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Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate

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Abstract

The influence of in situ plasticization of chlorpheniramine maleate (CPM) on Eudragit® RS PO from hot-melt extruded matrix tablets, and from compressed granules prepared by thermal processing was investigated. CPM was studied as both a model drug substance and as a solid-state plasticizer for the acrylic polymer. Triethyl citrate (TEC) was incorporated into the polymer blend as a liquid plasticizer for the polymer. The influence of TEC and CPM concentration on the dissolution properties of CPM tablets was investigated. The glass transition temperature (T_g) of the samples was determined by modulated differential scanning calorimetry (MDSC). The morphologies of the granules formed by hot-melt extrusion and hot-melt granulation processes were investigated by scanning electron microscopy. The addition of 12% TEC to the polymer reduced the T_g by 32.5 °C, while the reduction in the T_g for the same level of CPM was 16.4 °C. The effect of TEC levels on drug release was dependent on the tablet preparation method. At high TEC levels, the release rate of CPM decreased in tablets prepared by direct compression and tablets made from compressed granules that had been prepared by high shear hot-melt granulation. However, the CPM release rate increased from hot-melt extruded tablets with increasing blends of plasticizer in the extruded tablets. An increase in the CPM content in the tablets resulted in an increase in the drug release rate. During high shear hot-melt granulation, the model drug adhered to the polymer to form a porous discontinuous structure. Following hot-melt extrusion, the drug was distributed at a molecular level in the continuous polymeric structure. The influence of both CPM and TEC levels on the drug release rate from these polymeric drug delivery systems was shown to be a function of whether the granules or tablets were formed by either hot-melt granulation or hot-melt extrusion, as well as the plasticization effects of both TEC and CPM on the acrylic polymer. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Eudragit® RS PO; Chlorpheniramine maleate; Triethyl citrate; Plasticization; Hot-melt granulation; Hot-melt extrusion

1. Introduction

Plasticizers are incorporated into pharmaceutical polymers to facilitate thermal processing (Repka and McGinity, 2000a), to modify drug

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release from polymeric systems (Bodmeier and Paeratakul, 1990; Flosser et al., 2000; Mulye and Turco, 1994; Wu and McGinity, 1999) and to enhance the mechanical properties (Gutierrez-Rocca and McGinity, 1994; Repka and McGinity, 2000b; Wang et al., 1997; Wu and McGinity, 1999) and surface appearance of the dosage form (Wilson, 1995). When incorporated into a polymeric material, a plasticizer improves the workability and flexibility of the polymer by increasing the intermolecular separation of the polymer molecules (Sears and Darby, 1982). This results in a reduction in elastic modulus, tensile strength, polymer melt viscosity and glass transition temperature (T_g). The polymer toughness and flexibility is improved and lower thermal processing temperatures can be empolyed (Rauwendaal, 1994). For instance, pharmaceutical polymers used in film coating typically require a plasticizer in order to reduce brittleness and to enhance polymer coalescence and film formation (Wheatley and Steuernagel, 1997). The plasticizer reduces both the glass transition temperature of the polymer and the minimum film formation temperature. As a result, the temperature required for film coating is reduced.

In selecting the appropriate plasticizer for a polymeric material, the plasticization efficiency and compatibility must be considered which may be determined by measuring the glass transition temperature of the polymeric material as a function of plasticizer concentration. Differential scanning calorimetry (DSC) is typically used to measure the polymer glass transition temperature, however, this technique is not always sensitive enough to identify T_gs for certain polymers. Modulated differential scanning calorimetry (MDSC) has been shown to be more effective in separating thermal events, and provides greater resolution and sensitivity due to the application of a modulated rather than a linear temperature program (Coleman and Craig, 1996; Ferrero et al., 1999). A second run is performed to erase the different thermal histories of the samples (Hatakeyama and Quinn, 1999).

Wu and McGinity reported that solid non-traditional plasticizers including methylparaben and drugs such as ibuprofen and chlorpheniramine maleate were able to plasticize and lower the glass transition temperature of polymeric films prepared from aqueous latex dispersions of Eudragit® RS 30 D (Wu and McGinity, 1999). Eudragit® RS PO is a copolymer of acrylic and methacrylic esters with a low content of quaternary ammonium groups. It has been used to prepare matrix tablets by direct compression (Boza et al., 1999), and wet granulation techniques (Palmieri et al., 1999; Sanghavi et al., 1990).

