

## Citric acid as a solid-state plasticizer for Eudragit RS PO

Sandra U. Schilling, Navnit H. Shah, A. Waseem Malick, Martin H. Infeld and James W. McGinity

### Abstract

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

### Introduction

Hot-melt extrusion is a simple method to produce solid dispersions/solutions of poorly water-soluble drugs to increase their release rate (Forster et al 2001a) and is an alternative method to tablet compression or film coating to manufacture controlled-release dosage forms of highly soluble drugs (Follonier et al 1994; Crowley et al 2004). The large variety in die shapes allows the manufacture of various dosage forms, such as tablets, pellets or films (Repka et al 1999). The extrudate can also be ground to a powder and compressed into tablets or used for dry powder coating (Zheng et al 2004). Benefits of melt extrusion include efficient and continuous processing, the elimination of solvents and the absence of compressibility requirements for the excipients in the formulation.

The inclusion of a plasticizer into the powder blend is generally necessary since most pharmaceutical polymers exhibit high glass transition temperatures ( $T_g$ ). Plasticized polymers soften at a lower temperature and yield a lower melt viscosity, and thus can be melt processed at lower temperatures. Most pharmaceutical plasticizers employed today are in the liquid state (e.g. organic esters (citrates and phthalates) and polyols (glycerol, PEGs with low molecular weight)). Several solid compounds such as lidocaine HCl (Aitken-Nichol et al 1996), methylparaben (Wu & McGinity 2003), ibuprofen (Wu & McGinity 2001; de Brabander et al 2002), chlorphenamine maleate (Zhu et al 2002b), tartaric acid (Mididoddi et al 2006) and indometacin (Zhu et al 2006) have been reported previously to exert plasticizing effects on polymers of pharmaceutical interest. Solid-state plasticization is thought to occur through distribution of the plasticizer in the molten polymer after being

Drug Dynamics Institute, College of Pharmacy, University of Texas at Austin, Austin, TX 78712, USA

Sandra U. Schilling, James W. McGinity

Hoffmann-LaRoche, Inc., 340 Kingsland St., Nutley, NJ 07110, USA

Navnit H. Shah, A. Waseem Malick, Martin H. Infeld

**Correspondence:** S. U. Schilling, 1 University Station, Campus Mail Code A1902, Austin, TX 78712, USA. E-mail: sshilling@mail.utexas.edu

melted or dissolved during extrusion, and occupation of active binding sites following the same mechanisms as with liquid plasticizers. Therefore, the solid compound must be sufficiently soluble in the polymer, and an interaction between both materials is necessary to achieve plasticization (de Brabander et al 2002).

The application of solid-state plasticizers is advantageous compared with liquid plasticizers. The mixing process before extrusion is more efficient, and the higher homogeneity of the obtained powder formulation yields an enhanced uniformity of the final product. Improved flow properties assure a stable and continuous powder flow through the extruder. Further important advantages are the higher thermal stability of most solid-state plasticizers and the decreased weight loss due to evaporation during the melt extrusion process. A lower tendency of plasticizer leaching or migration upon storage has also been discussed (Rahman & Brazel 2004).

Citric acid (CA) is a widely used excipient in pharmaceutical formulations as an acidifying agent to decrease the microenvironmental pH in enteric-coated dosage forms (Nykänen et al 2001, 2004; Bruce et al 2003). Researchers have further used CA as a hydrophilic carrier for poorly soluble drugs in solid dispersions produced by co-melting techniques to increase the dissolution rate and bioavailability (Summers & Enever 1976; Timko & Lordi 1979).

The CA molecule has a high capacity for hydrogen-bond formation and thus possesses a potential to interact with, and plasticize, certain pharmaceutical polymers. Bruce et al (2003, 2005) reported a plasticizing effect of CA on Eudragit L 30D-55 and Eudragit S100 when incorporated into either enteric film coatings or matrix tablets, respectively. Wan et al (1992, 1993) found CA to be beneficial for wall formation in spray-dried HPMC microcapsules. Chitosan films cast from aqueous CA solutions were shown to exhibit a high flexibility, demonstrating CA to be a good plasticizer for this polymer (Remuna-Lopez & Bodmeier 1996; Park et al 2002).

The application of Eudragit RS PO as carrier polymer in hot-melt extruded matrix systems has been previously reported (Zhu et al 2002a). The objective of this study was to investigate the ability of CA to function as a solid-state plasticizer for the melt extrusion of Eudragit RS PO. The properties of extruded tablets and cast films containing different levels of CA were determined. The solubility of the organic acid in the polymer was studied by modulated differential scanning calorimetry (MDSC) and powder X-ray diffraction (PXRD). The mechanical properties of cast films were investigated and the CA release from extruded tablets was observed over 12 h. Since the anhydrous form of CA exhibits different properties when compared with the monohydrate, both materials were processed separately with the acrylic polymer and the properties of the resulting tablets were evaluated.

