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Research paper

Properties of melt extruded enteric matrix pellets

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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 possible 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 h 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 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 1 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.

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 h 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 pro-

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tection [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 that 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 h 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 h 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 h 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 was 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.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (Theo) was selected as the water-soluble model drug and was purchased from Spectrum Chemicals (Gardena, CA). Hydroxypropyl methylcellulose acetate succinate (HPMC AS, Aqoat®, Shin-Etsu) was used in two grades (LF and HF) and kindly provided by Biddle Sawyer (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).

2.2. Preparation of melt extruded pellets

Powder blends for extrusion (10 g) 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 500 μm 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 1–3. The diameters of the extruded strands were measured with a manual micrometer (Mituoyo model C1012EBS, Aurora, IL) prior to cutting.

2.3. 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 min and then ramped to 180 °C at 10 °C/min with a modulation of 0.5 °C every 40 s. 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.

2.4. 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 h, 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 0.2 M 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 10 μl 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 100.0 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).

2.5. 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 Sci-

Table 1
Compositions of blends, extrusion parameters and diameters of extruded strands containing 10% theophylline and different enteric polymers.

Polymer	TEC (% based on polymer)	Temperature (°C)	Torque (N cm)	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

All extrusions were conducted using a screw speed of 100 rpm.

Table 2
Formulations and process parameters for Eudragit® S100 based matrix pellets containing 10–40% theophylline (Theo) and 40% TEC based on polymer content.

Theo (%)	Eudragit® S100 (%)	TEC (%)	Torque (N cm)	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

All extrusions were conducted at 140 °C and using a screw speed of 75 rpm.

Table 3
Compositions and process parameters of Eudragit® S100 matrix pellets containing 30% theophylline and different plasticizers.

Eudragit® S100 (%)	Plasticizer (20%)	Temperature (°C)	Torque (N cm)	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

All extrusions were conducted using a screw speed of 75 rpm.

entific 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 at several magnifications using Smart SEM V05.02.03 software.

2.6. 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 from 5° to 40° at a step size of 0.05° with a dwelling time of 2 s, corresponding to a scanning rate of 1.5°/min.

3. Results and discussion

3.1. 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, Eudragit® L100, Eudragit® 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 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 to exit through the 500 μm die and produced torque values exceeding the alarm setting (368 N cm). 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 ± 23 μm and 598 ± 8 μm for Aqoat® LF and Aqoat® HF grade) compared to the polymethacrylates (diameters of 967 ± 65 μm and 883 ± 12 μm 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 during 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 h) and pH 6.8 (HPMC AS LF, Eudragit® L100) or pH 7.4, respectively, (HPMC AS HF, Eudragit® S100) are shown in Fig. 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 h. 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 h. 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 h. 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 (see also Section 3.5). 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