Hot-melt extrusion is one of the most widely applied processing techniques in the plastics industry. For pharmaceutical systems, several research groups have recently demonstrated that thermal processing of pharmaceutical powders is a viable method to prepare granules, sustained release tablets (McGinity et al., 2000; Zhang and McGinity, 1999, 2000) and transdermal drug delivery systems (Repka and McGinity, 2000a,b, 2001a,b). For pharmaceutical applications, hot-melt extrusion offers many advantages over traditional processing techniques. Solvents and water are not needed for processing, therefore fewer processing steps are needed and time-consuming drying steps are eliminated. There are no requirements on the compressibility of the active ingredients and the entire procedure is simple, continuous and efficient (McGinity et al., 2000).

The objectives of this study were to demonstrate the influence of the in situ solid-state plasticization of chlorpheniramine maleate (CPM) on Eudragit® RS PO and to investigate the physicochemical properties of the resulting composite tablets. Tablets were prepared by hot-melt extrusion and by direct compression. In addition, tablets were also compressed from granules prepared by a high shear hot-melt granulation technique. CPM was used as both a model drug and as a solid-state plasticizer in this study. A liquid plasticizer, triethyl citrate (TEC), was also incorporated into the formulations. Plastization effect and the microstructure of these composites were investigated to explain the drug release mechanism from tablets prepared by the different technologies.

2. Materials and methods

2.1. Materials

Chlorpheniramine maleate was purchased from Spectrum Quality Products (Gardena, CA). The other materials were kindly supplied by various manufactures: Eudragit® RS PO, Röhm America (Piscataway, NJ); triethyl citrate, Morflex (Greensboro, NC).

2.2. Preparation of high shear hot-melt granules

Granules were prepared by a high shear hot-melt granulation process using a Robot Coupe Vertical Batch Processor (Model RSI 3VG, Robot Coupe Scientific Industrial Division, Ridgeland, MS). Three S-blades were assembled in the 3-l stainless steel chamber. The processing temperature was maintained at 60 °C by circulating Thermal M fluid (100 °C) (Julabo USA, Kutztown, PA) in the jacket surrounding the chamber. The temperature inside the chamber was monitored using a thermal probe. The CPM and Eudragit® RS PO were blended at a speed of 1500 rpm for 2 min. During this time, TEC was also incorporated into the powder blend. The blended material was heated until granules were formed between 60 and 70 °C. After mixing for 10 min, the granules were cooled to 25 °C. Granules in the 20–40 mesh range (850–425 μ) were retained for further evaluation.

2.3. Preparation of hot-melt extruded tablets

Tablets were prepared by hot-melt extrusion using a vertical single screw Randcastle Model RCP-0750 Microtruder® (Randcastle Extrusion Systems, NJ). The operating temperatures for Zone 1, Zone 2, Zone 3, and Zone 4 (die) were 90, 105, 110, and 115 °C, respectively. The screw rotation speed was 20 rpm and the die diameter was 6.0 mm. Hot-melt extrudates were cut manually into tablets with a weight of approximately 100 mg. Samples were stored at 25 °C/60%RH in HDPE closed containers until further study.

2.4. Preparation of hot-melt extruded granules

Hot-melt extruded granules were made with a model RCP-2.0 Pelletizer (Randcastle Extrusion Systems, NJ) by pelletizing the hot-melt extrudates prepared by the process described in Section 2.3. Granules in the 20–40 mesh range (850–425 μ) were retained for further evaluation.

2.5. Tablets preparation

High shear hot-melt granules, hot-melt extruded granules as well as a dry powder blend of CPM and excipients including the plasticizer TEC (High shear blending was used for the incorporation of the TEC into the dry powder blend) were compressed into tablets (6 mm die) on a Carver laboratory press (Fred Carver) with a compression force of 2000 kg. High shear blending of the powder mix with the TEC was conducted with a Robot Coupe Vertical Batch Processor for 2 min to ensure a uniform distribution of the TEC throughout the powder. The tablet weight was approximately 100 mg.

2.6. Dissolution studies

The release of CPM and TEC from tablets was evaluated according to the USP 24 basket method. The dissolution media consisted of 500 ml of distilled water maintained at 37 °C. The basket rotation speed was set at 100 rpm, and at predetermined intervals, a 3.0 ml volume of sample was passed through a 10 μ filter and analyzed for both CPM and TEC. The concentration of CPM was measured using a Beckman DU-65 UV spectrophotometer at 261 nm. The concentration of TEC in the dissolution medium was measured using the HPLC method described below.

