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Citric acid monohydrate as a release-modifying agent in melt extruded matrix tablets

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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 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.

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 (Crowley et al., 2007). 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 (Sprockel et al., 1997). 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 form design of 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 with 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 (Forster et al., 2001), PEO (Li et al., 2006), HPMC (Verreck et al., 2003) or Eudragit® EPO (Zheng et al., 2007) 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 (Rambali et al., 2003) and surfactants (Zhu et al., 2006b; Ghebremeskel et al., 2007) have been successfully used to enhance the drug solubility in the dissolution medium and to improve powder wettability. Polymeric or low-molecular weight

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additives with high aqueous solubility can enhance drug dissolution due to leaching into the dissolution medium and formation of a porous network (Sprockel et al., 1997). Water-soluble excipients of low-molecular weight that are miscible with the polymer can simultaneously function as plasticizer and pore former. Zhu et al. (2006a) reported increased drug release rates when high TEC levels were incorporated into diltiazem hydrochloride matrix tablets due to leaching of the plasticizer during dissolution.

Citric acid has been widely used as an acidifying agent in solid oral dosage forms (Siepe et al., 2006; Tatavarti and Hoag, 2006). Solid dispersions of poorly soluble APIs in citric acid produced by co-melting techniques exhibited increased dissolution rates (Chiou and Riegelman, 1969; Summers and Enever, 1976; Timko and Lordi, 1979). Furthermore, the plasticizing effects of citric acid monohydrate (CA MH) on certain acrylic polymers including Eudragit® L 30D-55 (Bruce et al., 2003), Eudragit® S100 (Bruce et al., 2005) and Eudragit® RS PO (Schilling et al., 2007) 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 a Eudragit® RS PO matrix (Zhu et al., 2006a). Drug release from extruded composites was investigated as a function of drug particle size and 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.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride, citric acid monohydrate (powder, USP), 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 three different particle 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).

2.2. Thermogravimetric analysis (TGA)

The thermal stability of DIL HCl, CA MH, anhydrous citric acid, and Eudragit® RS PO was evaluated by TGA. A powder sample of approximately 10 mg was accurately weighed into an aluminum pan and placed into the furnace of a PerkinElmer 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).

2.3. Drug–polymer binding study

A stock solution of DIL HCL in phosphate buffer pH 6.0 (0.1 mg/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., Inc., Edison, NJ) at 200 rpm. After 24 h, 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.

2.4. 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 to 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 heating run.

2.5. 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 zones 1 to 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 advantageous 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.

2.6. 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 four times at 20 PSI, followed by three analytical runs at the same pressure. The equilibration rate was set to 0.0050 PSI/min.

2.7. Manufacture of melt extruded tablets

A total of 15 formulations (Table 1) were processed using a vertical single-screw extruder (Randcastle single-screw extruder, model RCP 0750 Microtruder, Cedar Grove, NJ). Powder blends (150–200 g) 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

Table 1
Composition of tablets prepared by hot-melt extrusion

No.	Category	Experiments	Formulation label	DIL HCl amount (g)	Particle size (μm)	CA MH amount (g)	Eudragit® RS PO amount (g)
1	Constant polymer (60%)	Processibility, helium pycnometry, dissolution testing, SEM, PXRD	RS60-40/0	40	75–150	0	60
2			RS60-30/10	30	75–150	10	60
3			RS60-20/20	20	75–150	20	60
4			RS60-10/30	10	75–150	30	60
5			RS60-20/20S	20	75–150	20 Sucrose	60
6			RS60-20/20N	20	75–150	20 NaCl	60
7			RS60-20/20P	20	75–150	20 PEG	60
8	Constant API to polymer ratio (1:4)	Dissolution testing, PXRD	DIL75/RS-0	20	<75	0	80
9			DIL200/RS-0	20	150–250	0	80
10			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

four heating zones and the transition time through the barrel was less than 4 min. 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.

2.8. 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 h. 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 as six 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).

2.9. 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 mm × 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 (R^2 < 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 (R.S.D. < 2.4% at each tested concentration, n = 6).

2.10. 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 2θ range employing a Philips Electronic Instrument (Type 42273) with Cu Kα radiation operating at 45 kV and 40 mA. The samples were scanned between 5° and 50° at a step size of 0.03° and a dwelling time of 1 s (scanning rate of 1.8°/min).