## Materials and Methods

### Materials

Citric acid monohydrate (CA MH) (powder, USP) and anhydrous CA (powder, USP) were purchased from Spectrum

Chemicals (Gardena, CA). The monohydrate was ground with a mortar and a pestle and passed through a 60-mesh sieve (250  $\mu\text{m}$ ) before use. Eudragit RS PO was donated by Degussa Röhm America (Piscataway, NJ), while Cab-O-Sil M-5P was provided by Cabot Corp. (Billerica, MA).

### Manufacture of hot-melt extruded tablets

The anhydrous CA (25% based on the total weight) or CA MH (0–30% based on the total weight) was geometrically diluted with the polymer and blended. Cab-O-Sil M-5P (0.5%) was included into the formulations to promote a constant powder flow during the extrusion process. The blends were manually fed through a hopper into an extruder (single-screw extruder, model RCP 0750 Microtruder; Randcastle, Cedar Grove, NJ) and processed at temperatures between 90 and 140°C, depending on the processability of the formulation. The screw speed was set to a maximum of 20 rev min<sup>-1</sup>, while the motor load was limited to 0.700 drive amperes, and the pressure did not exceed 200 PSI (1.379 MPa). The molten polymer strand exited through a circular 6 mm die and was manually cut into 250 mg tablets.

### Preparation of films

Eudragit RS PO and CA MH (0–30%) were dissolved in 50 mL acetone so that 15% (w/v) solutions were obtained. The films were cast onto leveled 15 × 15 cm<sup>2</sup> teflon-coated plates and allowed to dry at room temperature for 24 h, followed by an additional 24 h in a 40°C oven to facilitate solvent removal. After the drying process, uniform rectangular specimens (15 mm × 70 mm × 300  $\mu\text{m}$ ) were cut and stored at 25 ± 1°C and 50 ± 5% relative humidity for at least 48 h before analysis. Film thickness was measured at 6 different locations along the entire length of the film with a manual micrometer (model ID C1012EBS; Mitutoyo, Aurora, IL). Only films with an average thickness of 280–320  $\mu\text{m}$  and a variation of less than 30  $\mu\text{m}$  (10%) were used for analysis.

### Influence of CA concentration on extrusion process parameters

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

### Thermal analysis

The solubility of CA in the extrudates and the influence of CA on the glass transition temperature of Eudragit RS PO were studied by MDSC with a TA Instrument model 2920 (New Castle, DE). Extrudates containing 0–30% CA MH were ground to a fine powder, and 8–12 mg samples were accurately weighed into aluminium pans and sealed. The samples were heated from –30 to 170°C at a rate of 10°C/min with the modulation set to ±1°C every 60 s and a nitrogen

flow of 40 mL min<sup>-1</sup>. The maximum amount of CA MH that could be incorporated into the extrudate without exhibiting any melting peak for the organic acid during the first heating run was reported as the solubility limit.

### X-ray diffraction analysis

The degree of CA crystallinity in ground extrudates was evaluated by PXRD using a Philips Electronic Instrument type 42273 (Mount Vernon, NY). Samples were analysed in the 2-theta range from 5 to 50° with a step size of 0.05° every 4 s. They were exposed to a Cu-K alpha radiation under 40 kV and 40 mA. The crystallinity of extrudates containing increasing monohydrate levels or anhydrous CA was compared with the physical mixture, and the influence of the extrusion temperature on the crystallinity of CA MH was investigated.

### Physico-mechanical properties of films

The mechanical properties of the cast films were investigated using an Instron Model 4201 equipped with Bluehill 2.5 material testing software (Instron, Norwood, MA). The procedure was based on the ASTM D 882 guideline for mechanical testing of thin films (ASTM-Guideline 2002). The rectangular strips were fixed between two hydraulic grips with an initial grip separation of 50 mm and stretched at a rate of 25 mm min<sup>-1</sup>. The effect of the CA MH level on the tensile strength, elastic modulus and elongation of the films was studied. The tensile strength was calculated by dividing the maximal load by the initial cross-sectional area of the film, while the elastic modulus was determined as the slope of the initial linear part of the load-strain curve. The elongation was reported as the absolute increase in length of the film at the moment of break. All values were the average of at least 6 determinations.

