplete melting and lack of temperature equilibrium, while late values were too low as a result of polymer degradation.

The torque after 5 minutes was monitored over a period of 2 minutes when a reproducible equilibrium torque was achieved for each composition and temperature level. The natural logarithms of the torque values were plotted against the reciprocals of the absolute temperature for all formulations (Fig. 6.1). The Ea values were calculated from the slope using equation 2 (Table 6.2). High R^2-values were obtained for the linear correlation (0.984-0.999), confirming the constancy of the E_a-values over the investigated temperature range. For unplasticized Eudragit® S100, the flow activation energy was highest at 106.4kJ/mol. Attributed to the low polymer chain mobility, high temperatures were necessary to overcome the energetic barrier against the viscous flow of the polymer melt within the extruder. When TEC, methylparaben or PEG 8000 was incorporated into the blend at a 10 or 20% level, the plots shifted to lower temperatures (higher 1/T) values, demonstrating that the torques (and hence the melt viscosities) decreased due to plasticization of the polymer. These findings were in agreement with previously reported results obtained for Eudragit® L100-55 blends plasticized with TEC and PEG 3350 [23]. The E_a-values for plasticized Eudragit® S100 decreased to 80-86kJ/mol (10% plasticizer) and 45-59kJ/mol (20% plasticizer), respectively. This behavior was expected since

plasticizers increase the chain mobility by reducing attractive forces between the polymer molecules, resulting in a lower barrier against plastic flow during hot-melt extrusion and a reduced sensitivity of the viscosity to the processing temperature.

These results demonstrated that all tested compounds facilitated the viscous flow of the Eudragit® S100 and can be used to efficiently plasticize the polymer. Plasticizers at the 20% level decreased the resistance to plastic flow to a higher degree than at the 10% level. Therefore, in terms of processibility, plasticizers at the high level should preferably be used for the preparation of melt extruded pellets.

6.4.2 Solid-state properties of the drug and solid-state plasticizers

Physical mixtures and extrudates were studied by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to investigate the influence of thermal processing on the solid-state properties of the model drug and the solid-state plasticizers. The composition of the pellet formulations, the extrusion temperatures and the diameters of the extruded strands are listed in Table 6.1. The DSC thermograms of physical mixtures containing 20% methylparaben or PEG 8000 showed characteristic melting peaks at 123°C (methylparaben) or 61°C (PEG 8000), respectively (Fig. 6.2). In the extrudates, these melt transitions were absent, indicating that the solid plasticizers dissolved in the polymer during hot-melt extrusion and remained in the amorphous state during cooling. These results were confirmed by PXRD analysis where the extrudates were devoid of peaks characteristic for the crystalline plasticizers (data not shown).

The thermogram of Eudragit® S100 displayed two broad endothermic events which represented the evaporation of unbound water below 100°C and the thermal degradation of the polymer at 200-250°C. This degradation peak interfered with the theophylline melting peak, and thus drug crystallinity was studied by PXRD. As

previously reported for hot-melt extrudates containing diltiazem hydrochloride and citric acid monohydrate, interactions between a crystalline drug and a plasticizer may promote drug solubilization in the polymer during extrusion at temperatures below the drug melting point [24]. All produced extrudates exhibited peaks in the PXRD patterns that were characteristic for anhydrous theophylline. The theophylline peaks for extrudates containing only 10% plasticizer were of lower intensity when compared to extrudates containing 20% plasticizer. These findings demonstrated that high extrusion temperatures rather than the presence of larger plasticizer amounts promoted theophylline solubilization during extrusion, and were in agreement with previous results [13]. Solubilization of the drug during thermal processing may lead to physical instabilities in the form of surface recrystallization during storage when the drug solubility in the polymer is exceeded [25]. Therefore, higher plasticizer levels (20% absolute or 40% based on the polymer weight) should be used to enable the extrusion of Eudragit® S100 at lower temperatures and to improve the storage stability of the pellets.

6.4.3 Influence of plasticizer type and level on the release properties and HME yield of Eudragit® S100 pellets

Numerous studies addressing the effects of plasticizers on the physicochemical properties of free films and on the drug release properties of film-coated products have been published in the literature. Generally, a decrease in drug release rate was observed with higher degree of plasticization due to enhanced polymer coalescence during the coating process [26], resulting in reduced water permeability [27] and improved mechanical integrity of the film [28]. Furthermore, aqueous solubility of the plasticizer could be correlated with increased drug release rates. Hydrophilic plasticizers leached

into the dissolution medium and promoted water uptake and crack formation in the film [29, 30], while lipophilic plasticizers remained in the coating during dissolution [31, 32].

Few studies, however, have investigated the mechanisms by which plasticizer type and concentration affect the dissolution properties of drugs from melt extruded, polymeric matrix systems. Zhu and coworkers showed that the release rate of water-soluble model drugs from hot-melt extruded tablets increased at higher TEC levels due to a faster drug diffusion through water-filled channels that were formed when the plasticizer leached from the matrix. In contrast, increased TEC levels produced slower drug release rates from coated pellets due to enhanced film coalescence, and from compressed matrix tablets due to promoted particle binding [33, 34]. Analogous to film coated systems, plasticization of matrix systems with water-soluble compounds correlated with faster release rates, while lipophilic plasticizers retarded the drug release [35, 36].

As can be seen in Table 6.3 and Fig. 6.3 and 6.4, the theophylline release from Eudragit® S100 pellets was similar and remained below 10% in acid when moderately soluble TEC (1 part dissolves in 15 parts water) or slightly soluble methylparaben (1 part dissolves in 400 parts water) was used as the plasticizer. At low pH, Eudragit® S100 was insoluble and polymer dissolution was negligible, so that drug release was expected to be primarily governed by diffusion processes. Increasing the plasticizer level from 0 to 10 or 20% did not compromise the gastric resistance of the pellets. Higher extrusion temperatures were used for the extrusion of pellets without plasticizer or 10% plasticizer and promoted the formation of completely coalesced matrices. Pellets containing PEG 8000 yielded a faster drug release rate at the 10% level (18.2% released after 2 hours in SGF without pepsin), and a complete loss of the enteric properties at the 20% level (83.2% released after 2 hours) (Fig. 6.5). Although PEG is very water soluble (50%), its

high molecular weight should impede rapid PEG migration into the dissolution medium during the acidic phase. The presence of high PEG amounts in the pellet matrix may promote water penetration and hence increase drug diffusion through the hydrated polymer matrix.

After 2 hours in acid, the pH was increased to 7.4 to allow ionization and dissolution of the polymer. At high pH, theophylline could be released from the matrix by different mechanisms including polymer surface erosion, diffusion through swollen polymer gels, or diffusion though water filled channels that were generated by bulk polymer erosion or dissolution of soluble plasticizers. The drug release rates in Table 6.3 were calculated from the slopes of the linear portion of the release profiles in Fig. 6.3-6.5 after pH change (R^2 = 0.988-0.998 for the initial 45 minutes). It could be demonstrated that low levels of TEC or PEG 8000 did not significantly alter the theophylline release rate in buffer when compared to pellets without plasticizer, while the presence of 10% methylparaben slightly promoted the drug release.

Increasing the amount of plasticizer to 20% resulted in a significantly faster drug release rates for TEC- and methylparaben-plasticized pellets. The release rate in buffer was not calculated for pellets with 20% PEG 8000 since most of the drug had already been liberated during the acidic phase. Faster drug release rates from matrices containing high plasticizer levels might be attributed to facilitated water penetration, resulting is accelerated polymer ionization and pellet dissolution. Bruce and coworkers demonstrated that an increase of TEC from 12 to 23% in melt extruded Eudragit® S100 tablets promoted drug release due to a faster onset of TEC dissolution from the matrix after pH change [37]. Similarly, faster drug release rates at higher plasticizer level due to enhanced water ingression were observed for hot-melt extruded matrix tablets based on Eudragit® L100-55 and TEC [38].

Surprisingly, pellets comprising 20% methylparaben exhibited a significantly faster drug release rate than the TEC-plasticized pellets with 78.4% released versus 59.8% released in 1 hour after pH change. This result was unexpected since TEC exhibits higher aqueous solubility and possesses mores sites for hydrogen bonding than methylparaben. Fadda and colleagues reported that the dissolution time of plasticized Eudragit® S100 films correlated to a larger extent with the ability of the plasticizer to interact with the polymer than with the aqueous solubility of the plasticizer. Strong plasticizer – polymer interactions disrupted the polymeric structures and increased the local mobility of the carboxylic acid groups, making them more accessible for ionization and promoting film dissolution [39]. It was further observed that methylparaben-plasticized Eudragit® S100 showed an increased tendency for elastic recovery upon die exit, since the extruded strands exhibited a significantly larger diameter (Table 6.1). This elastic expansion of the matrix might decrease the packing density of the polymeric chains and facilitate water penetration, resulting in faster drug release rates.

A mixture design of experiments was employed to identify the optimum plasticizer type and amount for the extrusion of Eudragit® S100 pellets. Three response parameters were selected including minimum drug release after 2 hours in acid, maximum yield of extruded material and maximum drug release after 45 minutes in buffer (Table 6.3). As expected, the yield increased with the plasticizer level and decreased with the amount of Eudragit® S100 in the formulation, since lower melt viscosities enhanced the extrudate output (Fig. 6.6). While the dissolution rate in acid was dependent on the type of plasticizer present in the formulation, the drug release in buffer was rather independent of the plasticizer type at the low level, but increased significantly for the 20% level. The extrusion of pellets with 20% methylparaben produced the highest yield and exhibited the most favorable release properties. Statistical analysis of

the experimental results suggested the optimized composition to contain methylparaben as the plasticizer at a 19.5% level.

6.4.4 Mechanical properties of extruded matrix pellets

Most post-pelletization procedures including functional coating, compression into tablets, or filling into gelatin capsules require low friability and high mechanical strength of the multiparticulates. In the current study, the mechanical strength of hot-melt extruded pellets was determined by diametral compression, a method that has been reported to be adequate for mechanical strength evaluation of spherical specimens and regularly shaped cylinders [17]. As can be seen in Fig. 6.7, melt extruded pellets without plasticizer exhibited the highest tensile strength with 40.4 MPa. The tensile strength values of the melt extruded Eudragit® S100 pellets were higher than those reported for wet-massed extruded pellets containing dispersions of acrylic polymers as granulation binder [15, 40]. However, a comparison of the mechanical strength data obtained for melt extruded cylindrical pellets to wet-massed spherical pellets is difficult due to differences in the used materials, specimen size and geometric shape. Wet-massed pellets mainly fail by adhesive or cohesive fracture or crack propagation of flaws in case of porous pellets [15]. In contrast to wet-massed matrices, hot-melt extruded dosage forms generally exhibit very low porosity, which is attributable to the high temperature and pressure during the extrusion process [41]. Hence, pore-mediated crack initiation and breakage by crack propagation are rather unlikely mechanisms of failure. Furthermore, melt extruded matrices are highly coalesced and held together by intermolecular forces and physical entanglement between polymeric chains, while wet-massed pellets remain agglomerates of distinct particles. This difference in strength of cohesive forces and the lack of pores were responsible for the high mechanical strength of the melt extruded pellets.

The presence of a plasticizer in the formulation led to a decrease in the mechanical strength of the extruded pellets (Fig. 6.7). This observation was expected since plasticizers attenuate the interactions between polymer chains [42], and in agreement with previous reports on wet-massed pellets containing increasing amounts of plasticizer in an acrylic binder dispersion [40]. Pellets without plasticizer and pellets containing 10% plasticizer underwent failure by brittle fragmentation as seen by a sharp decline in stress after pellet fracture. The mechanical properties of these pellets were dominated by the polymer, which has a high glass transition temperature and is brittle at room temperature. The tensile strength values for pellets containing methylparaben and TEC were similar and plateaued at 10%, since no significant decrease in tensile strength was detected for pellets with 20% plasticizer. In contrast, pellets containing 20% PEG 8000 showed a further significant decrease in tensile strength, and underwent plastic deformation post failure as seen by a yield point instead of a peak in the load-deflection profile. PEG itself is a soft, waxy material that has been used to increase the plastic deformability of microcrystalline cellulose pellets during tableting [43]. PEG was further shown to function as a cushioning excipient for the direct compression of functionally coated pellets due to its ability to deform plastically under low yield pressures [44]. It is likely that both factors, the plasticizing effect of PEG on the acrylic polymer and the tensile properties of PEG itself contributed to the decreased mechanical strength and increased tendency to plastic deformation of pellets containing high amounts of PEG 8000.