2.11. 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 h 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 20 mA 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.

2.12. 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 f_2 similarity factor was calculated for the dissolution profiles from the means of % released at each time point (Shah et al., 1998).

3. Results and discussion

3.1. Thermal stability

The TGA experiments (Fig. 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. (2006a). 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

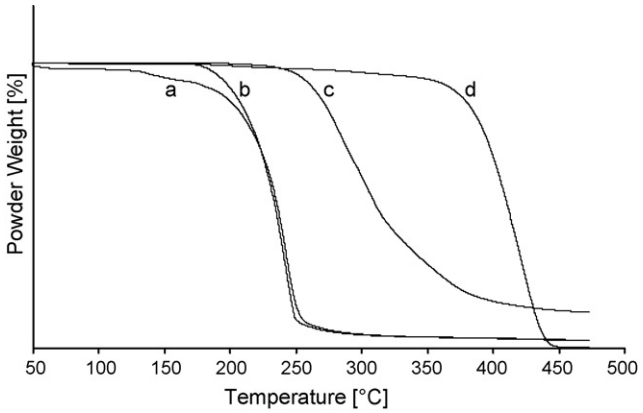

Fig. 1. Thermal gravimetric analysis of: (a) citric acid monohydrate, (b) anhydrous citric acid, (c) diltiazem hydrochloride and (d) Eudragit® RS PO.

melting point, demonstrating the thermal stability at the extrusion temperatures.

3.2. 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 Sallam (1999) reported the complex formation between ammoniomethacrylates and salts of acidic drugs in phosphate buffer solutions which was mainly attributed to electrostatic interaction. In addition, non-electrostatic 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 (Zhu et al., 2006b). 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. 2). These results were consistent with the findings reported previously by Follonier et al. (1995).

3.3. 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

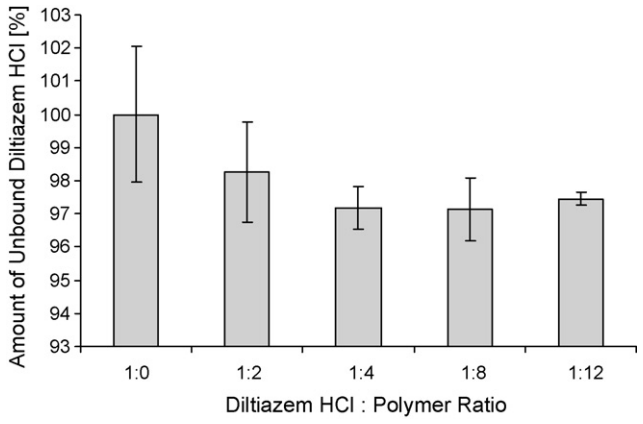

Fig. 2. Binding of diltiazem hydrochloride to Eudragit® RS PO as a function of the drug-to-polymer ratio ($n = 3$, error bars represent the standard deviation).

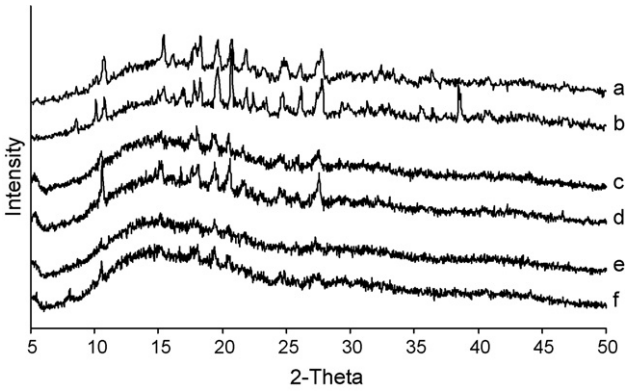

Fig. 3. Powder X-ray diffraction patterns of physical mixtures (PMs) and hot-melt extrudates (HMEs) containing 5–20% diltiazem hydrochloride (DIL HCl) in Eudragit® RS PO. (a) HME with 20% DIL HCl, (b) PM with 20% DIL HCl, (c) HME with 10% DIL HCl, (d) PM with 10% DIL HCl, (e) HME with 5% DIL HCl and (f) PM with 5% DIL HCl.

binary system of CA MH and Eudragit® RS PO has been previously investigated by our group (Schilling et al., 2007). 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 (Zhu et al., 2006a). 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. 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) 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 simulta-