### Content of volatile components in films

The content of volatile components in films equilibrated at 25 ± 1°C and 50 ± 5% relative humidity for 48 h was determined to exclude large amounts of moisture or residual solvent as plasticizing agents. The technique was based on the USP Loss on Drying method and was carried out in a moisture analyzer AND MF-50 (A&D Engineering, Inc., Milpitas, CA). Approximately 1 g of film material was accurately weighed and spread as a single layer in a circular aluminium dish that was dried beforehand until weight constancy was obtained. The sample was kept at a constant temperature of 110°C until the weight loss per minute did not exceed 0.02%/min. The content of volatiles was reported as the average percent weight loss from 3 tested specimens.

### Citric acid release study

Release studies from melt extruded tablets containing 25% CA MH or anhydrous CA and processed at a die temperature of 120°C were carried out according to the USP 30 procedure

for extended release dosage forms in a USP apparatus 2 (paddle method; Varian, Cary, NC). Phosphate buffer pH 6.0 (900 mL, 37°C) was used as the dissolution medium, and the paddle speed was set to 100 rev min<sup>-1</sup>. For each determination, 6 samples consisting of 2 tablets (500 mg) were analysed over 12 h. The actual CA content was determined after complete destruction of the tablets with a Polytron homogenizer (Kinematica Inc., Newark, NJ). The percent CA released from the tablets was calculated from the actual CA content of each sample as a function of time.

### Citric acid assay

A Waters HPLC System (Milford, MA) equipped with a C<sub>18</sub>-reversed phase column (Capcell PAK, 3 × 100 mm; Shiseido Co., Tokyo, Japan) and a UV-detector set to 212 nm (996-PDA detector; Waters Inc., Milford, MA) was utilized to determine the CA content in the dissolution samples. The method was based on the findings of Ding et al (2006). The column temperature was held constant at 30°C during analysis and the injection volume was 20 µL. Phosphate buffer (10 mM), which was adjusted to pH 2.4 with concentrated phosphoric acid, and methanol were used as the mobile phase (95:5) at a constant flow rate of 0.5 mL min<sup>-1</sup>. The low pH of the mobile phase was necessary to prevent ionization of the trivalent organic acid during analysis. The relationship between CA content and UV signal was found to be linear with a correlation coefficient of 0.99997 over the range 2–200 µg mL<sup>-1</sup> (corresponding to 1.44–144.00% of CA MH in tested samples). The reproducibility for multiple injections (n = 3) exhibited less than 2.0% relative standard deviation for each tested concentration.

### Statistical analysis

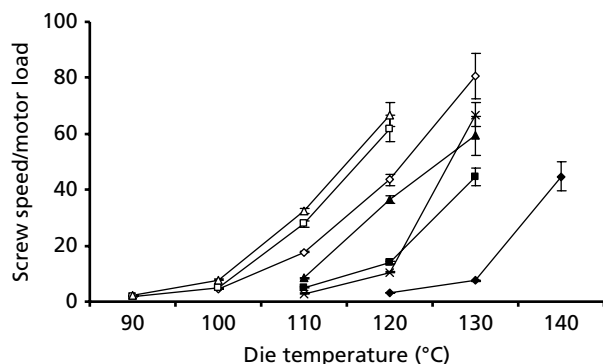
Minitab Release 14 Statistical Software (Minitab Inc., State College, PA) was employed to carry out statistical analysis on extrusion, physico-mechanical and dissolution data. All tests were based on the 95% confidence interval or on the closest provided value (Mann–Whitney), respectively. The effect of the CA MH concentration and the formulation type (anhydrous CA or CA MH) on the extrusion process parameters was analysed by Kruskal–Wallis test and pairwise Mann–Whitney median comparisons (nonparametric analysis, n = 3). The value for the screw speed/motor load quotient obtained for an extrusion at 120°C die temperature was selected as the response parameter since all formulations could be processed at this temperature. The influence of the CA MH concentration on the film properties (elastic modulus, tensile strength and elongation) was evaluated using one-way analysis of variance followed by post-hoc Tukey's test (n = 6). A univariate two-factor analysis of variance design with repeated measures on one factor (time) and Tukey's test were applied to determine the effect of the formulation type on the CA released at each sampling time point (n = 6). Also, the f<sub>2</sub> similarity factor (Shah et al 1998) was calculated from the means of % released at each time point to compare the entire dissolution profile of both investigated formulations.