6.5 CONCLUSION

The results of this study demonstrated that the plasticizer type and level influenced the processibility by hot-melt extrusion, the solid-state properties of the

incorporated drug, the mechanical strength and the drug release properties of Eudragit® S100 matrix pellets. The three selected plasticizers (PEG 8000, TEC and methylparaben) reduced the extrusion torque, the relative melt viscosity and the activation energy for the viscous flow of the polymer in a concentration dependent manner. The solid-state plasticizers were distributed within the polymer matrix in the amorphous state after hot-melt extrusion, while the model drug theophylline remained crystalline. High extrusion temperatures used for processing blends with low plasticizer levels promoted drug solubilization in the polymer and may lead to physical instabilities during storage. The drug release in acidic conditions remained below the required limit of 10% after 2 hours when slightly water-soluble methylparaben or moderately soluble TEC was used, independent of the plasticizer level. Pellets with water-soluble PEG 8000 showed increased drug release rates in acid at the 10% level and a complete loss of enteric properties at the 20% level. Low plasticizer levels did not influence the drug release rate at pH 7.4, while pellets plasticized with 20% TEC or methylparaben released the drug at a significantly faster rate. The mechanical strength of melt extruded pellets was high and decreased when plasticizers were added to the formulation. Pellets containing 20% PEG 8000 exhibited significantly lower tensile strength values and an increased tendency of plastic deformation.

Efficient plasticizers should be used at the high level (20%) for the hot-melt extrusion of Eudragit® S100 pellets to enhance process output and avoid high extrusion temperatures. Methylparaben at the 20% level was shown to be the most adequate plasticizer in terms of processibility and dissolution properties of the enteric matrix pellets.

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6.7 TABLES

Table 6.1: Composition of hot-melt extruded Eudragit® S100 pellets, extrusion temperatures and diameters of the extruded strands.

Plasticizer	Plasticizer Amount [%]	Eudragit® S100 [%]	Theophylline [%]	Extrusion Temp. [°C]	Strand Diameter ± SD [µm]
none	0	70	30	220	598 ± 16
TEC	10	60	30	180	687 ± 19
TEC	20	50	30	140	655 ± 36
PEG 8000	10	60	30	180	640 ± 17
PEG 8000	20	50	30	140	625 ± 21
Methylparaben	10	60	30	180	737 ± 17
Methylparaben	20	50	30	140	773 ± 32

Table 6.2: Activation energies for the viscous flow of unplasticized Eudragit® S100 and melts plasticized with either TEC, PEG 8000 or methylparaben (MP) as calculated from the slopes of the Arrhenius plots.

Formulation	none	10% TEC	10% PEG	10% MP	20% TEC	20% PEG	20% MP
E_a [kJ/mol]	106.4	80.3	86.4	83.7	58.5	45.6	51.8
R^2	0.992	0.999	0.995	0.999	0.990	0.984	0.984

Table 6.3: Experimental plan of the mixture design and observed responses for hot-melt extruded Eudragit® S100 pellets containing 30% theophylline and three plasticizers (TEC, PEG 8000 or methylparaben = MP) at two levels (10 or 20%). Release rates were calculated for the initial 45 minutes after pH change. (*) significantly higher values (one-way ANOVA with $\alpha = 0.05$ and $p < 0.0001$, Tukey Kramer post hoc).

Plasticizer Type	Plasticizer Level [%]	HME Yield [%]	Release in Acid after 2 hrs [%]	Release in Buffer after 45 min [%]	Release Rate [%/ hr ± SD]	R^2-Value (Release Rate)
none	0	6.4	5.91± 0.13	31.28 ± 1.88	33.60 ± 2.56	0.988
TEC	10	12.0	4.18 ± 0.18	28.22 ± 1.46	32.38 ± 2.02	0.998
TEC	20	18.3	7.14 ± 0.04	51.77 ± 1.71	59.83 ± 2.24*	0.997
MP	10	13.3	5.66 ± 0.17	36.66 ± 1.56	41.78 ± 2.09*	0.997
MP	20	23.3	3.85 ± 0.08	61.61 ± 0.82	78.44 ± 0.91*	0.997
PEG	10	9.0	18.23 ± 0.42	41.32 ± 3.51	31.52 ± 4.85	0.980
PEG	20	15.5	83.24 ± 1.98	90.69 ± 0.95	-	-

6.8 FIGURES

Figure 6.1: Influence of plasticizer type and level on the Arrhenius plots for blends containing Eudragit® S100 and 30% theophylline. (△) no plasticizer; (×) 10% PEG 8000; (□) 10% TEC; (◆) 10% methylparaben; (▲) 20% PEG 8000; (■) 20% TEC; (◇) 20% methylparaben.

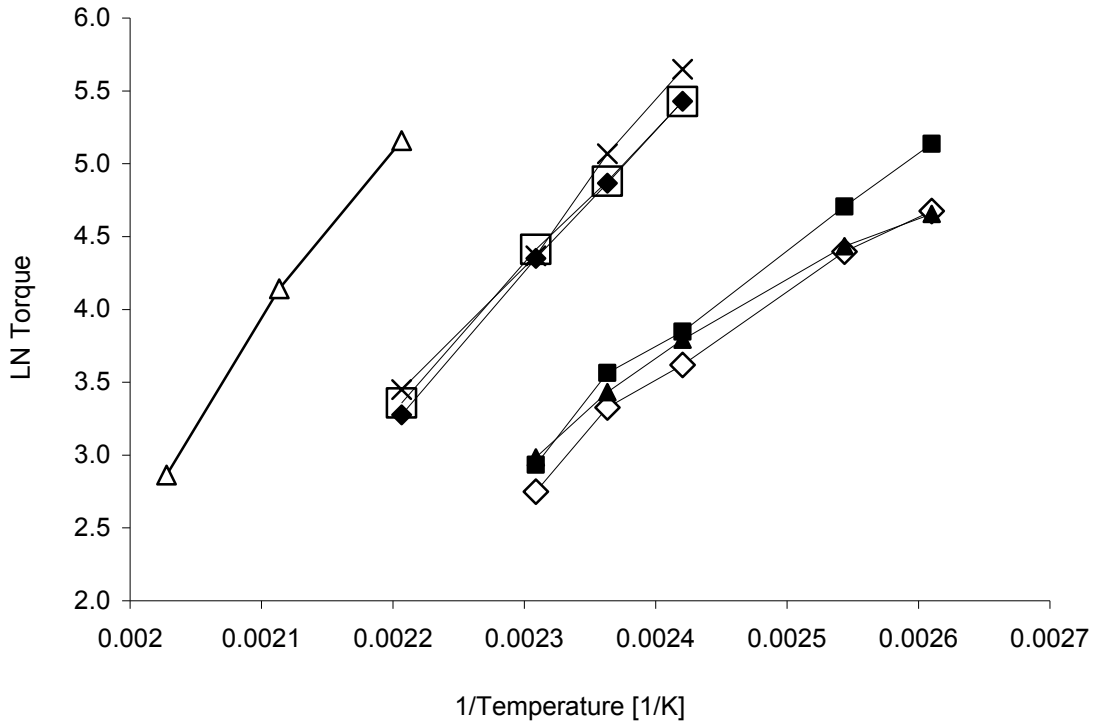


Figure 6.2: Differential scanning calorimetry profiles of physical mixtures (PM) and hot-melt extrudates (EX) containing Eudragit® S100, 30% theophylline (Theo) and 20% methylparaben (MP) or PEG 8000.

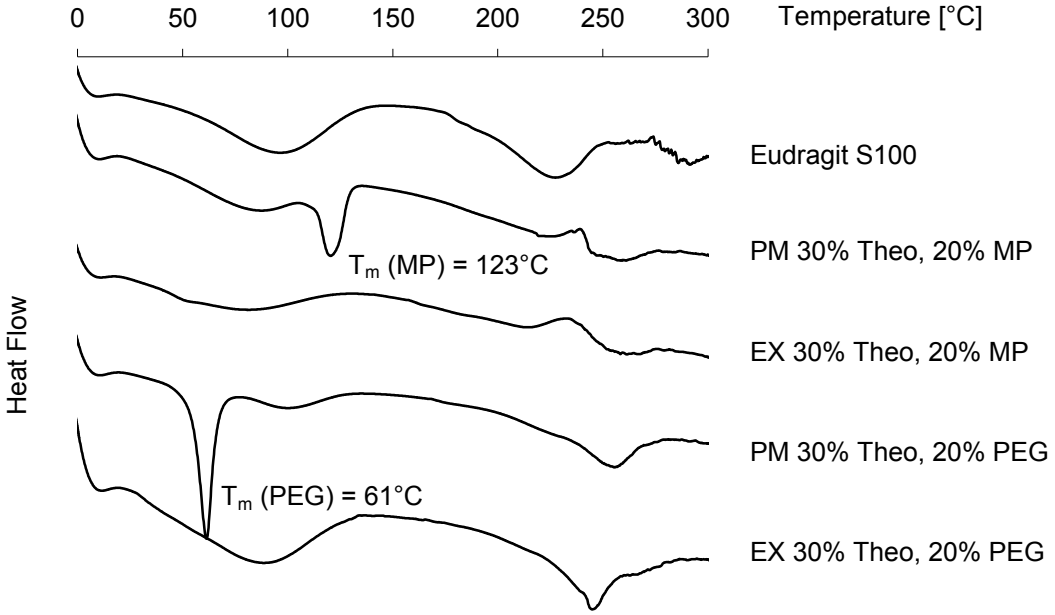


Figure 6.3: Influence of TEC content on the drug release from melt extruded pellets containing 30% theophylline and Eudragit® S100 as the matrix former.
(×) no plasticizer, (◆) 10% TEC, (□) 20% TEC.
Dissolution: USP paddle apparatus, 50 rpm, 37±0.5°C, n = 3, 2 hours in 750 ml SGF pH 1.2 without pepsin, after 2 hours pH change to pH 7.4 by addition of 250 ml 0.2M tribasic phosphate buffer and NaOH solution.