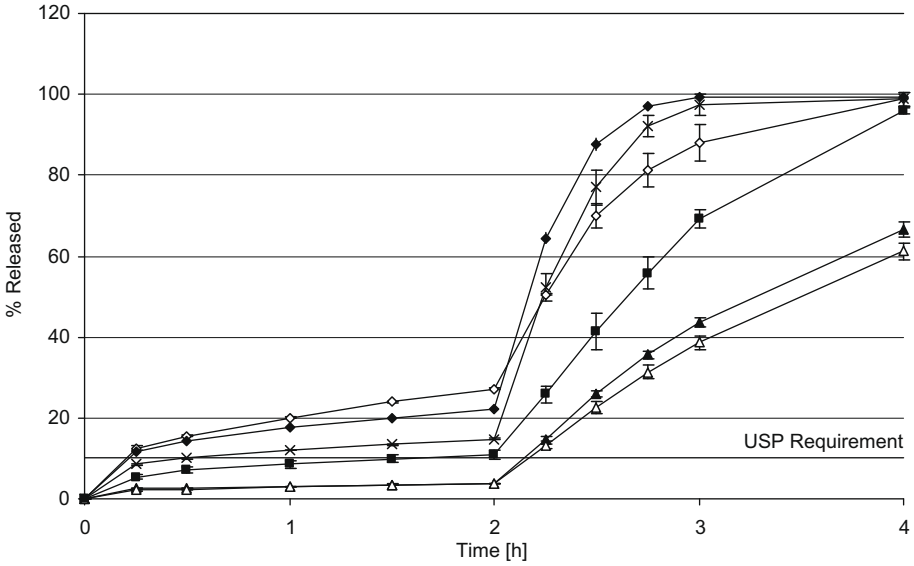

Fig. 1. Influence of the matrix polymer on the release properties of enteric matrix pellets. All formulations contained 10% theophylline. (◇) HPMC AS LF, 15% TEC, (♦) HPMC AS HF, 15% TEC, (×) HPMC AS HF, 9% ATBC, (△) Eudragit® L100, 20.8% TEC, (▲) Eudragit® S100, 20.8% TEC, (■) HPMC AS HF + Eudragit®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

Eudragit® S100 released the drug to a lesser extent over 2 h 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 h 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 h 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 h in the buffer, HPMC AS was completely released into the dissolution medium whereas 37% Eudragit® L remained within the film even after 8 h [24].

Eudragit® S100 was selected as the matrix material for the preparation of pellets as it provided excellent 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.

3.2. 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 2). The increase in plasticizer content from 30% to 40% not only 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. 1) to pellets plasticized with 40% TEC based on the polymer weight (Fig. 2), an increase in drug release from 3.76% to 6.10% was observed after 2 h in acid, while the release after 2 h 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 ± 12 μm (30% TEC) to 870 ± 23 μm (40% TEC). However, as illustrated in Fig. 3, increasing the drug load resulted in reduced swelling as the extrudate diameter decreased to 727 ± 35 μm (20% theophylline), 655 ± 36 μm (30% theophylline) and 537 ± 21 μm (40% theophylline) (One-way ANOVA, $\alpha = 0.05$, $p < 0.001$). The drug did not melt during

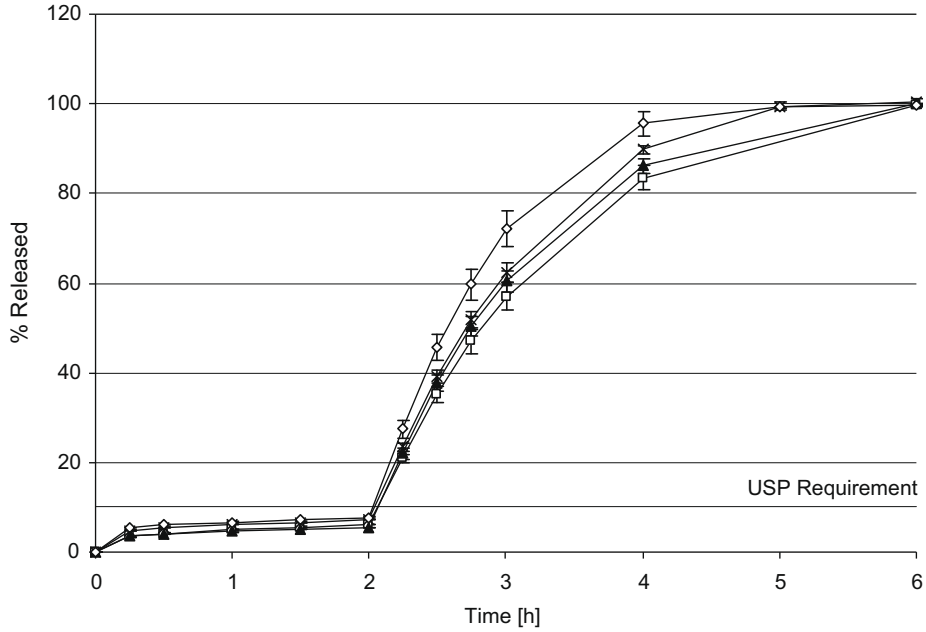

Fig. 2. Influence of the theophylline loading on the release properties of Eudragit® S100 matrix pellets. (□) 10%, (▲) 20%, (×) 30% and (◊) 40% theophylline. Dissolution: USP paddle apparatus, 50 rpm, 37.0 ± 0.5 °C, n = 3, 2 h in 750 ml SGF pH 1.2 without pepsin, after 2 h pH change to pH 7.4 by addition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