## Results and Discussion

### Influence of CA on extrusion parameters

Formulations containing Eudragit RS PO with 0–30% CA MH or 25% anhydrous CA, based on the total formulation weight, were extruded at temperatures between 90 and 140°C, with a screw speed of 20 rev min<sup>-1</sup> or less, so that the motor load was maintained below 0.700 drive amperes. Improved processability of a powder blend by plasticization of the polymer yields a higher screw speed and a lower motor load for a predefined extrusion temperature. Plasticizers act by interposing themselves between polymer chains and disrupting cohesive interactions, thus resulting in a more malleable polymer with a lower melt viscosity. Since the resistance of the polymeric melt towards the rotating movement of the screw decreases, the load required of the motor is diminished. Consequently, the blend can be processed at higher screw rotation speeds without exceeding the safety motor load or screw pressure limits. To consider the influence of both parameters, the quotient of the highest applicable screw speed divided by the necessary motor load was investigated as a function of the CA content. This quotient can be interpreted as an index of processability of the formulation at the preset die temperature, and improved processability due to plasticization became noticeable as high quotients at lower temperatures.

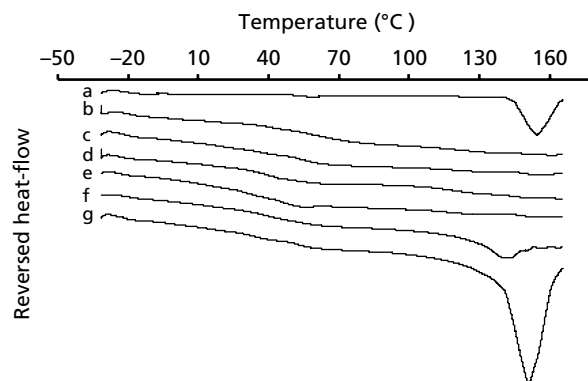
Figure 1 shows the screw speed/load ratios for formulations with increasing CA MH levels at different extrusion temperatures (end zone). A relatively high temperature of 140°C was necessary to extrude the pure polymer at a screw speed of 20 rev min<sup>-1</sup>, while blends containing CA MH could be processed at lower temperatures (130–110°C). Statistical analysis using the Kruskal–Wallis test demonstrated a significant influence of the CA MH concentration on the response parameter at 120°C die temperature ( $P=0.003$ ). A pairwise median comparison by Mann–Whitney test showed that the



**Figure 1** Influence of citric acid monohydrate (CA MH) concentration and anhydrous citric acid on the extrusion parameters (screw speed divided by motor load) for the melt extrusion of Eudragit RS PO as a function of die temperature. ◆, pure Eudragit RS PO; Eudragit RS PO with (■) 10% CA MH, (▲) 15% CA MH, (◇) 20% CA MH, (□) 25% CA MH and (△) 30% CA MH; ×, 25% anhydrous CA; (n=3, error bars represent the standard deviation).

screw speed/motor load quotient significantly increased when the CA MH concentration was changed from 0 to 10, 15 and 20 to 25% (significant difference in all medians). The improved processability of blends comprising higher CA MH level at increased screw speeds under a reduced motor load indicated a decrease in melt viscosity and made an extrusion at lower temperatures possible. The absence of a statistically significant difference between the 25 and 30% CA formulation suggested that the plasticizing effect of CA MH plateaued at these concentrations. This ceiling effect coincided with the solubility limit of CA MH in Eudragit RS PO as determined by MDSC (Figure 2), supporting the hypothesis that only dissolved CA functioned as a plasticizer. These results demonstrated that the CA MH acted as a plasticizer or as a thermal lubricant (or both) on Eudragit RS PO when the polymer was melt extruded.

The results in Figure 1 further illustrate that CA MH facilitated the extrusion process more efficiently than the anhydrous form, since significantly higher screw speed/motor load values were obtained for the 20 and 25% CA MH formulation when compared with the blend with 25% anhydrous CA at three temperature levels (110–130°C). This phenomenon can be explained by the lower melting point of the monohydrate and its higher tendency to interact with the polymer due to lower cohesive forces when compared with the anhydrous form; CA MH has a melting point of 135°C, while anhydrous CA melts at 155°C (determined by DSC, data not shown). It can be assumed that the melting point of the monohydrate was further depressed through interactions with the Eudragit RS PO, so that at least a softening during extrusion, and consequently an enhanced distribution of the organic acid in the polymer melt, was promoted. Recrystallization of CA MH after cooling of the extrudate to room temperature did not occur in tablets containing up to 20% CA, since the interactions between Eudragit RS PO and CA MH enabled the CA MH to remain dissolved in the extrudates. The anhydrous form, having a higher melting point and more stable lattice structure, did not melt or dissolve completely in the polymer



**Figure 2** MDSC thermograms (1st runs) of hot-melt extrudates containing 0–30% citric acid monohydrate (CA MH). Physical mixture of 10% anhydrous CA in Eudragit RS PO (a); extrudate with 0% CA MH (b), 10% CA MH (c), 15% CA MH (d), 20% CA MH (e), 25% CA MH\* (f) and 30% CA MH\* (g). \*An excess of CA MH solubility in the extrudates led to re-crystallization in the anhydrous form.

during processing. These differences in solubility were supported by PXRD data. As only molecularly dispersed CA can function as a plasticizer, the monohydrate with its higher solubility in Eudragit RS PO was more effective in reducing the polymer's melt viscosity, and hence improving its processability for melt extrusion, than the anhydrous form.