2.7. HPLC method for TEC

A HPLC method was used to determine the release of TEC from the hot-melt extrudates (Bodmeier and Paeratakul, 1991). The chromatographic system consisted of a Waters 501 HPLC pump, a Waters 486 tunable absorbance detector set at 220 nm, a Waters 712 WISP sample injec-

tor, and a Waters C18 3.9 × 300mm μBondabpak analytical column (10 μm). The mobile phase consisted of a mixture of methanol:water (70:30 v/v). The retention time for TEC was 5.0 min. Linearity of the system was demonstrated over the working sample concentration range with a correlation coefficient of 0.99. A lack of interference from the other ingredients was demonstrated, and the reproducibility of the system for multiple injections ($n = 6$) was less than 0.5% relative standard deviation.

2.8. Modulated differential scanning calorimetry

A modulated differential scanning calorimeter (TA Instruments, Model DSC 2920 Modulated DSC) was used to determine the solid-state plasticization effect of CPM on the Eudragit® RS PO as well as the plasticization effect of TEC on the Eudragit® RS PO. Approximately 5–10 mg of sample was accurately weighed and hermetically sealed in an aluminum pan. The sample was equilibrated at −10 °C for 2 min. The temperature of the samples was then ramped from −10 to 160 °C at a rate of 5.0 °C/min. Modulation was set at ±1.0 °C every 60 s. The samples were cycled twice to remove thermal history. The glass transition temperature was measured in the second cycle as the step transition in the plot of reversible heat flow versus temperature. The MDSC was calibrated using an abbreviated calibration method with an indium standard prior to sample analysis.

2.9. Scanning electron microscopy

Samples were coated with gold-palladium for 60 s under an argon atmosphere using a Pelco® Model 3 sputter coater (TED Pella, Tustin, CA) in a high vacuum evaporator equipped with an omni-rotary stage. The morphologies of the samples were investigated by using a Hitachi S-4500 Scanning Electron Microscope (Hitachi, Ibaraki-Ken, Japan) at 15 kV at two magnifications (100 × and 1000 ×).

3. Results and discussion

3.1. Plasticization and drug release

3.1.1. Influence of TEC concentration on drug release

The profiles in Fig. 1 demonstrate the influence of TEC levels on the dissolution properties of directly compressed tablets formulated with a dry powder blend of CPM and excipients or granules prepared by high shear hot-melt granulation. Drug release was greater than 80% in 2 h for tablet formulations containing no TEC. Tablets formulated using hot-melt granules containing no TEC released CPM faster than tablets of the dry powder blend. Due to the loss of surface moisture during the hot-melt granulation process, no interaction between drug and polymer was observed when TEC was not present in the formulation, resulting in a faster release rate of drug from tablets containing granules prepared by high shear hot-melt processing.

When TEC was incorporated into the formulations, the drug release rate decreased for both

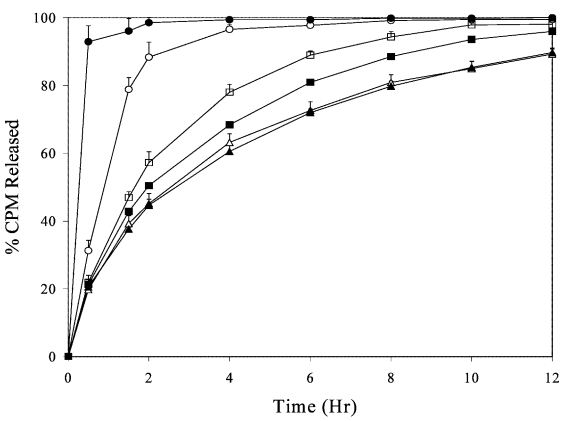

Fig. 1. Influence of triethyl citrate levels on the dissolution properties of Eudragit® RS PO tablets containing chlorpheniramine maleate (10%, w/w), prepared by direct compression of powder blend (DC) or high shear hot-melt granules (HMG). Compression force: 2000 kg. Dissolution: USP 24 basket method, 100 rpm, 500 ml distilled water as the dissolution medium, 37 °C ($n = 3$). (○): 0% triethyl citrate, DC; (□): 4% (w/w) triethyl citrate, DC; (△): 7% (w/w) triethyl citrate, DC; (●): 0% triethyl citrate, HMG; (■): 4% (w/w) triethyl citrate, HMG; (▲): 7% (w/w) triethyl citrate, HMG.