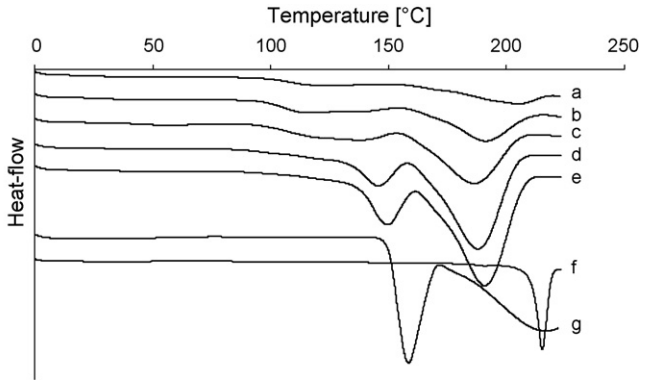

Fig. 4. Differential scanning colorimetry profiles of diltiazem hydrochloride (DIL HCl) and anhydrous citric acid (CA) and physical mixtures thereof. (a) DIL HCl/CA 7:1, (b) DIL HCl/CA 3:1, (c) DIL HCl/CA 1:1, (d) DIL HCl/CA 1:3, (e) DIL HCl/CA 1:7, (f) pure DIL HCl and (g) pure anhydrous CA.

neous 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 $MPa^{1/2}$ versus 25.52 $MPa^{1/2}$) or Hoy (20.85 $J^{1/2}/cm^{3/2}$ 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 seven between the solubility parameters of two components has been associated with a high degree of miscibility (Greenhalgh et al., 1999).

3.4. 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. 5). Since hot-melt extrusion exerts a combination of melting and mechanical processes (Forster and Rades, 2002), the processibility of a formulation depends on the 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. 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 (Gryczke, 2007), 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 (Schilling et al., 2007). 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 concentrations.

The plasticizing effect of CA MH on the acrylic polymer was supported by the results of Helium pycnometry (Fig. 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.

3.5. 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 (Zhang and McGinity, 2000) or functional excipients (Crowley et al., 2004). 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

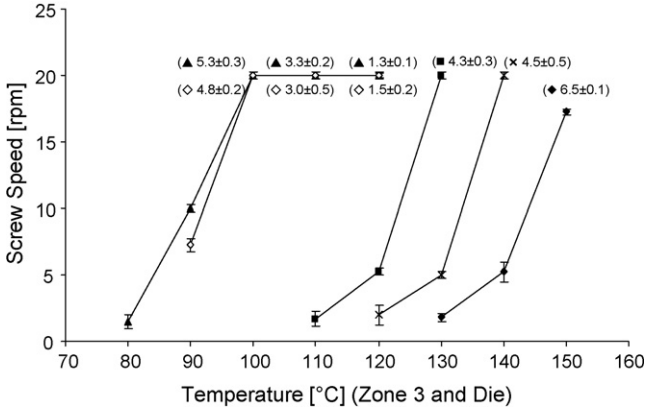

Fig. 5. Influence of the diltiazem hydrochloride (DIL HCl) to citric acid monohydrate (CA MH) ratio on the screw speed applied for the melt extrusion of Eudragit® RS PO (constant level of 60%) as a function of temperature. (×) Pure Eudragit® RS PO. Eudragit® RS PO with (◆) 40% DIL HCl, (■) 30% DIL HCl 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.

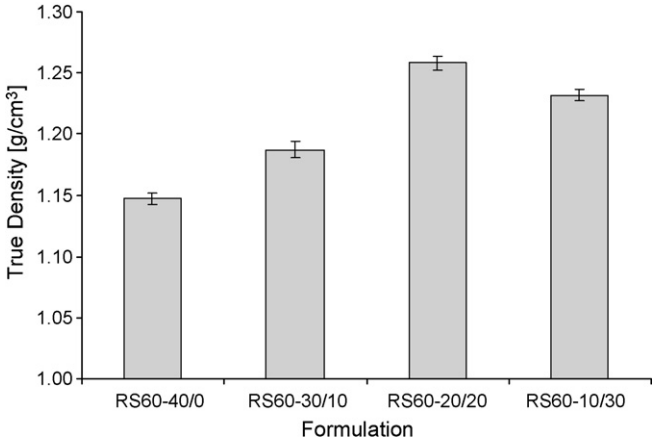

Fig. 6. Influence of the diltiazem hydrochloride (DIL HCl) to citric acid monohydrate (CA MH) ratio on the true density of hot-melt extrudates containing Eudragit® RS PO at a 60% level ($n = 6$, error bars represent the standard deviation).