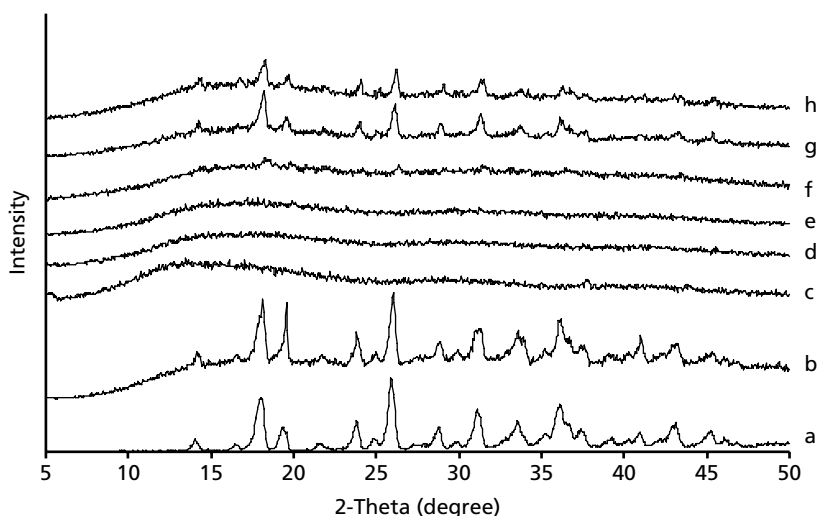
### Solubility of CA in Eudragit RS PO

Solubility of the solid plasticizer in a polymer is crucial since only molecularly distributed plasticizer is able to interact with the polymer chains and hence reduce cohesion forces. The CA molecule possesses a high capacity for hydrogen bonding, which was reported to be responsible for the stability of the amorphous state and prevents its recrystallization in solid dispersions (Timko & Lordi 1979). Hydrogen-bond formation between the CA molecules and the Eudragit RS PO chains should account for a sufficient solubility and a plasticizing effect of the organic acid in the polymer melt.

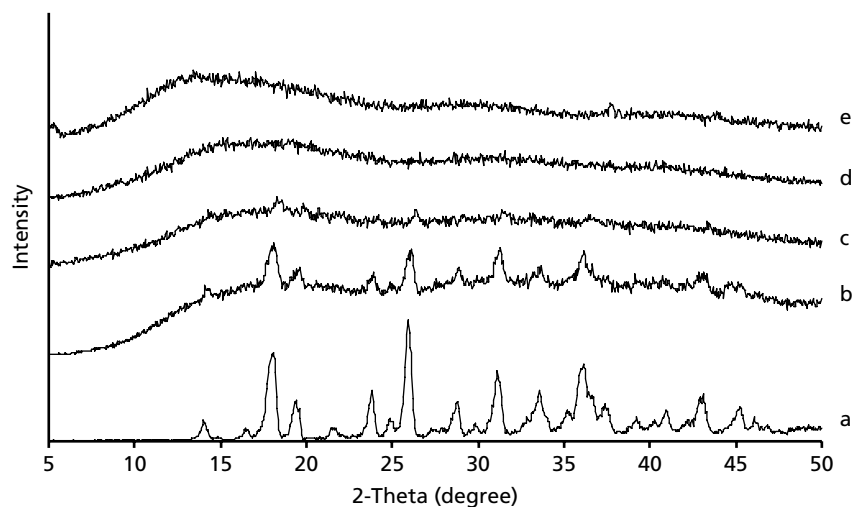
The solubility of CA in Eudragit RS PO hot-melt extrudates was studied by MDSC and PXRD. Thermal analysis of extrudates containing 0–30% CA MH was carried out over a temperature range of  $-30$  to  $170^{\circ}\text{C}$ . The MDSC method yielded sufficient sensitivity to detect a melt endotherm for 10% crystalline CA in a physical mixture with Eudragit RS PO (Figure 2). All thermograms exhibited a single glass transition for the acrylic polymer at  $35$ – $55^{\circ}\text{C}$ . Extrudates with high CA levels (25 or 30%) displayed an additional endothermic event at  $144$  or  $152^{\circ}\text{C}$ , respectively. This peak was attributed to the melting of anhydrous CA when the solubility of CA in the polymer was exceeded and excess CA re-crystallized from the solid solution in the anhydrous form. Concentrations of up to 20% CA MH in extruded polymer resulted in one-phase amorphous systems with a single  $T_g$  and no melting endotherm. In these cases, the organic acid melted or

dissolved in the polymer during the extrusion process and remained dispersed at a molecular level in the solidified polymer after cooling. The corresponding extrudates were transparent strands, supporting the existence of a molecular dispersion, while extrudates comprising 25% CA MH or higher levels were opaque.