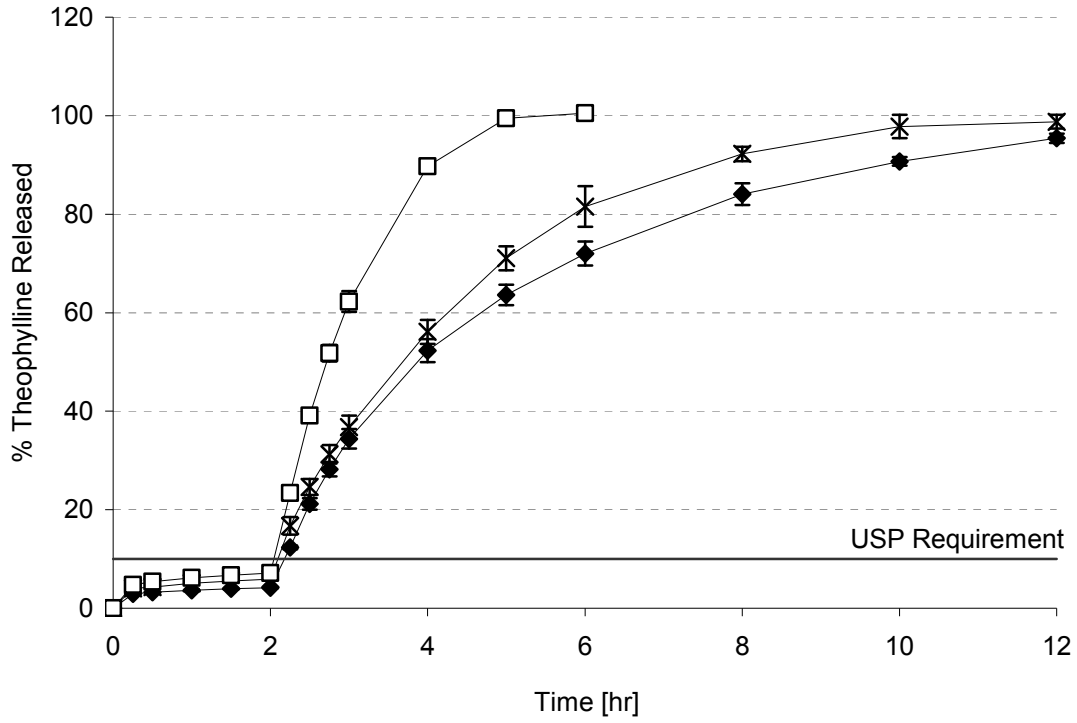


Figure 6.4: Influence of methylparaben content on the drug release from extruded pellets containing 30% theophylline and Eudragit® S100 as the matrix former.
(×) no plasticizer, (◆) 10% methylparaben, (□) 20% methylparaben.
Dissolution: USP paddle apparatus, 50 rpm, 37±0.5°C, n = 3, 2 hours in 750 ml SGF pH 1.2 without pepsin, after 2 hours pH change to pH 7.4 by addition of 250 ml 0.2M tribasic phosphate buffer and NaOH solution.

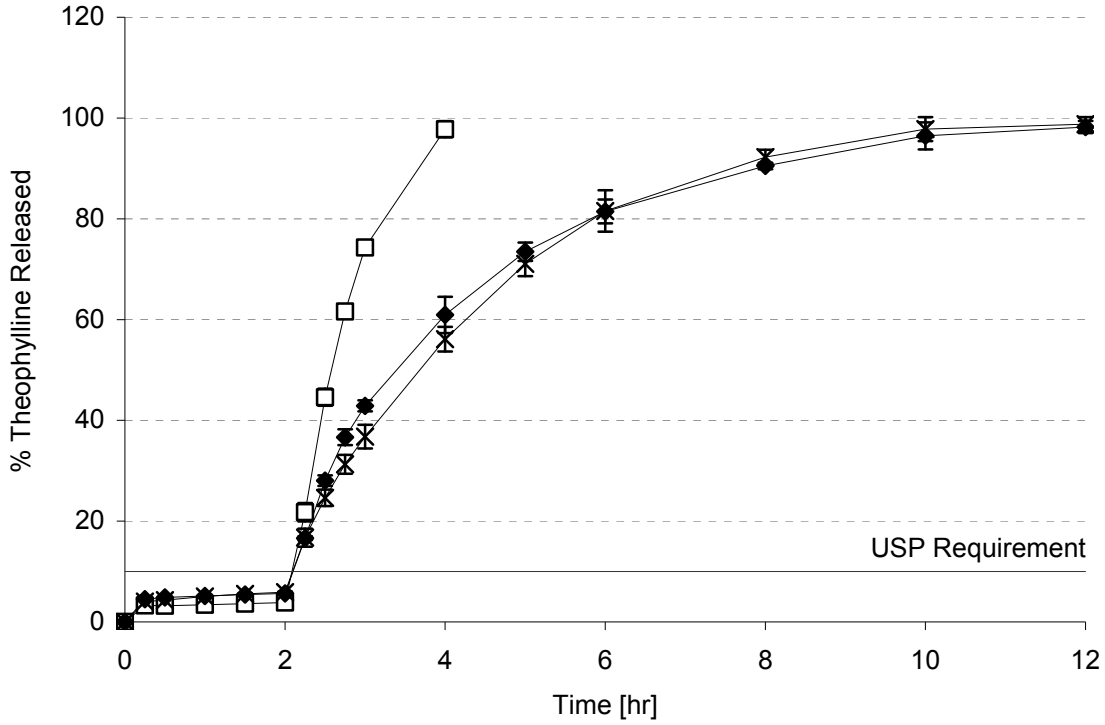


Figure 6.5: Influence of PEG 8000 content on the drug release from extruded pellets containing 30% theophylline and Eudragit® S100 as the matrix former.
(×) no plasticizer, (◆) 10% PEG, (□) 20% PEG.
Dissolution: USP paddle apparatus, 50 rpm, 37±0.5°C, n = 3, 2 hours in 750 ml SGF pH 1.2 without pepsin, after 2 hours pH change to pH 7.4 by addition of 250 ml 0.2M tribasic phosphate buffer and NaOH solution.

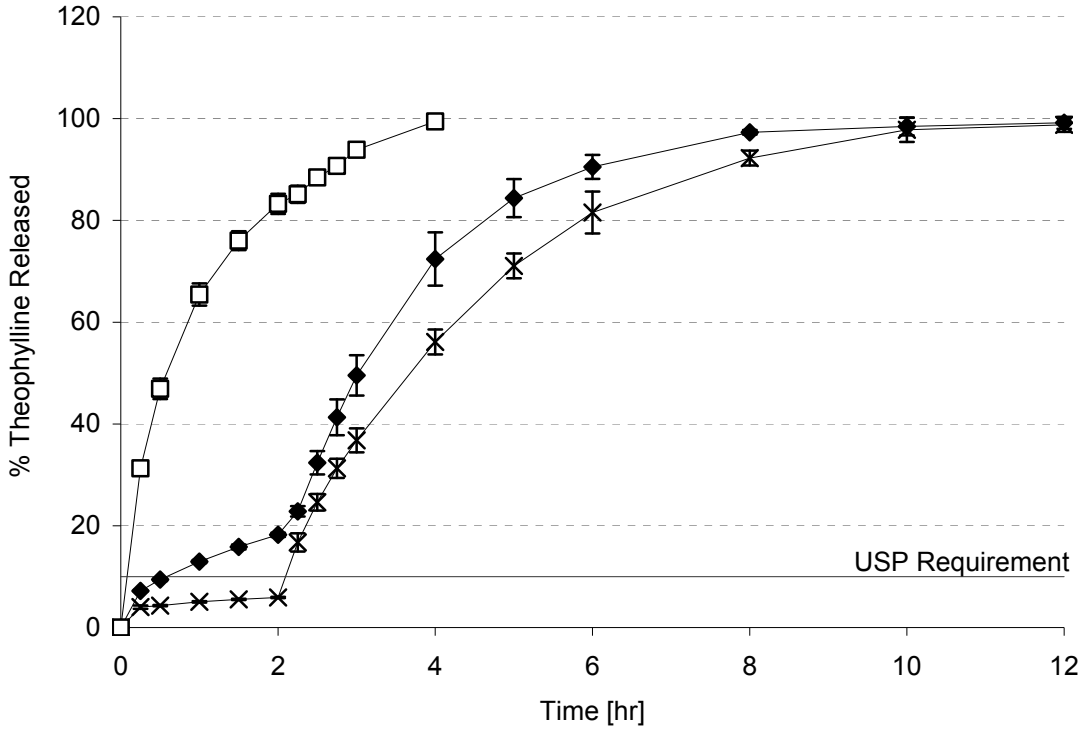


Figure 6.6: Graphic analysis of the effects of plasticizer type and amount on the release properties in acid pH 1.2 and buffer pH 7.4, and on the hot-melt extrusion (HME) yield as obtained by the mixture design of experiments. The optimized composition consists of 30% theophylline (constant), 50.52% Eudragit® S100 and 19.48% methylparaben (MP).

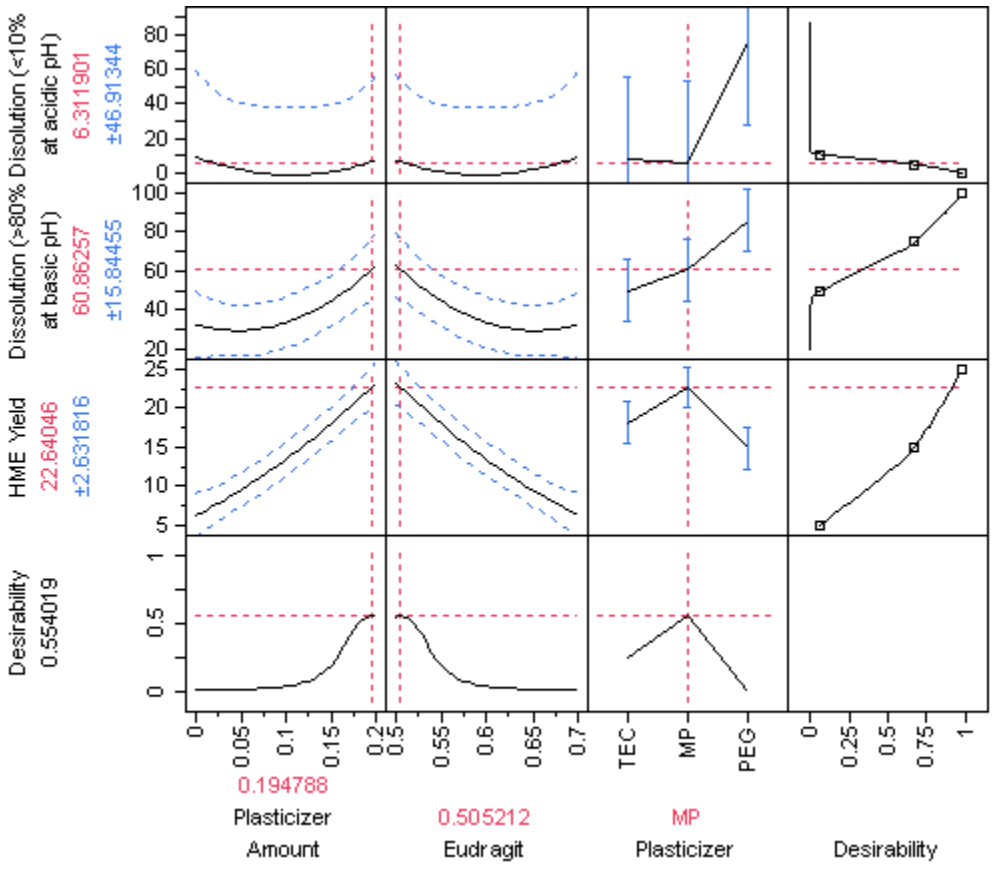
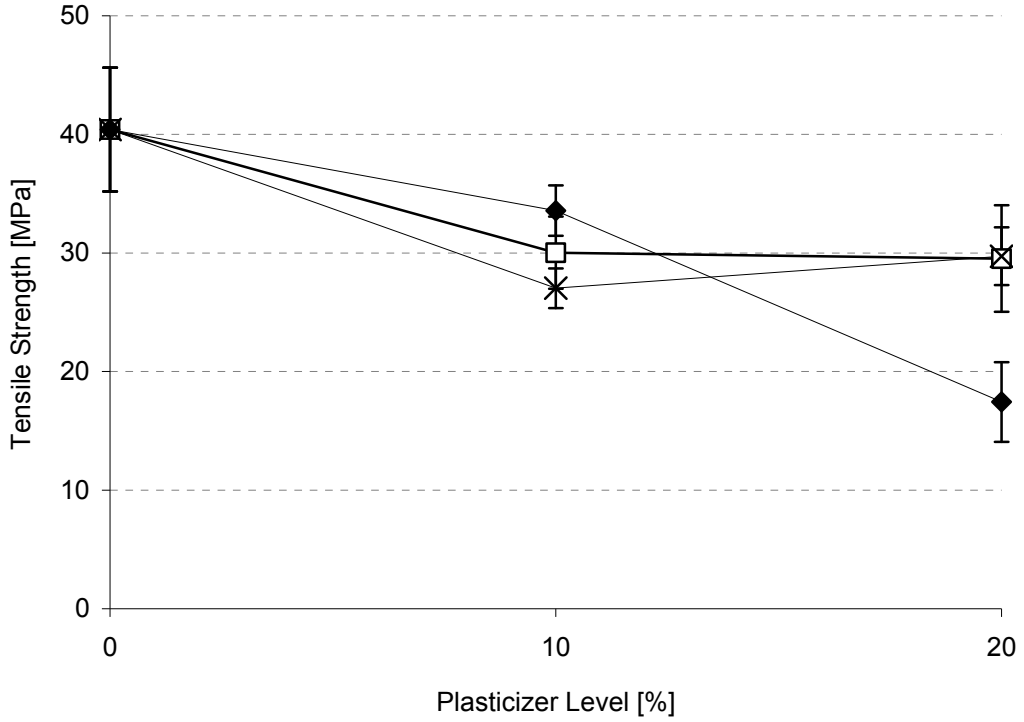


Figure 6.7: Tensile strength of melt extruded Eudragit® S100 pellets containing 30% theophylline as a function of plasticizer type and level.
(×) Methylparaben; (□) TEC; (◆) PEG 8000.
Diametral compression analysis of individual pellets (mean ± SD, n = 6).