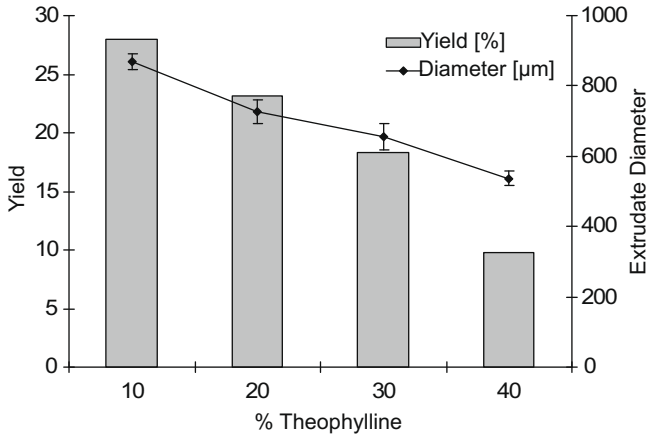

Fig. 3. Influence of the theophylline content on the extrudate diameter and process yield for the extrusion of Eudragit® S100 matrix pellets.

extrusion (melting point = 277 °C) and remained as a crystalline powder (see also Section 3.5). 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 are often 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. 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 h 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.

3.3. Plasticization efficiency of various plasticizers on Eudragit® S100

Plasticizers are traditionally low molecular weight compounds that are added to polymers to modify their physicomechanical 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 is the 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 500 µm 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 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

Table 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

based on the polymer weight were studied by MDSC, and the *Tg* was determined in the second heating cycle (Fig. 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. 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 500 μm 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].

3.4. 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.

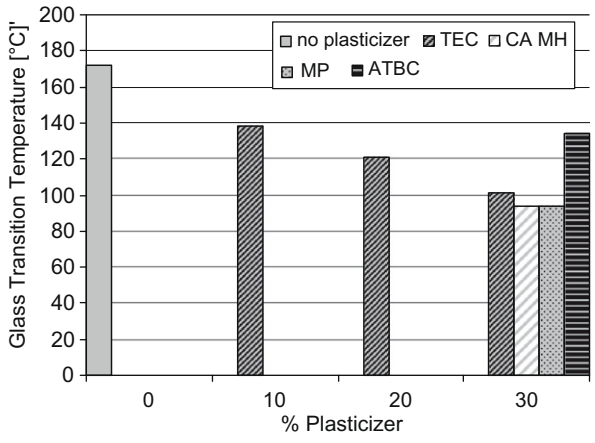

Fig. 4. Influence of different compounds on the glass transition temperature of Eudragit® S100 as determined by MDSC.

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 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 h 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.