The solubility of CA in Eudragit RS PO was further investigated by PXRD. Extrudates processed at  $110^{\circ}\text{C}$  and containing 10, 20, 25 or 30% CA MH or 25% anhydrous CA were compared. Figure 3 shows that extrudates with 10 and 20% CA MH were completely amorphous, while the 25% CA MH sample exhibited peaks of low intensity, suggesting a low degree of crystallinity for this formulation. The diffraction patterns of extrudates containing 25% anhydrous CA or 30% CA MH exhibited more distinct peaks and hence an increased degree of crystallinity. The results demonstrated that the solubility of the monohydrate form was exceeded at concentrations of 25% or higher. The excess of the CA MH solubility in the extrudates led to re-crystallization of citric acid in the anhydrous form. These findings were in agreement with the results from the MDSC experiments. The solubility of the anhydrous CA in the acrylic polymer was lower than that of the monohydrate; however, the peak intensity of anhydrous CA in the extrudate was reduced when compared with the physical mixture, which suggested that there was a partial dissolution of anhydrous CA in the polymer during extrusion. The lower solubility of the anhydrous form was attributed to the higher stability of the intermolecular lattice due to stronger cohesive forces, resulting in a higher melting point and a lower tendency to interact with the polymer. The monohydrate form softened or melted during the extrusion process, which facilitated its molecular distribution between the polymeric chains, while the anhydrous lattice remained intact to a higher degree. These findings support the previously reported differences in extrusion process parameters.



**Figure 3** Influence of citric acid (CA) concentration and type (anhydrous form or monohydrate = MH) on the crystallinity of hot-melt extrudates obtained at  $110^{\circ}\text{C}$ . PXRD patterns of anhydrous CA powder (a), physical mixture of Eudragit RS PO and 25% anhydrous CA (b), Eudragit RS PO powder (c), extrudate with 10% CA MH (d), extrudate with 20% CA MH (e), extrudate with 25% CA MH\* (f), extrudate with 30% CA MH\* (g), and extrudate with 25% anhydrous CA (h). \*An excess of CA MH solubility in the extrudates led to re-crystallization in the anhydrous form.



**Figure 4** Influence of extrusion temperature on the crystallinity of hot-melt extrudates containing 25% citric acid monohydrate. PXRD patterns of anhydrous citric acid powder (a), extrudate obtained at 100°C\* (b), extrudate obtained at 110°C\* (c), extrudate obtained at 120°C (d), and Eudragit RS PO powder (e). \*An excess of CA MH solubility in the extrudates led to re-crystallization in the anhydrous form.

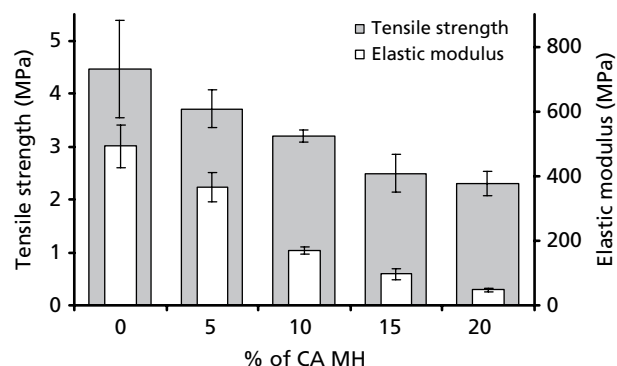
Extrusion temperature was found to influence the degree of CA crystallinity in the extrudates (Figure 4). Extrudates containing 25% CA MH and processed at 100, 110 and 120°C die temperature were selected for further PXRD studies, since the CA solubility in the polymer was exceeded at this CA concentration. An increase in the processing temperature led to a decrease in CA crystallinity. The degree of crystallinity in samples extruded at 110°C was lower than for the 100°C samples, while extrudates processed at 120°C were amorphous. These findings demonstrated that a sufficiently high extrusion temperature either led to an increased miscibility between the components, or that the formation of a stable amorphous two-phase system was promoted. Since similar tendencies were observed for samples with other CA levels, it can be concluded that the higher the content of CA MH in the formulation, the higher the required extrusion temperature for the formation of a non-crystalline extrudate.