Chapter 7: Study of Formulation and Processing Factors that Impact the Applicability of Hot-Melt Extrusion for the Embedment of Enteric Coated Particles into Multiparticulate Monolithic Matrices

Abstract:

The objective of this study was to investigate a novel application of hot-melt extrusion for the preparation of multiparticulate matrices with preserved delayed drug release properties. Particles of different mechanical strength (theophylline granules, extruded and spheronized pellets and layered microcrystalline cellulose spheres) were enteric coated with an aqueous Eudragit® L30D-55 dispersion and characterized regarding potency, moisture content, dissolution properties and tensile strength by diametral compression analysis. Six hydrophilic polymers including polyethylene glycols, poloxamers and polyethylene oxides were studied as carrier materials for the particle extrusion. Dissolution testing of hot-melt extruded matrices showed that the particles remained enteric after extrusion in poloxamer 407 independent of their mechanical strength, which demonstrated that the film and particle integrity was not compromised by mechanical forces. However, the drug release properties were dependent on the nature of the carrier polymer. The miscibility between the carrier materials and the enteric coating polymer was studied by differential scanning calorimetry. High miscibility correlated with increased film permeability and higher drug release in acidic media due to a partial solubilization of the film coating by the carrier polymer during the extrusion process. Poloxamer 407 exhibited a lower miscibility with the enteric polymer than the polyethylene glycols or poloxamer 188. Matrices containing up to 40% enteric pellets in poloxamer 407 were compliant with the USP requirements for delayed drug release dosage forms, and the release profile remained stable when stored at room

temperature for one year. It was demonstrated that drug granules of low mechanical strength and coated with brittle Eudragit® L30D-55 could be successfully processed into enteric, multiparticulate matrices by hot-melt extrusion, but failed the enteric test when directly compressed into tablets.

7.1 INTRODUCTION

Oral dosage forms providing controlled drug delivery can be classified as monolithic or multiple-unit systems. Biopharmaceutical advantages of multiple-unit dosage forms include reduced gastric transit time, reduction of food effects and a more uniform distribution along the intestinal tract, promoting higher and less variable bioavailabilities [1]. With regard to the final dosage form, monolithic systems are preferred to ensure patient compliance and dosing accuracy. Post-processing technologies include compression of the controlled release particles into multiparticulate tablets or particle filling into capsules. Tableting of functionally coated particles has experienced increasing popularity due to several advantages over encapsulation techniques. Multiparticulate tablets can be manufactured at lower costs and higher output rates than capsules using commonly available tablet presses. Tablet dosage forms are less sensitive to moisture, may be divided to increase dosing flexibility and are less susceptible to tampering when compared to capsules [2].

However, the tableting of functionally coated particles is technologically more challenging than the compression of traditional powder blends. The exertion of unidirectional compaction forces on particles such as pellets, granules or microspheres may induce their deformation and/ or fragmentation. Functionally coated particles may experience a loss of their controlled release properties when the film coating is damaged

during the compaction process. This problem has been reported for particles coated with brittle polymers including ethylcellulose [3-5], Eudragit® RS/RL mixtures [6] or enteric polymethacrylates [7-9]. Strategies to preserve the modified release properties during compression include the application of films of high flexibility [7, 8, 10] or increased thickness [7, 11, 12], reducing the tablet surface area [13] or using appropriate cushioning excipients [9, 14, 15]. However, particles with highly flexible films are more difficult to prepare, tend to agglomerate during compression and are more susceptible to storage instabilities. Pellet tackiness and agglomeration has been reported for pellets coated with flexible Eudragit® NE 30D films [16]. Partial film fusion of pellets coated with Eudragit® FS 30D during tableting has been associated with slow tablet disintegration [12]. Films that are applied as aqueous dispersions and exhibit low glass transition temperatures may experience physical aging due to continuing coalescence during storage, resulting in decreasing drug release rates as a function of storage time and temperature [17]. The requirement for controlled release particles to remain intact during compression implicates that these particles do not contribute to tablet hardness in form of plastic deformation, densification or brittle fragmentation. As a result, tablet strength decreases and tablet friability increases when high particle loads are present in the tablet [18]. Large amounts of cushioning and highly compressible tableting excipients limit the particle load, but become necessary to absorb compaction forces, to physically separate the particles during compression and to produce tablets of acceptable hardness with low friability. Differences in particle size and density between pellets and tableting excipients further promote blend segregation during tableting and may result in poor content uniformity of the final multiparticulate tablets. Increasing the particle loads in the formulation or granulation of the filler has been demonstrated to improve content uniformity [19, 20].

Hot-melt extrusion has been recognized as a valuable technology for the preparation of a large variety of pharmaceutical dosage forms including matrix tablets, pellets, films and implants [21, 22]. The objective of this study was to investigate a novel application of hot-melt extrusion as an alternative method to tableting for the preparation of multiparticulate monolithic matrices comprising enteric coated particles with preserved delayed release characteristics. Our hypothesis was that shortcomings as they are encountered with pellet compaction technologies may be overcome by using hot-melt extrusion. Unidirectional compaction forces which potentially damage the integrity of the particle core and the film coating are absent during extrusion, making the process amenable to particles of low mechanical strength or particles with brittle film coatings. Relevant formulation and processing factors influencing the properties of multiparticulate, melt extruded tablets were investigated in the current study. Three types of particles exhibiting differences in mechanical strength (theophylline granules, pellets and layered microcrystalline cellulose spheres) were enteric coated with Eudragit® L30D-55 and characterized regarding tensile strength and dissolution properties. The thermal behavior of six potential carrier polymers for the particle extrusion was studied, and their thermal miscibility with the coating polymer was analyzed by differential scanning calorimetry to evaluate potential film solubilization during the extrusion process. The influence of the carrier polymer, particle load and the particle strength on the preservation of the enteric properties during hot-melt extrusion was investigated. The release properties of a poloxamer 407 matrix comprising 30% soft enteric granules were compared to a directly compressed tablet, and the stability at ambient storage conditions was studied.

7.2 MATERIALS

Anhydrous theophylline, glycerol monostearate (powder, food grade) and polysorbate 80 (Tween® 80, NF) were purchased from Spectrum Chemicals (Gardena, CA). Avicel® PH-101 (NF) and Ac-Di-Sol® were donated by FMC BioPolymer (Newark, NJ), and hypromellose E3 (Pharmacoat® 603) was obtained from Shin-Etsu (Tokyo, Japan). Kollidon® K25, theophylline granules, poloxamer 188 (Lutrol® F 68) and poloxamer 407 (Lutrol® F 127) were kindly provided by BASF Corp. (Ledgewood, NJ). Polyethylene glycols (PEG 4000 and 8000, Carbowax Sentry™), polyethylene oxide 100K (PEO 100K, Sentry Polyox™ WSR N-10 NF) and polyethylene oxide 200K (PEO 200K, Sentry Polyox™ WSR N-80 NF) were donated by Dow Chemical Company (Midland, MI). Microcrystalline cellulose spheres (MCC spheres, Ceolus™ CP-305) and Ceolus™ KG-802 were kind gifts from Asahi Kasei America, Inc. (New York, NY). Triethyl citrate (TEC) was provided by Vertellus (Greensboro, NC), and Eudragit® L30D-55 and Eudragit® L100-55 were donated by Evonik (Piscataway, NJ).

7.3 METHODS

7.3.1 Preparation of core pellets

Pellets containing 30% theophylline were prepared by wet-mass extrusion and spheronization. The drug and Avicel® PH-101 (62.5%) were premixed in a kitchen aid mixer (St. Joseph, MI), and an aqueous Kollidon® K25 solution (equivalent to 7.5% Kollidon® K25 in the final dry formulation) was added under stirring to form a wet mass of appropriate consistency. After manual pre-kneading, the mass was processed with a Benchtop granulator (LCI Corp., Charlotte, NC) equipped with a 0.6 mm screen and operated at a blade rotation speed of 50 rpm. The extruded strands were transferred into a

spheronizer (Caleva Model 120, Dorset, UK) and mesmerized at 700 rpm for 3 minutes. After oven drying at 40ºC for 24 hours, the pellets were sieved and the 300-500 μm fraction was used for functional coating.

7.3.2 Active layering of MCC spheres

A binder solution (2%) was prepared by dissolving hypromellose E3 in deionized water under magnetic stirring. Theophylline (10%) was added to the binder solution under high-shearing with a Polytron homogenizer (Kinematica Inc., Newark, NJ), and the obtained suspension was homogenized for another 10 minutes. The theophylline-binder dispersion was sprayed onto MCC seed cores (Ceolus™ CP-305, particle size 300-500 μm) in a Strea-1 fluidized-bed coater (Aeromatic-Fielder, Bubendorf, Switzerland) with bottom set-up and a Wurster column. The dispersion was stirred during the process and applied with a peristaltic pump through a 1.0 mm nozzle at an atomizing air pressure of 1.5 bars. The inlet temperature was 75°C and the outlet temperature was 50-51°C. The dispersion was sprayed at 10 g per minute and kilogram to obtain MCC spheres with a potency of 10% theophylline. The dried particles (40ºC, 24 hours) were sieved, and the 300-500 μm fraction was used for the enteric coating trial.

7.3.3 Moisture content

The moisture content of the core particles (granules, pellets or active MCC spheres) was determined after equilibration at 25±1°C and 50±5% RH for 24 hours and prior to enteric coating using a moisture analyzer AND MF-50 (A&D Engineering, Inc., Milpitas, CA). In accordance with the USP loss on drying method, 1 g of particles was accurately weighed into a dried aluminum dish and maintained at 110ºC until a constant

weight was achieved (weight loss below 0.02%/ min). The average percent weight loss of three measurements was reported as the moisture content.

7.3.4 Functional film coating

Drug-layered MCC spheres, theophylline granules (300-500 μm) and self-made pellets were film coated to a polymer weight gain of 50% in the above described fluid bed coater using an aqueous dispersion of Eudragit® L30D-55. The composition of the coating dispersion is shown in Table 7.1, and the dispersion was prepared as recommended by the polymer manufacturer [23]. The process parameters are detailed in Table 7.2. The polymeric dispersion was stirred continuously throughout the coating process to prevent the sedimentation of solids. The film coated particles were dried and sieved, and the 300-500 μm fraction was selected for further analysis and processing.