(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-h dissolution in phosphate buffer pH 6.0 (Fig. 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 (Leuenberger et al., 1987), 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 (Leuenberger et al., 1995). 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 h. 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 soluble material does not dissolve in the matrix polymer, pore formation is dependent on the particle sizes of the soluble materials in the formulation (Sprockel et al., 1997). 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 h 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 et al. (1996) 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. 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. 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

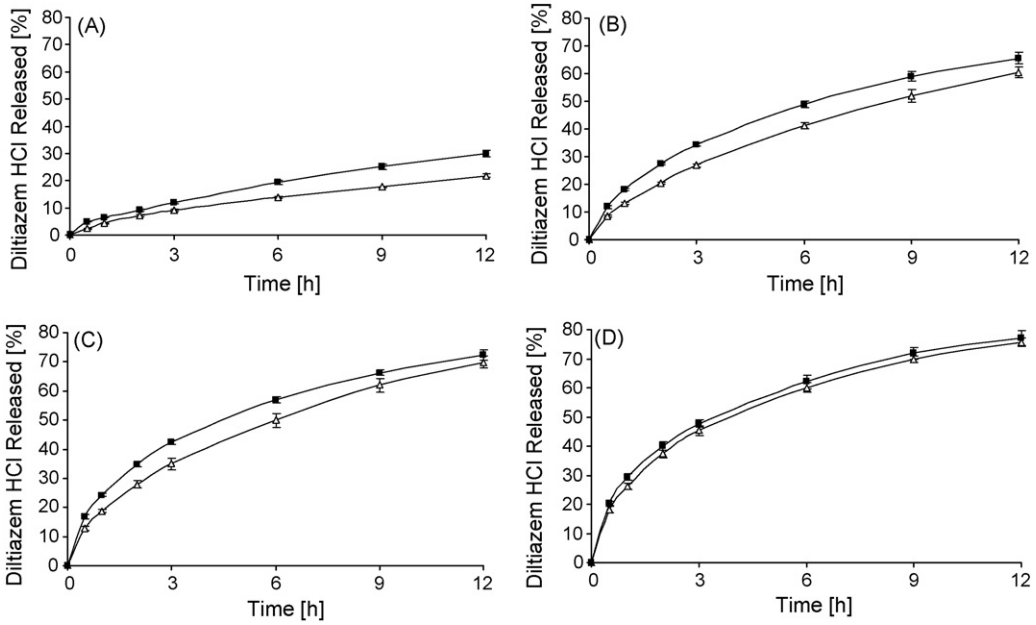

Fig. 7. Influence of the diltiazem hydrochloride (DIL HCl) particle size in the extrusion blend and the addition of citric acid monohydrate (CA MH) on the drug release from extruded Eudragit® RS PO matrix tablets with constant DIL HCl to polymer ratio (1:4). (△) Small DIL HCl particle size (<75 μm) and (■) 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, $n = 6$.

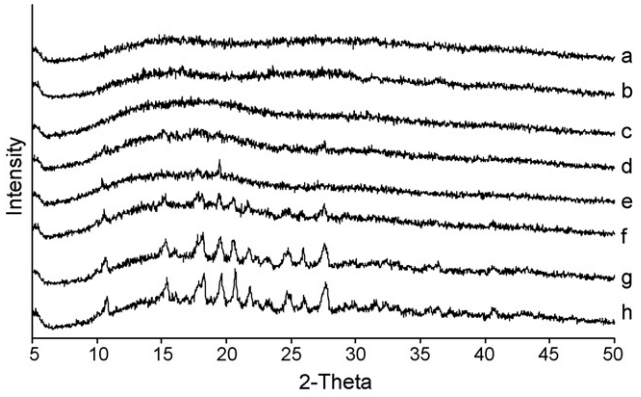

Fig. 8. Influence of citric acid monohydrate (CA MH) concentration and diltiazem hydrochloride (DIL HCl) particle size on the crystallinity of hot-melt extrudates. PXRD patterns of extrudates with constant DIL HCl to Eudragit® RS PO ratio (1:4) and (a) DIL HCl (<75 μm)/CA MH 2:3, (b) DIL HCl (150–250 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 and (h) DIL HCl (150–250 μm) and no CA MH.