#### Plasticizing effect of CA on Eudragit RS PO

The mechanism of CA-induced facilitation of the Eudragit RS PO extrusion process was expected to be due to plasticization. Since the interactions between the polymeric chains were reduced by the incorporation of a plasticizer, a shift in the polymer's glass transition to lower temperatures should be detectable as a function of an increasing CA concentration. The data obtained by MDSC (Figure 2), however, showed only a very slight decrease in the  $T_g$  with increasing CA MH levels in the extrudates and hence did not convincingly demonstrate a plasticizing effect. This observation might be attributed to the fact that unplasticized Eudragit RS PO possesses a low  $T_g$  around 60°C, and that the change in heat capacity was not distinct.

Plasticizers also decrease the stiffness and increase the flexibility of polymeric films. To demonstrate the plasticizing properties of CA MH on Eudragit RS PO, films were produced applying a casting-solvent evaporation technique. Films containing 0–30% CA MH based on the total weight

were cast from acetone solutions and their physico-mechanical properties were investigated. The tensile strength and the elastic modulus characterize the stiffness of a film and are directly proportional to the force that is required for film-stretching, whereas the maximal elongation correlates with the film flexibility. The presence of a plasticizer in a film formulation generally results in a decrease in the tensile strength as well as the modulus, and an increase in the elongation. Films cast from solutions containing 20% CA or less were smooth and transparent, confirming the solubility of the organic acid in Eudragit RS PO up to this concentration. Higher levels of CA, such as 25 or 30%, however, led to films with macroscopically visible crystals on the film surface and exhibited dramatically altered mechanical properties. These films were very brittle and readily broke when being attached to the grips of the Instron, and thus they were not analysed. The data in Figure 5 demonstrate a reduction in the tensile



**Figure 5** Influence of citric acid monohydrate (CA MH) concentration on the tensile strength and elastic modulus of films containing 0–20% CA MH ( $n=6$ , error bars represent the standard deviation). Films were stored at  $25 \pm 1^\circ\text{C}/50 \pm 5\%$  relative humidity for 48 h before analysis.

strength from 4.46 to 2.30 MPa when the CA MH concentration was increased from 0 to 20%. According to the results of analysis of variance and Tukey's test, the tensile strength values for the 0%, 10% and 20% level were significantly different. The decrease in the elastic modulus from 492 to 48 MPa with increasing CA concentrations was found to be significant for the 0, 5, 10 and 15% level, but not for the 20% level. The elongation increased only insignificantly at low CA concentrations ( $0.76 \pm 0.21$  mm to  $1.65 \pm 0.20$  mm for 0% and 10%, respectively), while the 15 and 20% level exhibited significantly higher elongation values ( $7.59 \pm 1.01$  cm and  $10.89 \pm 1.07$  cm, data not shown). These findings for the physico-mechanical properties of the polymeric films support the hypothesis that CA functioned as a plasticizer for Eudragit RS PO.

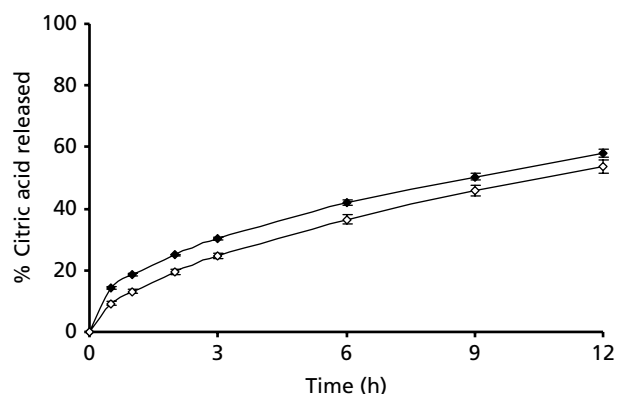
Adsorbed water and residual acetone are able to exert plasticizing effects in cast films. The high hygroscopicity of CA is well known (Peng et al 2001). To exclude adsorbed moisture and residual solvent as possible reasons for the observed changes in film properties at higher CA levels, the content of volatile components of the films was determined (data not shown). The volatile content was low in all films ( $3.28 \pm 0.08\%$  to  $3.85 \pm 0.18\%$ ,  $n=3$ ) and not dependent on the CA concentration, so that their influence on the mechanical properties was deemed negligible and the observed changes were attributed to the differences in the CA level.