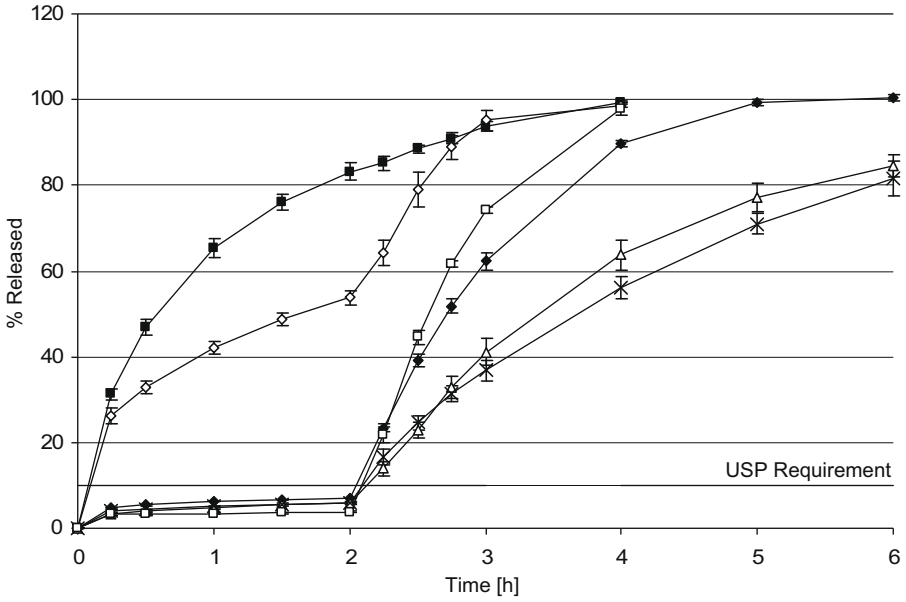

Fig. 5. Influence of the type of plasticizer on the drug release from Eudragit® S100 matrix pellets. All formulations contain 30% theophylline and 20% plasticizer. (■) PEG 8000, (◇) CA MH, (□) MP, (♦) TEC, (△) ATBC, (×) no plasticizer. Dissolution: USP paddle apparatus, 50 rpm, 37.0 ± 0.5 °C, n = 3, 2 h in 750 ml SGF pH 1.2 without pepsin, after 2 h pH change to pH 7.4 by addition of 250 ml 0.2 M tribasic phosphate buffer and NaOH solution.

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 h in acid. This finding suggests that leaching of plasticizer during dissolution and drug diffusion through pores was 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.

3.5. 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. 6). The drug itself was found to be of irregular shape and crystalline, with a wide particle size distribution and agglomerates (Fig. 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. 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. 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