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 (f_2 = 79). Tablets including less CA MH yielded lower similarity factors (f_2 = 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.

3.6. 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. 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 (2θ = 10.7, 15.4, 18.2, 19.5, 20.7 and 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 in 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 (2θ). 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 (Crowley et al., 2004). 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.

3.7. 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 h. 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. 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-h 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 h. The difference in the amount of API released between the three tablet formulations containing drug and CA MH in varying ratios was small with f_2 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 et al. (1998), release profiles with a f_2 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 $f_2 \geq 65$).

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

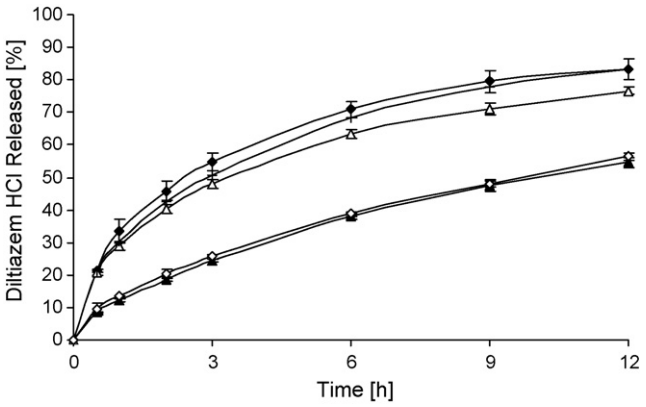

Fig. 9. Influence of the diltiazem hydrochloride (DIL HCl) to citric acid monohydrate (CA MH) ratio and the pH of the dissolution medium on the drug release from extruded Eudragit® RS PO matrix tablets containing 60% polymer. (+) 10% DIL HCl and 30% CA MH, release in phosphate buffer pH 6.0, (♦) 20% 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 and (▲) 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, $n = 6$.

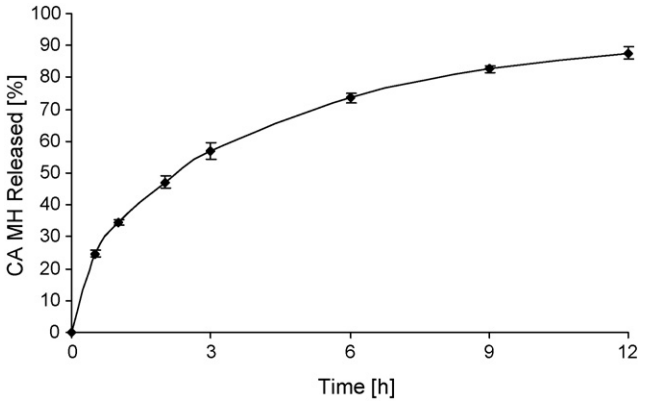

Fig. 10. Release of citric acid monohydrate (CA MH) from extruded Eudragit® RS PO matrix tablets containing 60% polymer, 20% diltiazem hydrochloride and 20% CA MH. Dissolution: USP paddle method, 900 ml phosphate buffer pH 6.0 as dissolution medium, 37 °C, 50 rpm, $n = 6$.

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 (Nie et al., 2004), trimethoprim (Tatavarti & Hoag, 2006) and dipyridamole (Siepe et al., 2006) 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 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 (Espinoza et al., 2000). 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. 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 XXIX) with a f_2 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. 10), with 56.92% being released after 3 h in phosphate buffer pH 6.0 (HPLC assay described in Schilling et al., 2007). 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 (nos. 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 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. 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.