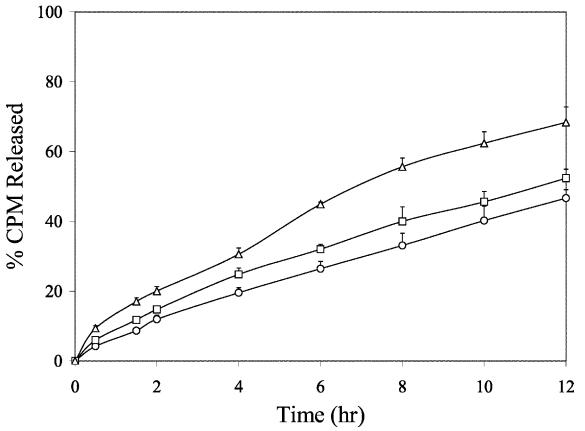

Fig. 2. Influence of triethyl citrate levels on the dissolution properties of Eudragit® RS PO hot-melt extruded tablets containing chlorpheniramine maleate (10%, w/w). Dissolution: USP 24 basket method, 100 rpm, 500 ml distilled water as the dissolution medium, 37 °C ($n = 3$). (○): 0% triethyl citrate; (□): 4% (w/w) triethyl citrate; (△): 7% (w/w) triethyl citrate.

tablet preparations, as shown in Fig. 1. The drug release data were fitted to the Higuchi equation (Higuchi, 1963), and the drug release rate constants were calculated and determined to be diffusion-controlled processes (Goracinova et al., 1995). The drug release rate constant decreased from 32.8 to 28.1% $h^{-1/2}$ when the TEC level increased from 4 to 7% in the directly compressed tablet formulation. A decrease in the rate constant from 30.8 to 27.9% $h^{-1/2}$ was found when the TEC level increased from 4 to 7% in compacts containing granules prepared by the high shear hot-melt process. The decrease in the drug release rate constant was due to the presence of TEC in the interstices of the polymer, to increase the binding of the drug to the polymer, thus facilitating the formation of a continuous matrix structure which would decrease the diffusivity of the drug from the system. The addition of TEC further enhanced drug and polymer binding during thermal processing and, as a result, drug release rates from tablets formulated as a dry powder blend were faster than drug release rates from compressed tablets prepared from high shear hot-melt granules having 4% of TEC.

The influence of TEC levels on the dissolution release rate of CPM from hot-melt extruded tablets is seen in Fig. 2. The drug release rate constant was calculated to be 11.7% $h^{-1/2}$ for tablets containing no TEC. When 4 and 7% TEC were incorporated into the powder blend formulation, the release rate constants for the hot-melt extruded tablets containing Eudragit® RS PO and 10% CPM were increased to 13.8 and 18.6% $h^{-1/2}$, respectively. CPM drug release rates increased with increasing levels of TEC in the hot-melt extruded tablets, whereas in directly compressed tablets or tablets prepared from high shear hot-melt granules, a decrease in the drug release rate was seen. The high temperature and pressure of the hot-melt process converted the materials into a homogenous structure. For the directly compressed tablets and those prepared from the hot-melt granules, porous structures were formed. The TEC functioned to enhance the formation of a continuous matrix structure in the directly compressed tablet compact. The plasticizer also enhanced the adhesion of polymer particles in the granules prepared by the hot-melt granulation process. The water-soluble plasticizer, diffused from the hot-melt extruded tablets into the dissolution media, enhancing drug release as a result of channel formation in the tablet. This hypothesis was confirmed by determining the amount of TEC released from the hot-melt ex-

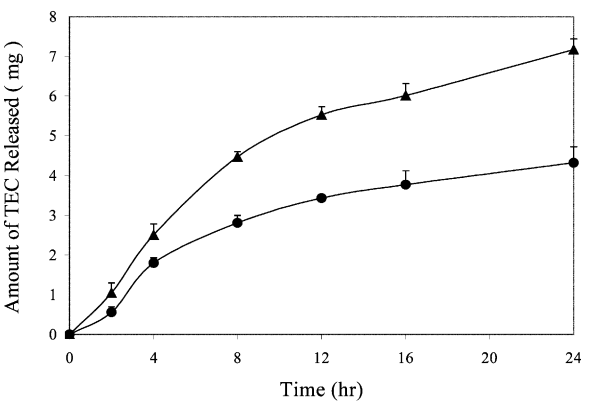

Fig. 3. Release of triethyl citrate from the hot-melt extruded Eudragit® RS PO tablets containing chlorpheniramine maleate (10%, w/w) with time. Dissolution: USP 24 basket method, 100 rpm, 500 ml distilled water as the dissolution medium, 37 °C ($n = 3$). (●): 4% (w/w) triethyl citrate; (▲): 7% (w/w) triethyl citrate.