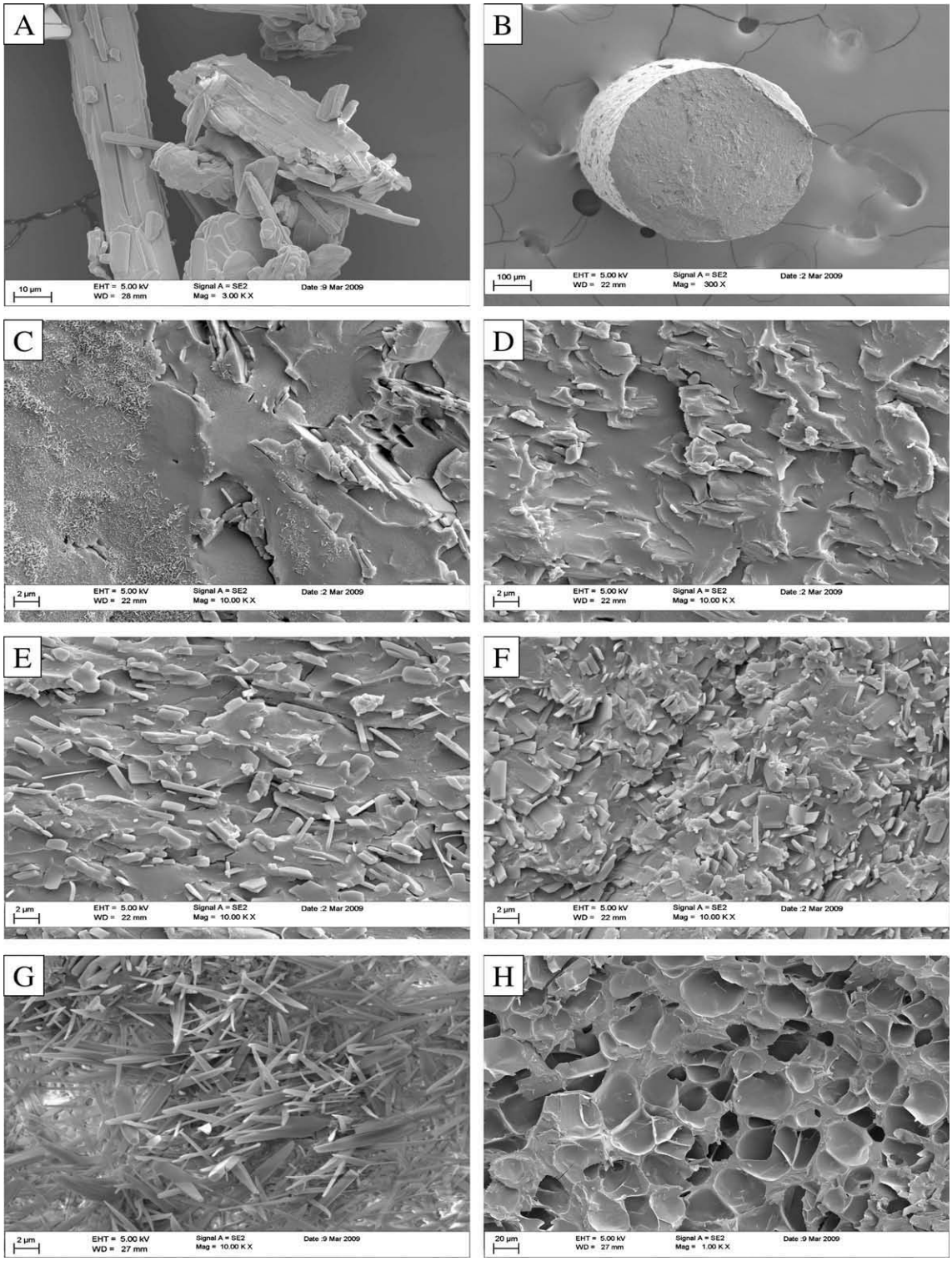

Fig. 6. SEM pictures of (A) theophylline powder; (B and C) extrudates without plasticizer; extrudates with (D) 20% methylparaben, (E) 20% TEC, (F) 20% PEG 8000, (G) 20% ATBC, (H) 20% CA MH.

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. 7). Unprocessed anhydrous theophylline was highly crystalline and exhibited characteristic peaks at 2-Theta = 12.9 and 26.7 (highlighted squares in Fig. 7), while Eudragit® S100 was completely amorphous. The limit of detection for crystalline theophylline using this method was below 5% as demonstrated in Fig. 7 for a physical mixture of Eudragit® S100 containing 5% crystalline drug. In all extrudates (EX), the drug was present in both the crystalline state and as the original polymorph since the diffraction patterns displayed the characteristic peaks of the

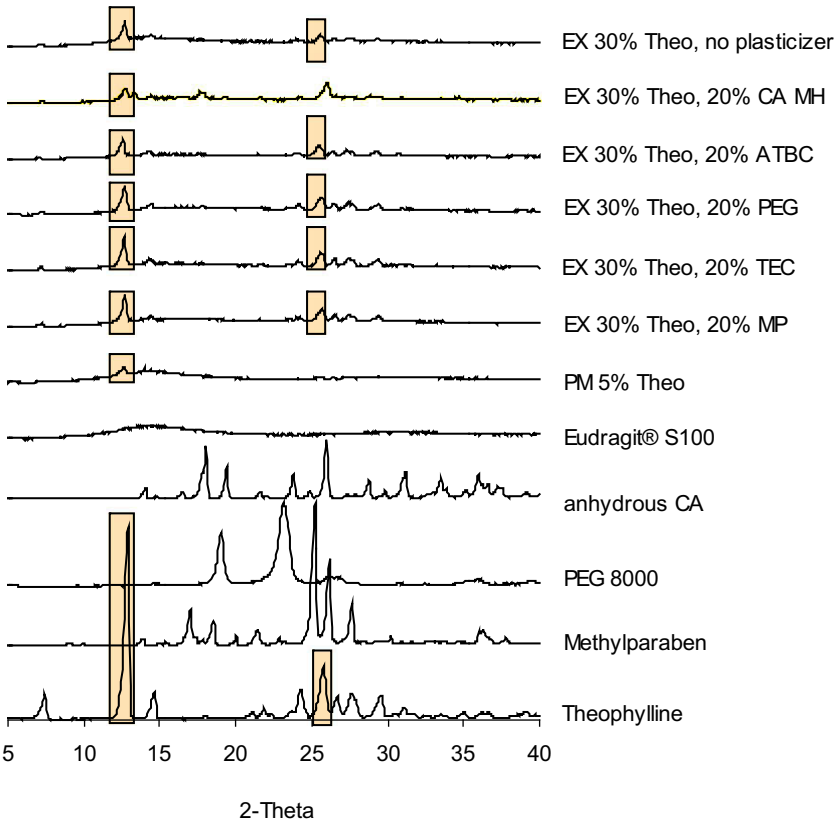

Fig. 7. Influence of different plasticizers on the crystallinity of melt extruded Eudragit® S100 matrix pellets (EX) containing 30% theophylline (Theo). (PM: physical mixture, characteristic theophylline peaks are highlighted).

unprocessed drug (Fig. 7, red squares[1]). 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 polymer 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.

4. Conclusions

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.

[1] For interpretation of color in Fig. 7, the reader is referred to the web version of this article.

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