Table 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

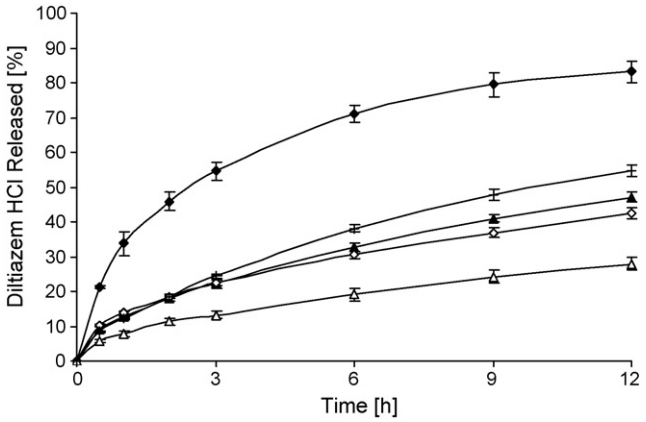

Fig. 11. Effect of pore forming excipients on the diltiazem hydrochloride (DIL HCl) release from extruded Eudragit® RS PO matrix tablets containing 60% polymer, 20% DIL HCl and 20% of (♦) citric acid monohydrate, (▲) sucrose, (◊) PEG 3350, and (△) NaCl. (+) Extrudate with 40% DIL HCl and no pore forming excipient. Dissolution: USP paddle method, 900 ml phosphate buffer pH 6.0 as dissolution medium, 37 °C, 50 rpm, $n = 6$.

3.8. 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 h dissolution in phosphate buffer pH 6.0 was visualized with scanning electron microscopy (Fig. 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