7.3.5 Mechanical strength testing

The tensile strength of the three different types of particles before and after enteric coating was determined with a Chatillon Universal Tension / Compression Tester Model TCD-200 (Ametek, Largo, FL) as previously described [24]. Briefly, a flat, circular steel plate was fitted onto a DFGS 50 digital force gauge and lowered in diametral direction towards an individual pellet at a crosshead speed of 2.5 mm/ min. The load-deflection data was collected using Chatillon Nexygen TCD force testing software. The mechanical strength was reported as the average tensile strength of 20 specimens and calculated using the Hiramatsu-Oka equation:

$$\sigma = \frac{2P}{\pi d^2}$$

The diameter (d) of each individual particle was obtained from the distance of the crosshead plate from the base at the moment of load buildup, and the maximum load (P) at which brittle fragmentation of the pellets occurred was used for the calculation of the tensile strength. Statistical analysis was performed with JMP® 7 software (SAS Institute Inc., Cary, NC) considering an α-level of ≤ 0.05 statistically significant. One-way ANOVA and post hoc Tukey-Kramer test were employed to evaluate the influence of the particle type on the mechanical strength. The mechanical strength before and after enteric coating was compared using the two-sided t-test for dependent data.

7.3.6 Hot-melt extrusion of multiparticulate matrices

Functionally coated particles (30%, unless stated otherwise) were blended with a hydrophilic carrier polymer (70%) and extruded into circular strands using a single screw Randcastle extruder (model RCP 0750 Microtruder, Nitralloy 135M screw, Cedar Grove, NJ) equipped with a 6 mm rod-shaped die. Six polymers were studied as the hydrophilic carriers including PEG 4000 and 8000, poloxamer 188 and 407 and PEO 100K and 200K. The temperature settings in the three heating zones and in the die zone were selected based on the melting point and the viscosity of the individual polymers and are listed in Table 7.3. The extruded strands were cooled to room temperature and cut with a razor blade to obtain tablets containing 200 mg enteric particles.

7.3.7 Differential scanning calorimetry

The miscibility between the enteric polymer and the carrier polymers was investigated by differential scanning calorimetry (DSC) to evaluate the potential for solubilization of the enteric film in the tablet matrix during hot-melt extrusion. Samples

(15±3 mg) were accurately weighed into aluminum pans, crimped sealed and placed inside the furnace of a Thermal Advantage Model 2920 (TA Instruments, New Castle, DE). The carrier polymers were heated either alone or in the presence of an equal amount of Eudragit® L100-55 at 10°C/ min to a temperature of 10 degrees above the extrusion temperature and kept isothermal at this temperature for 10 minutes to simulate the hot-melt extrusion process. After quench cooling to 0°C, a second run was performed using the same heating rate. The melting points of the carrier polymers are listed in Table 7.3, and the melting enthalpies were calculated by peak integration using TA Universal analysis 2000 software. The ratio of the melting enthalpies obtained for the second run divided by the melting enthalpies obtained for the first run was used to express the percentage of relative polymer crystallinity after thermal processing. The term "relative crystallinity" was used since the actual degree of crystallinity of the untreated semi-crystalline polymers was unknown.

7.3.8 Direct compression of multiparticulate tablets

Enteric coated granules (30%), microcrystalline cellulose (Ceolus™ KG-802, 65%) and superdisintegrant (Ac-Di-Sol®, 5%) were blended and directly compressed into round tablets (333 mg, equivalent to 100 mg particles) using a single station manual Carver Press (Fred Carver, Menomonee, WI) equipped with a concave, 10 mm diameter die (04-04, #91459, Natoli Engineering, Saint Charles, MO). The compression force was 5 kN, and the tablet hardness was 17.1 ± 1.6 kP as determined with a Varian VK 200 tablet hardness tester (Cary, NC). Two tablets (n = 3) were used for dissolution testing.

7.3.9 Dissolution studies

The dissolution properties of the enteric coated particles before and after hot-melt extrusion or direct compression into multiparticulate matrices were studied in a paddle apparatus (Vankel VK 7000, Varian, Cary, NC) according to the USP chapter <724> method A for delayed release articles. The bath temperature was maintained at 37.0±0.5°C, and the paddle rotation speed was set to 100 rpm. Specimens equivalent to 200 mg particles (n = 3) were initially tested in 750 ml simulated gastric fluid pH 1.2 (SGF without pepsin) for 2 hours, followed by additional 2 hours in phosphate buffer pH 6.8 after adding 250 ml of 0.2M tribasic phosphate buffer to increase the pH. Samples were withdrawn after selected time intervals using a Vankel VK 8000 auto sampler and assayed for theophylline content by HPLC.

7.3.10 Theophylline assay

The amount of theophylline released during dissolution testing was determined by HPLC analysis using a Waters HPLC system (Waters Inc., Milford, MA) equipped with a C_{18}-reversed phase column (Capcell PAK 3 mm*100 mm, Shiseido Co, Japan). The mobile phase consisted of 20 mM phosphate buffer and acetonitrile (9:1) and was delivered at a flow rate of 0.5 ml/min. Theophylline was eluted after 3.5 min, detected with a UV detector extracting at 271.5 nm (996-PDA, Waters Inc.) and quantified by peak area integration using Empower version 5.0 software (Waters Inc.). Linear correlation was confirmed between 0.1 and 100.0 µg/ ml (R^2 = 0.99997), and multiple injections yielded good reproducibility with RSD values between 0.08% (100.0 µg/ ml) and 1.77% (0.1 µg/ ml).

7.4 RESULTS AND DISCUSSION

7.4.1 Characterization of different types of particles

Three different multiparticulate drug carrier systems (theophylline granules, pellets and layered MCC spheres) were prepared and characterized regarding potency, moisture content and mechanical strength before and after functional coating with Eudragit® L30D-55. The potency and moisture content of the different particles before enteric film coating are given in Table 7.4. Drug granules contained 96.3% theophylline, were irregularly shaped and very friable. As can be seen in Fig. 7.1, the tensile strength of the granules was low and increased significantly by applying an enteric film coat (7.31±2.18 MPa before coating versus 9.53±2.75 MPa after coating, paired t-test, $p = 0.0036$). The potency of the extruded and spheronized pellets was intermediate between the granules and the layered MCC spheres (28.2% for pellets, 10.8% for MCC spheres). With regard to the tensile strength, pellets were significantly stronger than granules and significantly weaker that MCC spheres before enteric coating. Film coating did not alter the mechanical properties of the pellets (21.52±3.03 MPa before coating versus 20.03±3.38 MPa after coating, paired t-test, $p = 0.1329$). Uncoated MCC spheres exhibited the highest tensile strength which decreased significantly after film coating (33.58±5.36 MPa before coating versus 24.05±4.49 MPa after coating, $p < 0.0001$). Pellets and MCC spheres were highly spherical and exhibited low friabilities.

The differences in mechanical strength between the different types of particles were attributed to differences in their composition and manufacturing process. The degree of compaction during particle formation influenced the particle porosity and hence the tensile strength. High particle strength was further promoted by larger contents of MCC in the formulation due to the high plasticity of this material, which was confirmed

by the superior tensile strength of the MCC spheres. The influence of enteric film coating with Eudragit® L30D-55 on the mechanical properties was dependent on the tensile strength of the core material. The mechanical robustness of the soft theophylline granules could be enhanced by the application of the film coat. Eudragit® L30D-55 films were demonstrated to be relatively strong and exhibit high tensile strengths and elastic moduli [25]. Similar increases in crushing force after film coating have been previously reported for spheres coated with Eudragit® RS 30D/RL 30D [6] or Eudragit® L30D-55 [9]. Extruded and spheronized pellets exhibited an intermediate tensile strength before functional coating, and the application of a polymeric film did not alter their resistance to diametral compression forces. An independence of particle strength from functional coating has been demonstrated by other groups [26, 27]. These findings indicated that a fracture of the pellet core was the dominating failure mechanism during tensile testing, and that the core and the film exhibited similar mechanical properties. On the other hand, the tensile strength values of enteric MCC spheres decreased when compared to the uncoated material. In this case, the mechanical properties were mainly dictated by the high strength of the core material. The application of a film did not alter the load that was required for particle crushing, but increased the particle size, so that the calculated tensile strength values were smaller than for the uncoated MCC spheres. These results demonstrated that the influence of functional coating on the mechanical properties of the particles was dependent on the mechanical strength of the core material and increasing, decreasing or no effects on the tensile strength could be observed.

7.4.2 Influence of carrier polymers on the dissolution properties of enteric pellets after hot-melt extrusion

Hot-melt extrusion requires the presence of a thermoplastic carrier in the form of a malleable or meltable polymer, wax or lipid [21]. The behavior of the carrier in dissolution media in terms of dissolution rate and swelling characteristics controls the release rate of the active ingredient, and in the case of particle extrusion, the liberation of the multiparticulates from the matrix. Conventional multiparticulate tablets prepared by compaction methods may be formulated with a superdisintegrant to ensure rapid tablet disintegration and particle release in the stomach. The particle release from melt extruded tablets is mainly controlled by the dissolution rate of the carrier due to the lack of matrix disintegration. For this reason, carrier polymers should exhibit high aqueous solubilities and refrain from forming highly viscous gels in dissolution media. It is very important that the carrier exhibits low miscibility with the enteric polymer and a low glass transition temperature or melting point to allow hot-melt extrusion at moderate temperatures. High polymer miscibility and elevated processing temperatures would potentially promote a solubilization and damage of the enteric film during particle extrusion.

Semi-crystalline polymers with low melting points were advantageous since they solidified quickly and showed negligible elastic recovery (die swell) upon extruder exit. Furthermore, physical instabilities during storage in the form of plasticizer migration from the enteric film coat into the matrix or carrier migration into the film were less likely due to the small free volume and low permeability of semi-crystalline materials in the solid state. Six water-soluble polymers with low melting points and semi-crystalline properties were studied as potential carrier materials (Table 7.3): poloxamer 188 and 407, PEG 4000 and 8000, PEO 100K and 400K. The poloxamers and PEG's melted between 57 and 65ºC and could be extruded at temperatures below their melting points (47-55ºC)

since shearing of the material under elevated pressure promoted polymer softening. In a similar manner, it has been demonstrated that lipids can be extruded at temperatures below their melting ranges with 80-90% of the thermal binder remaining in the solid state during the extrusion process. These conditions were shown to reduce the matrix porosity and improve the storage stability of the lipid carrier, since complete melting and recrystallization of metastable modifications were avoided [28]. Polyethylene oxides needed to be processed above their melting point (70ºC) and showed pronounced elastic recovery (die swell), which was probably due to a higher percentage of amorphous regions in these polymers.

Differential scanning calorimetry was employed to investigate the influence of thermal processing on the crystallinity of the carrier polymers and their miscibility with Eudragit® L. All specimens were cycled twice, and the melting enthalpy as detected for the melting point of the crystalline part of the polymer in the second run was related to the melting enthalpy found in the first run, which was considered as 100% crystallinity. The results in Fig. 7.2 show that the relative crystallinity of the poloxamers and PEG's decreased only slightly after heating to 92-96% of their original crystallinity. The effect of thermal treatment on the crystallinity of the PEO's was more significant as it was reduced to 77-78% in the second cycle. This diverging thermal behavior could be explained by differences in molecular weight. The relatively low molecular weights and melt viscosities of the poloxamers and PEG's allowed a quick rearrangement of the disordered chains into ordered crystalline structures during the cooling period after the first cycle. This process was hindered within the highly viscous PEO melts due to the high molecular weights of these polymers (100,000 and 200,000), resulting in an increased portion of amorphous regions after the first heating.

The melting enthalpies of physical mixtures with Eudragit® L100-55 (1:1) in the first run were equivalent to those of the pure polymer. The melting enthalpies in the second cycle were lower due to decreased carrier crystallinity in the presence of the coating polymer (Fig. 7.2). These findings indicated a partial miscibility between all selected carriers and the enteric polymer at elevated temperatures. The formation of miscible phases with the highly viscous methacrylic polymer hindered the recrystallization process of the carrier during the cooling period. This phenomenon was most distinctive for the low molecular weight PEG (relative crystallinity of 9% in second run), and least for the PEO's (61-62%). The miscibility with poloxamer 188 or PEG 8000 was also high (21-24%), while poloxamer 407 yielded only moderate miscibility with the coating polymer (46% relative crystallinity in second run). These results suggested that the PEO's and poloxamer 407 were more suitable carriers for the melt extrusion of enteric particles coated with Eudragit® L30D-55 than the PEG's or poloxamer 188. However, all polymers exhibited a certain degree of miscibility with the coating polymer which might encourage film solubilization during extrusion and compromise the gastric resistance of the particles.