#### CA release from extruded tablets

The dissolution profile of CA from the polymer matrix was investigated to evaluate the capability of the system to retard the release of water-soluble active pharmaceutical ingredients (APIs). Leaching of hydrophilic plasticizers, such as TEC, from insoluble matrix systems during the dissolution process was demonstrated to impact the drug release rate and mechanism (Zhu et al 2002b). Hot-melt extruded matrices are characterized by a low porosity and a high tortuosity when compared with direct compressed or granulated dosage forms. The addition of hydrophilic compounds, such as CA, to the formulation will lead to an increased channel formation in the insoluble matrix when the system is exposed to the dissolution medium, allowing incorporated APIs to diffuse through the water-filled pores at a faster rate.

Dissolution studies with Eudragit RS PO matrix tablets containing 25% CA MH or anhydrous CA were carried out over 12 h in a pH 6.0 phosphate buffer (apparatus 2, paddle method). Since the maximal extrusion temperature ( $130^\circ\text{C}$ ) was below the decomposition temperature of CA, which has been reported to be thermally stable up to  $160^\circ\text{C}$  (Forster et al 2001b), and the transition time through the extruder did not exceed 4 min, thermal decomposition of CA was unlikely. The actual CA content of each tablet after complete destruction with a Polytron homogenizer was found to be 98.0–101.0% by HPLC analysis, supporting thermal stability and content uniformity of CA in the polymeric carrier after the extrusion process.

Although Eudragit RS PO is insoluble at all pH values and consequently controls the release of highly water-soluble components, a rapid release profile of the CA from the extrudates was expected due to the high water solubility of the organic acid, allowing a quick diffusion through channels



**Figure 6** Release of citric acid monohydrate and anhydrous citric acid from Eudragit RS PO tablets extruded at  $120^\circ\text{C}$ .  $\blacklozenge$ , formulation with 25% citric acid monohydrate;  $\diamond$ , formulation with 25% anhydrous citric acid. Dissolution: USP paddle method, 900 mL phosphate buffer pH 6.0 as dissolution medium,  $37^\circ\text{C}$ ,  $100 \text{ rev min}^{-1}$ ; ( $n=6$ , error bars represent the standard deviation).

formed in the polymer matrix. The pore formation in HPMC matrix systems through rapid CA leaching has been previously reported (Espinoza et al 2000). However, dissolution testing revealed an extended-release profile for CA with  $42.05 \pm 0.76\%$  and  $36.55 \pm 1.45\%$  released after 6 h and  $57.99 \pm 1.35\%$  and  $53.66 \pm 1.98\%$  released after 12 h for CA MH and anhydrous CA, respectively (Figure 6). The small surface area of the studied monolithic dosage form and the high affinity between the polymer and the organic acid, which is essential for plasticization, are two possible explanations for the slow CA release. Furthermore, the incorporated level of CA (25%) might have been below the minimal concentration necessary for continuous channel formation to allow percolation throughout the polymer matrix.

For the release of the monohydrate and the anhydrous CA, an  $f_2$  value  $> 50$  ( $f_2 = 66.90$ ) demonstrated the similarity of the dissolution profiles. The comparison of both profiles by repeated measures analysis of variance and Tukey's test showed a significantly lower release for the anhydrous form at each sampling time point. The difference in release rates can be explained by the different degree of crystallinity of the CA in the samples with anhydrous CA being more crystalline in melt extruded Eudragit RS PO. Since crystalline phases are more stable systems and possess a lower surface energy, they usually have a lower dissolution tendency than amorphous phases, resulting in a decreased dissolution rate when compared to non-crystalline systems.

#### Conclusions

This study demonstrated that citric acid (CA) functioned as an effective solid-state plasticizer in Eudragit RS PO films and hot-melt extrudates. The extrusion process was found to be facilitated by increasing the concentration of CA, and plateaued at 25% based on the total formulation weight. Citric acid monohydrate (CA MH) was more effective in improving the processability than the anhydrous form, with the higher plasticization efficiency of the monohydrate being attributed

to its higher solubility in the acrylic polymer. The solubility of CA MH in Eudragit RS PO was limited and dependent on the extrusion temperature. Concentrations of up to 20% CA MH were found to be soluble in extrudates as well as in cast films, while extrudates with 25% CA MH required an extrusion temperature of at least 120°C to remain amorphous. A reduction in the glass transition temperature of Eudragit RS PO extrudates by CA MH was not convincingly shown by MDSC data; however, the tensile strength and elastic modulus of polymeric films decreased as a function of CA level, while the elongation increased, indicating plasticization of the polymer. Dissolution studies demonstrated a slow and controlled release of CA from extruded tablets with the monohydrate form being released faster than the anhydrous form. In conclusion, citric acid monohydrate was shown to be sufficiently soluble in Eudragit RS PO and was successfully used for the plasticization of Eudragit RS PO when hot-melt extruded.

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