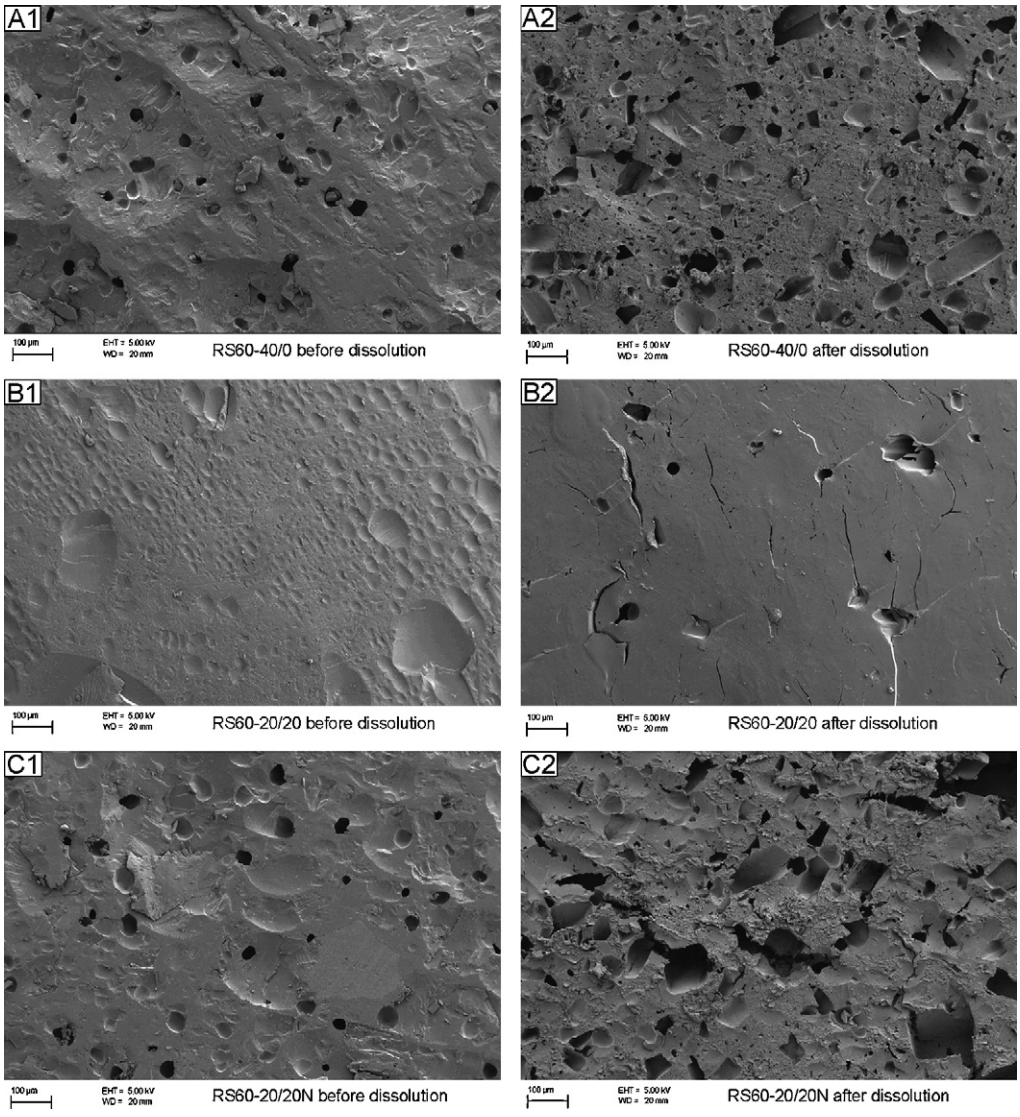

Fig. 12. SEM of hot-melt extruded tablets composed of 60% Eudragit® RS PO, and (A) 40% diltiazem hydrochloride (DIL HCl), (B) 20% DIL HCl and 20% citric acid monohydrate and (C) 20% DIL HCl and 20% NaCl. Pictures were taken before (X-1) and after (X-2) dissolution in phosphate buffer pH 6.0 over 12 h.

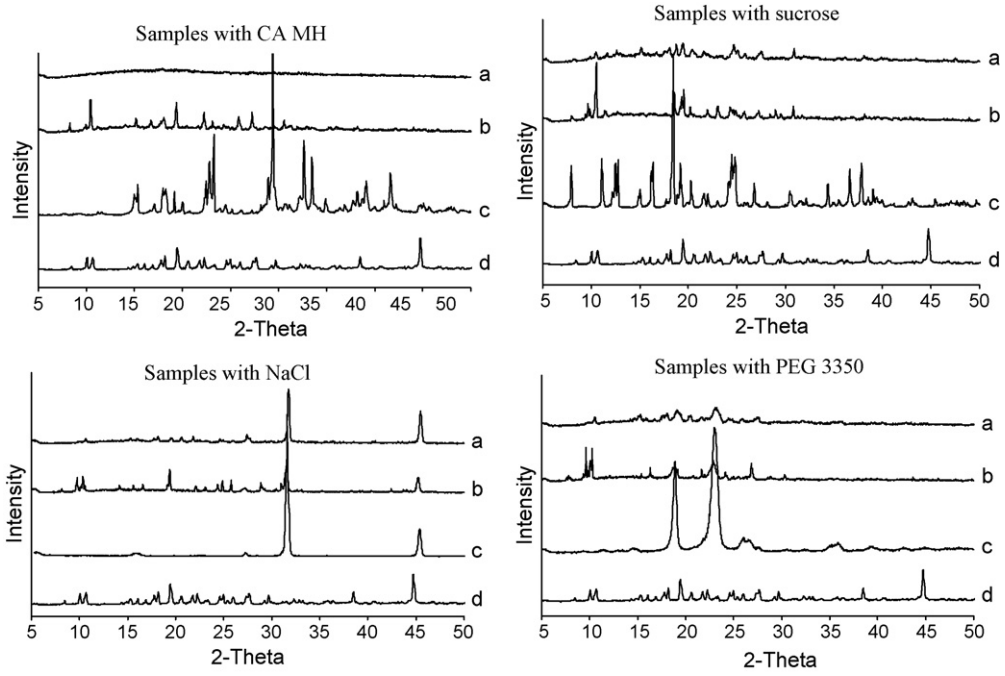

Fig. 13. Effect of pore forming excipients on crystallinity of diltiazem hydrochloride (DIL HCl) in extruded Eudragit® RS PO matrix tablets containing 60% polymer, 20% DIL HCl and 20% of either citric acid monohydrate (CA MH), sucrose, sodium chloride (NaCl) or PEG 3350. PXRD patterns of (a) hot-melt extrudates, (b) physical mixtures, (c) pore forming excipient and (d) DIL HCl.

release medium and the percolation of these soluble components through the inert matrix. Tablets containing CA MH as 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 h 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 30,000× 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 (data not shown).

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 h (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 h). 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 (Peng et al., 2001) 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 McGinity (2002) 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.

3.9. 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. 13). Patterns of crystalline DIL HCl exhibited numerous peaks in the 2θ range, and six characteristic peaks (10.7, 15.4, 18.2, 19.5, 20.7 and 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 and 27.7), NaCl (10.7, 15.4, 18.2, 19.5, 20.7 and 27.7) or PEG 3350 (10.7, 15.4, 20.7 and 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 due to 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. Conclusions

The present study demonstrated the suitability of CA MH to promote the release of a soluble model drug from hot-melt extruded Eudragit® RS PO matrices. Extrudates with drug only were partly 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 and 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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