The dissolution profiles of matrix systems containing 30% coated pellets are shown in Fig. 7.3. The release properties in acid were controlled by the permeability of the enteric film and, to a lesser extent, by the dissolution rate of the carrier. As expected from the findings of the DSC studies, the PEG 4000 based matrix yielded high drug release rates in acid with 14.6% theophylline released after 2 hours. Matrices prepared with poloxamer 188, PEG 8000 or the PEO's released the drug to a similar, intermediate extent in acid (9.9-11.2% after 2 hours). Lower molecular weight PEG's have been demonstrated to be unsuitable carriers for Eudragit® L30D-55 coated pellets in congealed matrices since they dissolved the coating and increased the film permeability

[29]. The high miscibility between Eudragit® polymers and PEG's was expected since PEG's are commonly used as plasticizers for polymethacrylic polymers [30]. The lowest drug release in acid was obtained for the poloxamer 407 matrix with 7.4% theophylline released after 2 hours.

The drug release in buffer pH 6.8 was mainly governed by the dissolution kinetics of the carriers since the enteric film dissolved rapidly. Polyethylene oxide matrices formed highly viscous gels acting as barriers towards penetrating water and diffusing drug, which resulted in the slowest drug release after 45 minutes in buffer (72.2% for PEO 100K and 66.3% for PEO 200K). The release profiles of the poloxamer 188 and PEG 4000 matrices were superimposable with those of the original pellets during the buffer phase (> 98.8% released after 45 min), attesting that the polymer matrix was dissolved and the theophylline release rate was only controlled by the dissolution rate of the enteric film. The release from the PEG 8000 matrices yielded an approximate 15-20 min lag phase in buffer, after which the drug was rapidly released to reach 93.4% after 45 minutes in buffer. Hot-melt extruded poloxamer 407 tablets provided an intermediate dissolution profile which was between the fast dissolving carriers and the highly viscous PEO's with 87.1% theophylline released after 45 minutes in buffer pH 6.8. The retarded matrix dissolution of poloxamer 407 compared to poloxamer 188 was attributed to the slightly higher molecular weight (9840–14600 versus 7680–9510) and a higher percentage of less hydrophilic polypropylene oxide units (PEO: PPO ratio of 1.8:1 versus 3.0:1 for poloxamer 188). Targeting the USP requirements of a minimum drug release below 10% in acid and a release higher than 80% in buffer, poloxamer 407 was selected as the particle carrier matrix for the remaining extrusion trials.

7.4.3 Influence of pellet loading on the properties of hot-melt extruded matrices

The properties of compressed tablets containing multiparticulates have been demonstrated to be influenced by the pellet-to-filler ratio. High amounts of pellets in the formulation increase the number of inter-particle contacts, leading to pellet deformation and film damage not only on the tablet surface, but also in the interior of the tablets. The drug release rate from pellets coated with Eudragit® L30D-55 was shown to increase as a function of the pellets content [7, 9]. Partial film fusion and pellet agglomeration during compaction may compromise rapid tablet disintegration as demonstrated for tablets containing Eudragit® FS 30D film coated pellets [12]. High pellet loads may further decrease the mechanical strength and increase the friability of the multiparticulate tablets [18].

Poloxamer 407 matrices containing an increasing amount of pellets (30, 40 and 50%) were prepared by melt extrusion, and their release characteristics were studied. Increasing the pellet load up to 50% did not compromise the processibility, and all formulations could be prepared using the same extrusion conditions. The hardened strands were not friable despite the relatively high amount of non-meltable material in the formulation. The influence of the pellet content on the delayed release properties is shown in Fig. 7.4. Poloxamer 407 matrices containing 30% or 40% enteric pellets were compliant with the USP requirement to release less than 10% of their drug content after 2 hours in acid (7.4% and 9.2%). However, the tablets prepared with 50% pellets failed this criterion with 14.8% theophylline released. Drug dissolution at the buffer stage was independent of the pellet loading and fulfilled the USP requirement to release more than 80% within 45 minutes (84-87%). These results demonstrated that the release properties in acid were the limiting factor for the amount of pellets that could be loaded into the

system, and that multiparticulate extrudates containing up to 40% pellets were in compliance with the USP criteria for delayed release articles.

7.4.4 Influence of type of particles on the preservation of the release properties after hot-melt extrusion

Previous studies by Beckert and coworkers have demonstrated that pellets with high mechanical strength were better able to withstand compression forces during tableting [7]. Excessive deformation or fragmentation of the particle core will result in stretching and eventual rupture of the functional film. As shown in Fig. 7.1, the three different types of particles (granules, pellets and MCC spheres) displayed significant differences in mechanical properties, with granules yielding the lowest and MCC spheres yielding the highest tensile strength. In contrast to compression technologies, an exposure of the coated particles to high unidirectional forces was absent during the hot-melt extrusion process. The shear forces acting on the particles during extrusion are dependent on the carrier viscosity, screw and extruder design and on the shear rate or screw rotation speed. Preliminary studies on pellets of different particle sizes demonstrated that the conveyance of pellets with diameters larger than 500 μm through the extruder was hindered, resulting in increased drug release rates in acid above 10%. Fig. 7.5 shows the influence of the core material on the percentage of theophylline released after 2 hours from melt extruded poloxamer 407 matrix tablets containing 30% enteric particles. All formulations were compliant with the USP criteria for the release in acid and in buffer pH 6.8. All multiparticulate matrices experienced a similar increase in % drug released after extrusion which was between 5.7 and 6.6% and independent of the mechanical strength of the embedded particles. These findings provided evidence that hot-melt extrusion is a suitable process to convert particles of low mechanical strength such as granulated drug

into monolithic dosage forms. Furthermore, the slight increase in drug release was more likely a result of partial solubilization of the film in the carrier polymer during extrusion due to partial polymer miscibility as demonstrated in the DSC study, than a result of mechanical rupture of the film.

7.4.5 Comparison of multiparticulate matrices prepared by hot-melt extrusion versus direct compression and storage stability

Our hypothesis was that hot-melt extrusion technology would be advantageous over direct compression for the preparation of multiparticulate tablets, especially when the particles are of low mechanical strength and coated with tough but brittle polymeric films. High drug loadings as necessary for the formulation of high-dose drugs reduce the mechanical strength of the multiparticulates [31]. Particles coated with polymers forming tough films and exhibiting high glass transition temperatures show reduced sticking tendency and enhanced storage stability when compared to particles coated with highly flexible films. As demonstrated by Zheng and coworkers, pellet agglomeration during the coating process and during storage could be prevented if Eudragit® L30D-55 was added to a Eudragit® NE 30D coating formulation. The presence of Eudragit® L30D-55 in the film coating also decreased the curing time and stabilized the drug release rate during storage [16].

For comparison purposes, tablets containing 30% enteric granules were prepared by direct compression using low compaction forces (5 kN) and a highly compressible MCC grade (Ceolus™ KG-802) as the filler material. The release properties of these tablets were compared to melt extruded poloxamer 407 matrices containing 30% enteric granules (Fig. 7.6). Direct compression of the soft granules coated with Eudragit® L30D-55 resulted in a significant increase in the amount of drug released in acid with 33.8%

released after 2 hours compared to 8.4% for the melt extruded formulation. This loss in gastric protection was presumably attributed to partial film rupture during compaction induced by particle fragmentation at the tablet surface. Similar observations have been reported by other groups for pellets coated with Eudragit® L30D-55 [7] or Kollicoat® MAE [8] when flexible polymers were absent in the coating formulation. The drug release from the melt extruded poloxamer 407 matrix remained below the 10% limit in acid, demonstrating that the enteric film remained to a large extent intact during hot-melt extrusion, and that high film flexibility and particle strength were not required to preserve the enteric release profile of the particles.

Furthermore, the stability of the dissolution profile was investigated after one year of storage at room temperature and ambient humidity. As shown in Fig. 7.6, the drug release after 2 hours in acid decreased only slightly from 8.4 to 7.5%, which was probably due to ongoing film coalescence during storage. The stability of the extruded dosage form could potentially be compromised by several factors including aging of the enteric film, aging of the carrier polymer and migration of the carrier into the enteric coating during storage. The latter mechanism has been proposed as explanation for the increase in drug release during storage at room temperature when pellets coated with TEC-plasticized Eudragit® RS were embedded in a PEG 4000 matrix. This effect was not observed for ethylcellulose coated pellets due to the higher glass transition temperature and lower affinity of this polymer to PEG 4000, impeding a migration of the carrier into the film [29]. Similar aspects and the higher molecular weight of poloxamer 407 compared to PEG 4000 were probably responsible for the good storage stability of the Eudragit® L30D-55 coated particles in hot-melt extruded poloxamer 407 matrices.

7.5 CONCLUSIONS

Enteric particles were prepared by fluidized bed coating of three different core materials, theophylline granules, pellets and layered MCC spheres, using an aqueous Eudragit® L30D-55 dispersion. The multiparticulates exhibited differences in tensile strength, and the effect of functional coating on the tensile strength depended on the initial strength of the uncoated core material.

The enteric particles were processed into multiparticulate matrix systems by hot-melt extrusion using low melting polymers with high aqueous solubility as carrier materials. The preservation of the delayed release profile was demonstrated to be independent of the mechanical strength of the extruded particles, but dependent on the nature of the carrier polymer. These results indicated that the enteric film was more susceptible to solubilization by the carrier polymer during the hot-melt extrusion process than to mechanical rupture due to shear forces. Poloxamer 407 was selected as the carrier since it showed only moderate miscibility with the enteric polymer and produced tablets with optimized dissolution properties. Matrices containing up to 40% enteric pellets in poloxamer 407 fulfilled the USP requirements for delayed release dosage forms to release less than 10% drug after 2 hours at pH 1.2 and more than 80% after 45 minutes at pH 6.8. In contrast to directly compressed tablets, the enteric properties of drug granules exhibiting low mechanical strength and coated with brittle Eudragit® L30D-55 could be successfully preserved when hot-melt extrusion in poloxamer 407 was used for the preparation of the multiparticulate matrices. The release properties of the multiparticulate poloxamer 407 matrices were further demonstrated to be stable for one year when stored at room temperature presumably due to the low tendency of the carrier to migrate into the enteric film.

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7.7 TABLES

Table 7.1: Formulation used for the enteric coating of theophylline particles.

Formulation	Percentage	Amount [g]
Eudragit® L30D-55	12% polymer in dispersion	400 (120g polymer)
TEC	10% based on polymer content	12
GMS	7.5% based on polymer content	9
Tween 80	40% based on GMS	3.6
Water	-	575.4
Solids content	14.46%	144.6
Dispersion	100%	1000

Table 7.2: Conditions used for the enteric coating of theophylline particles in a Strea-1 fluidized bed coater.

Parameter	Condition
Inlet temperature	36-38°C
Exhaust temperature	32-33°C
Nozzle diameter	1.0 mm
Spray rate	10 g/ (min*kg)
Drying conditions	Oven at 40°C, 48 hours

Table 7.3: Carrier polymers and temperature settings used for the hot-melt extrusion of enteric pellets into multiparticulate matrices.

Polymer	Supplier & Grade	Melting Point [°C]	Extrusion Temperature [°C]			
			Zone 1	Zone 2	Zone 3	Die
Poloxamer 188	BASF, Lutrol F68 NF Prill	57.1 ± 0.3	40	45	47	47
Poloxamer 407	BASF, Lutrol F127 NF Prill	58.9 ± 0.2	40	45	50	48
Polyethylene glycol 4000	Dow, Carbowax Sentry PEG 4000	63.8 ± 0.3	40	45	50	50
Polyethylene glycol 8000	Dow, Carbowax Sentry PEG 8000	64.3 ± 0.5	40	50	55	55
Polyethylene oxide 100K	Dow, Sentry Polyox WSR N-10	69.7 ± 0.2	55	70	75	75
Polyethylene oxide 200K	Dow, Sentry Polyox WSR N-80	69.9 ± 0.8	55	70	75	75

Table 7.4: Core materials used for the preparation of enteric film coated particles. The theophylline content was determined for the uncoated particles using HPLC (n = 3). The moisture content of the particles was determined as the loss on drying after equilibration at 22±1°C and 50±5% RH for at least 24 hours (n = 3).

Core Material	Supplier	Theophylline Content [%]	Moisture Content [%]
Drug Granules	BASF	96.3	2.15 ± 0.13
Pellets	Self-made	28.2	3.52 ± 0.08
MCC Spheres	Asahi Kasei	10.8	3.50 ± 0.25

7.8 FIGURES

Figure 7.1: Mechanical strength of three different types of particles before and after film coating with Eudragit® L30D-55.
(Diametral compression analysis, n = 20.)

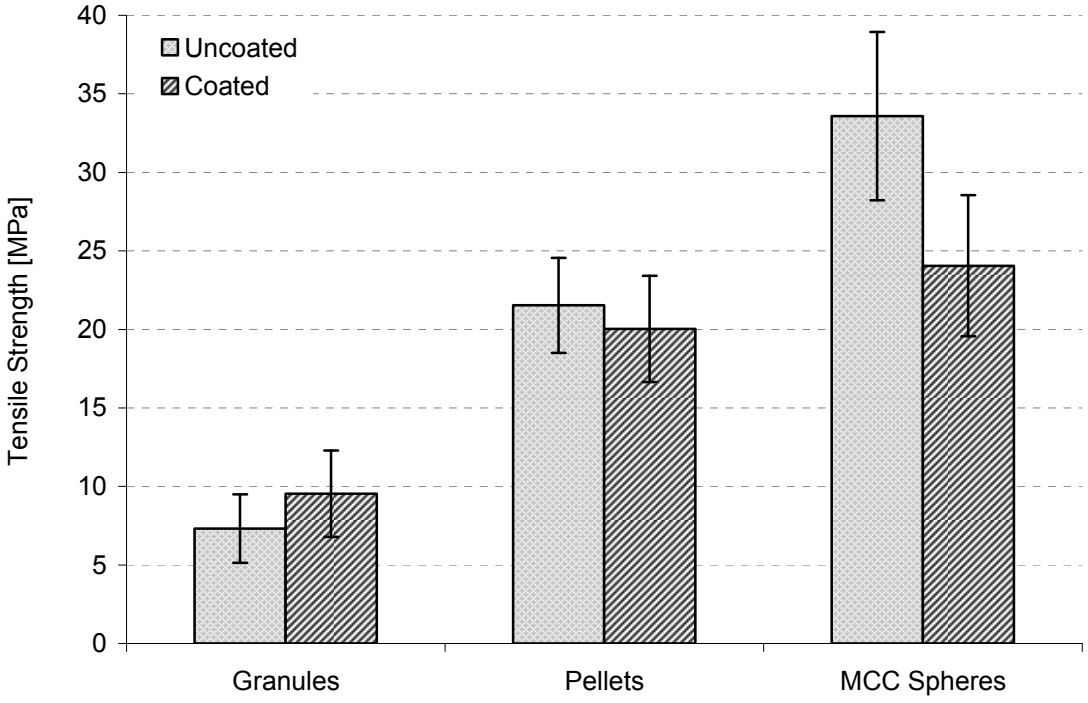


Figure 7.2: Influence of thermal processing and Eudragit® L in a 50:50 physical mixture on the degree of crystallinity of the carrier polymers.
(DSC, heating rate 10°/min, samples: 15±3mg, crimp-sealed in aluminum pans, cycled twice, n = 3. The relative crystallinity was calculated as the ratio of the melting enthalpies in the second run divided by the first run.)

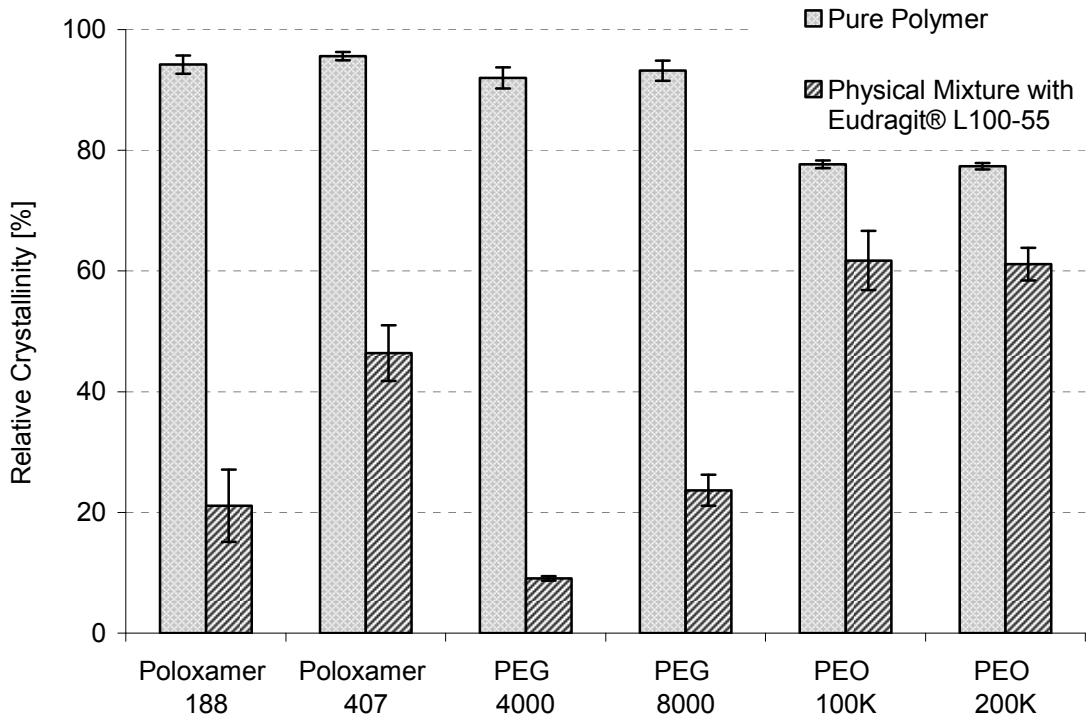


Figure 7.3: Influence of carrier polymer on the drug release properties of hot-melt extruded matrix tablets containing 30% enteric pellets. (×) Original enteric pellets, (▲) pellets in poloxamer 188, (△) pellets in poloxamer 407, (■) pellets in PEG 4000, (□) pellets in PEG 8000, (◆) pellets in PEO 100K, (◇) pellets in PEO 200K.
Dissolution: USP paddle apparatus, 100 rpm, 37±0.5°C, n = 3, 2 hours in 750 ml simulated gastric fluid pH 1.2 (without pepsin), after 2 hours pH change to pH 6.8 by addition of 250 ml 0.2M tribasic phosphate buffer.

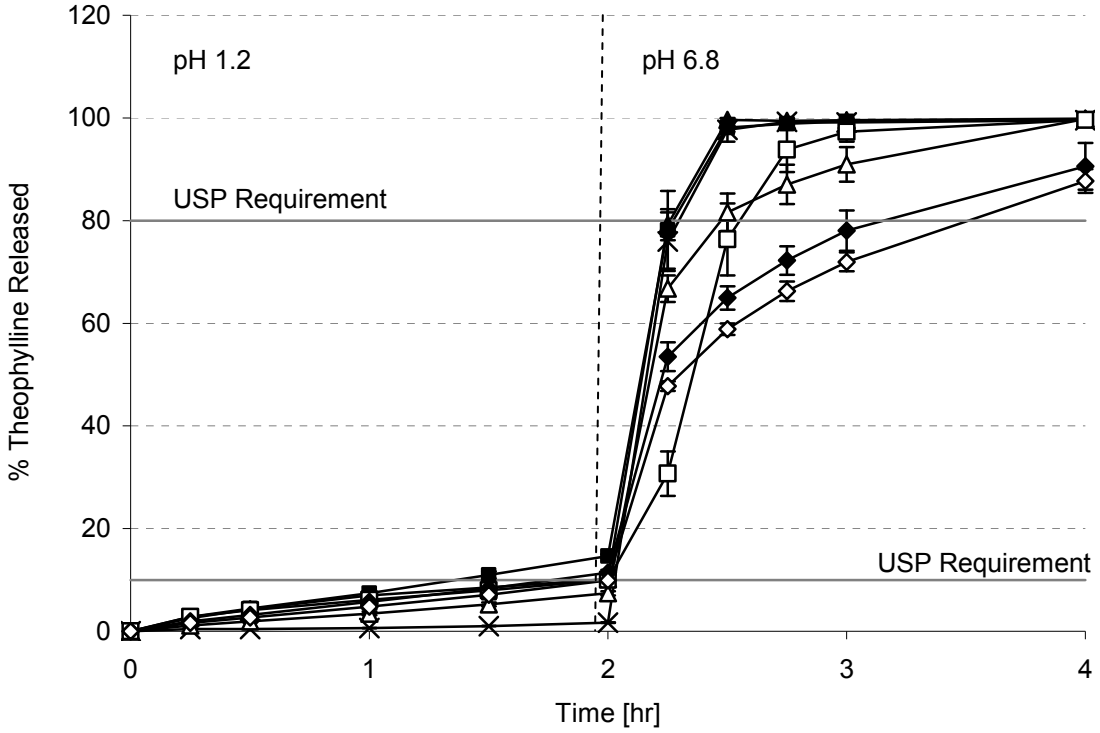


Figure 7.4: Influence of pellet loading on the drug release properties of hot-melt extruded poloxamer 407 matrices. (×) Original enteric pellets; Extrudates containing (△) 30% pellets, (◆) 40% pellets, (□) 50% pellets.
Dissolution: USP paddle apparatus, 100 rpm, 37±0.5°C, n = 3, 2 hours in 750 ml simulated gastric fluid pH 1.2 (without pepsin), after 2 hours pH change to pH 6.8 by addition of 250 ml 0.2M tribasic phosphate buffer.

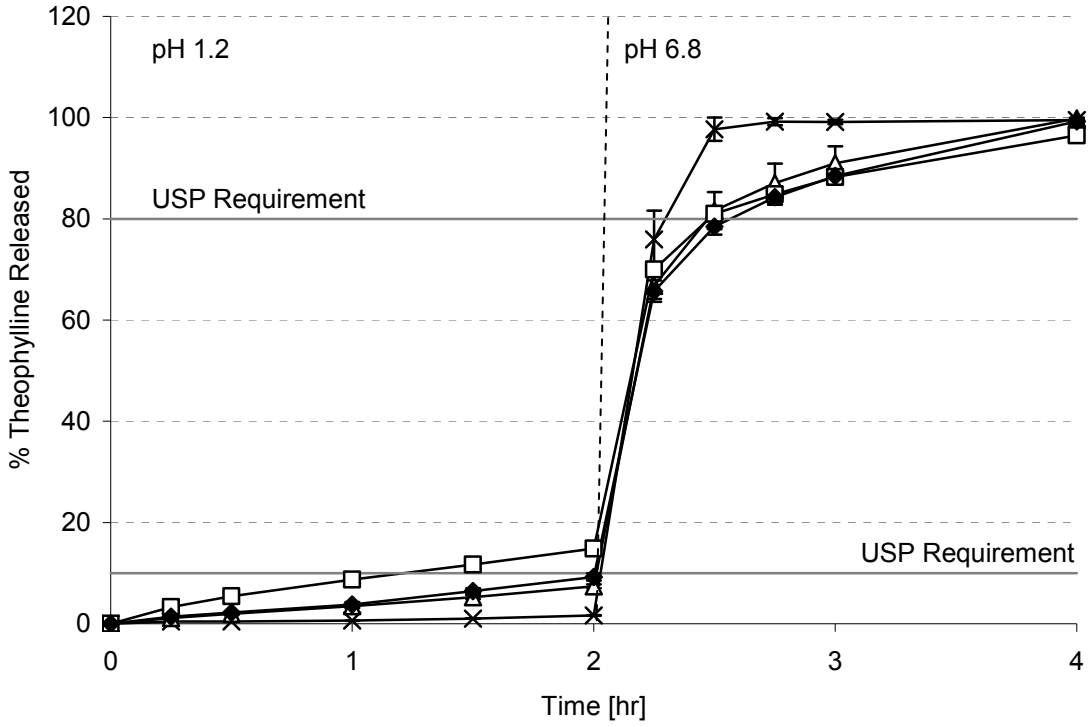


Figure 7.5: Influence of the particle type on the drug release in acid after 2 hours before and after hot-melt extrusion of 30% particles in poloxamer 407. Dissolution: USP paddle apparatus, 100 rpm, 37±0.5°C, n = 3, 750 ml simulated gastric fluid pH 1.2 (without pepsin).

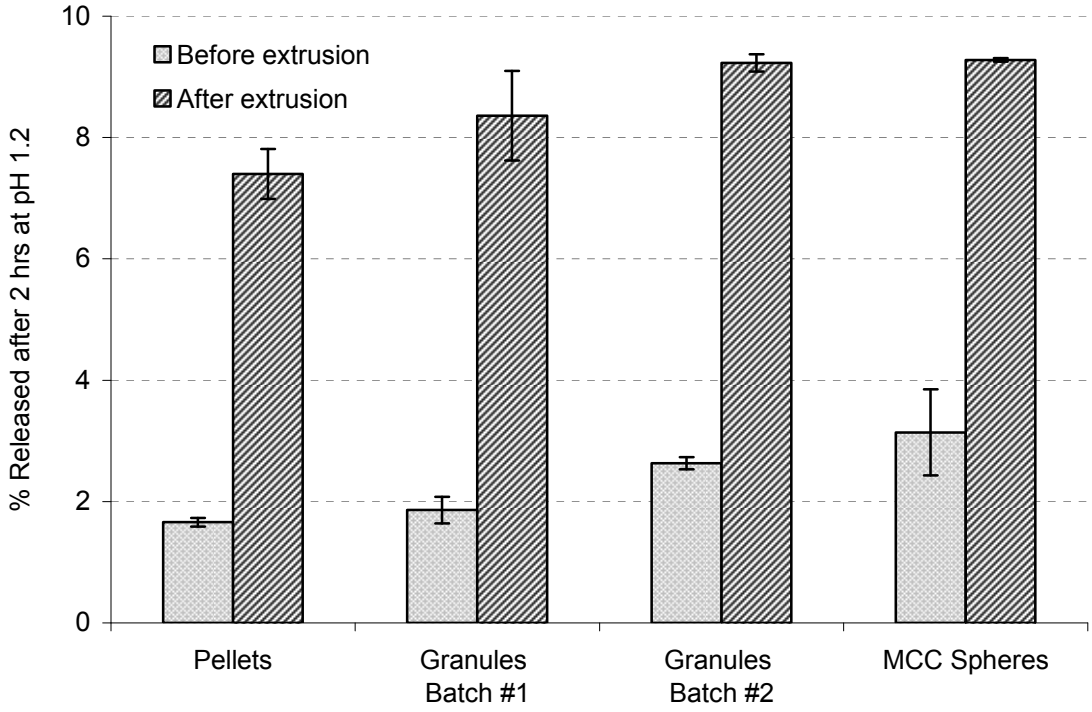
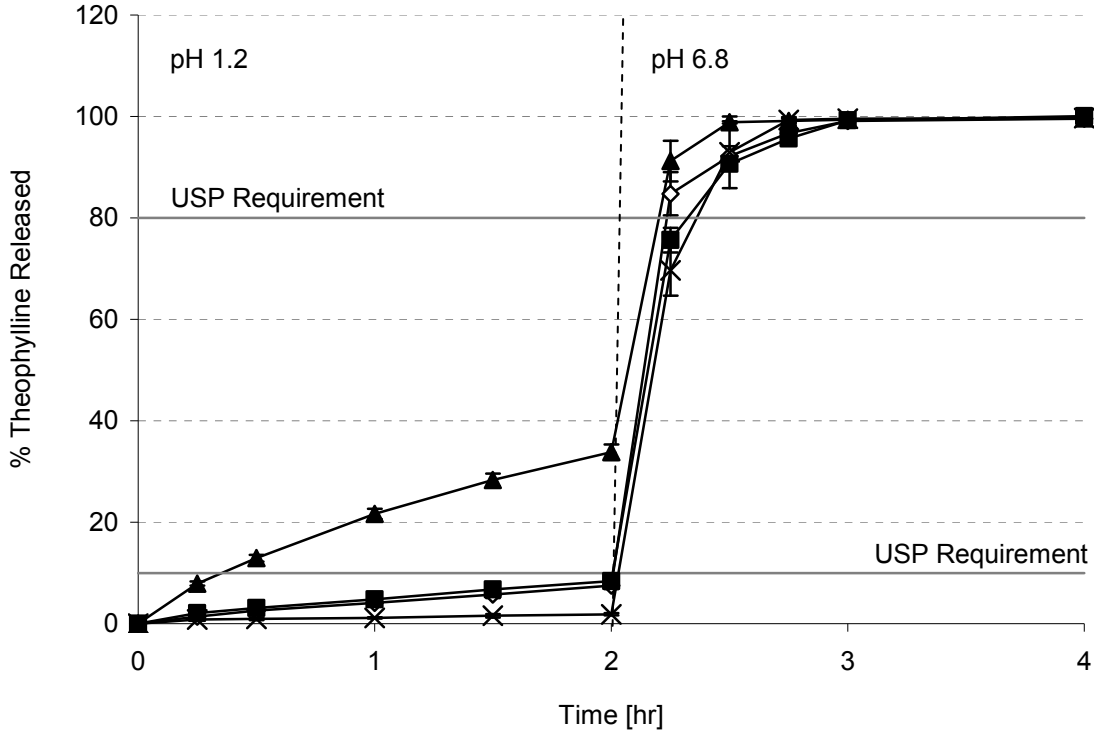


Figure 7.6: Influence of particle embedment method and storage on the release properties of enteric coated theophylline granules. (×) Original enteric granules, (■) fresh prepared hot-melt extruded matrix tablets containing 30% granules in poloxamer 407, (◇) hot-melt extruded matrix tablets containing 30% granules in poloxamer 407 after one year of storage at room temperature and ambient humidity, (▲) directly compressed tablets containing 30% granules in Ceolus™ KG 802.
Dissolution: USP paddle apparatus, 100 rpm, 37±0.5°C, n = 3, 2 hours in 750 ml simulated gastric fluid pH 1.2 (without pepsin), after 2 hours pH change to pH 6.8 by addition of 250 ml 0.2M tribasic phosphate buffer.



Chapter 8: Summary and Conclusion

Sustained release matrix tablets containing Eudragit® RS PO and citric acid as a solid-state plasticizer were prepared by hot-melt extrusion. It was demonstrated by tensile testing of plasticized films and in extrusion experiments that citric acid monohydrate functioned as an efficient plasticizer for the polymer when used at concentrations below the characteristic compatibility limit of the binary system. The anhydrous form of citric acid exhibited lower plasticization efficiency since its elevated melting point hindered a solubilization in the polymer during extrusion. The release rates of diltiazem hydrochloride from Eudragit® RS PO matrix tablets were increased and became independent of the initial drug particle when increasing levels of citric acid monohydrate were used as the processing aid. These release-enhancing effects of citric acid were demonstrated to be attributed to several mechanisms: The dissolution of citric acid from the matrix increased the porosity and hence the drug diffusion rate during dissolution testing. Solid-state interactions between citric acid and diltiazem hydrochloride depressed the drug's melting point below the extrusion temperature and enabled the fine dispersion of the melted drug in its amorphous state during extrusion. The plasticizing properties of citric acid further increased the free volume and permeability of the polymeric network to water penetration and drug diffusion.

Enteric matrix pellets with a diameter below 1 mm and containing up to 40% theophylline could be successfully prepared by hot-melt extrusion when plasticized Eudragit® S100 was employed as the matrix material. The manufacture of pellets using alternative enteric polymers was either compromised by a lack of thermal processibility (Eudragit® L100-55 and Eudragit® L100), or the pellets failed to provide gastric protection due to an elevated matrix permeability in acid (Aqoat® LF and HF).

Methylparaben, PEG 8000 and TEC showed high compatibility with Eudragit® S100, plasticized the polymer efficiently and facilitated a homogeneous dispersion of the drug in its original polymorphic form but at reduced particle sizes in the pellet matrix during hot-melt extrusion. Pellets containing ATBC, citric acid monohydrate or no plasticizer had to be extruded at high temperatures, resulting in partial drug solubilization and the recrystallization of needle-shaped theophylline crystals on the pellet surfaces. The aqueous solubility and the amount of plasticizer influenced the drug release rate. Plasticization with water-soluble compounds impaired gastric protection due to pore formation during the acidic stage, while pellets containing less soluble plasticizers (TEC, methylparaben, ATBC) or no plasticizer exhibited low drug release rates at pH 1.2. The mechanical strength of melt extruded pellets was high and decreased when plasticizers were added to the formulation. Eudragit® S100 matrix pellets that were efficiently plasticized with poorly or moderately soluble plasticizers exhibited low porosities during dissolution testing in acidic medium and could contain up to 40% drug without compromising the delayed-release properties.

Hot-melt extrusion was further used to embed enteric coated particles into hydrophilic matrices with the objective to preserve the delayed-release properties of the original particles. Matrices containing up to 40% enteric particles in poloxamer 407 fulfilled the USP requirements for delayed release dosage forms to release less than 10% drug after 2 hours at pH 1.2 and more than 80% after 45 minutes at pH 6.8. The extrusion process was demonstrated to be applicable for the embedment of soft drug granules that were coated with a brittle Eudragit® L30D-55 film, while directly compressed tablets containing the same enteric particles released more than 30% drug at pH 1.2 due to film rupture during compaction. The preservation of the delayed release profile was demonstrated to be independent of the mechanical strength of the extruded particles, but

dependent on the nature of the carrier polymer. A high miscibility between the enteric polymer and the carrier polymer promoted the solubilization of the enteric film in the matrix during extrusion and resulted in increased drug release rates in acidic media. These results indicated that the enteric film was more susceptible to solubilization in the carrier polymer than to mechanical rupture by shear forces during the hot-melt extrusion process. Poloxamer 407 was selected as the carrier polymer due to its dissolution properties and only moderate miscibility with the enteric polymer, and the prepared multiparticulate matrices exhibited stable dissolution profiles when stored for one year at room temperature.

In conclusion, hot-melt extrusion was demonstrated to be a versatile process that was successfully employed for the preparation of extended release tablets, delayed release matrix pellets and multiparticulate matrices. The selection of the type and amount of plasticizer in the formulation impacted not only the thermal processibility during extrusion, but also the drug-release performance of the final dosage form by influencing the matrix porosity and the solid-state properties of the drug.

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Vita

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Publications

Sandra U. Schilling, Hélène L. Lirola, Navnit H. Shah, A. Waseem Malick, James W. McGinity, "Influence of Plasticizer Type and Level on the Properties of Eudragit® S100 Matrix Pellets Prepared by Hot-Melt Extrusion", submitted to Journal of Microencapsulation, July 2009.

Sandra U. Schilling, Navnit H. Shah, Waseem Malick, James W. McGinity, "Properties of Melt Extruded Enteric Matrix Pellets", European Journal of Pharmaceutics and Biopharmaceutics, in press October 2009.

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