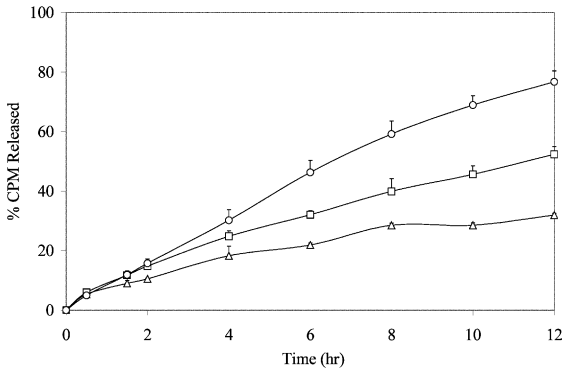

Fig. 4. Influence of chlorpheniramine maleate levels on the dissolution properties of hot-melt extruded chlorpheniramine maleate tablets containing Eudragit® RS PO and 4% (w/w) triethyl citrate. Dissolution: USP 24 basket method, 100 rpm, 500 ml distilled water as the dissolution medium, 37 °C ($n = 3$). (△): 6% (w/w) chlorpheniramine maleate; (□): 10% (w/w) chlorpheniramine maleate; (○): 14% (w/w) chlorpheniramine maleate.

truded tablets during the dissolution study, and these results appear in Fig. 3. The release of TEC from the hot-melt extruded tablets also followed the Higuchi diffusion model. TEC was completely released after 24 h for the tablets containing 4 and 7% TEC. The diffusion of TEC into aqueous media from cast films prepared from aqueous colloidal polymer dispersions had previously been reported by Bodmeier and Paeratakul (Bodmeier and Paeratakul 1992).

3.1.2. Influence of CPM concentration on drug release

The influence of CPM levels on the dissolution properties of tablets prepared by hot-melt extrusion is demonstrated in Fig. 4. Drug release rates increased with increasing amounts of CPM in the formulation. When 6, 10 and 14% CPM was incorporated into the extruded formulation, the drug release rates were calculated to be 9.11, 13.8, and 20.0% $h^{-1/2}$, respectively. Higher level of CPM corresponding to lower level of the polymer in the tablet, resulted in an increase in the drug release rate. As more drug is released from the tablet, more channels are produced, contributing to faster drug release rates. In addition, higher drug levels in the extruded tablet formulation produced a higher drug concentration gradient between the tablet and the dissolution medium. According to Fick's first law, the mass flux of a component per unit cross sectional area perpendicular to the direction of diffusion is proportional to its concentration gradient (Hines and Maddox, 1985), thus drug release rate was increased.

The influence of CPM levels on the dissolution profiles of CPM tablets prepared from the granules of the hot-melt extrudates was also investigated. Compared with the results in Fig. 4, drug release rates were faster from tablets prepared with hot-melt extruded granules than from tablets compressed with dry powder blends (Fig. 5). Granulation of brittle hot-melt extrudates increased drug release after compression, due to the brittle nature of the polymer and the formation of internal cracks within the granules during the compaction process. The granules having poor cohesive properties resulted in softened tablets with large voids between the granules as observed by SEM. Drug was released rapidly through both the voids between the granules and the cracks within the granules.

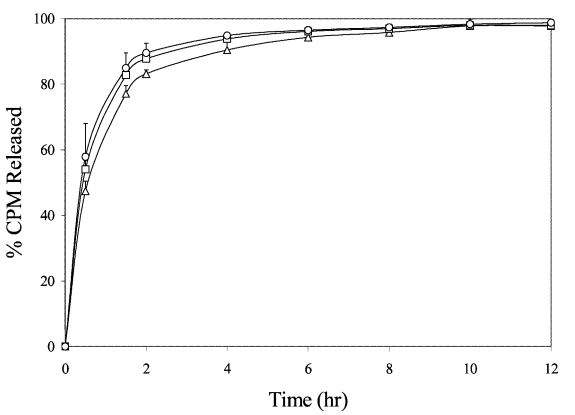

Fig. 5. Influence of chlorpheniramine maleate levels on the dissolution properties of chlorpheniramine maleate tablets containing Eudragit® RS PO and 4% (w/w) triethyl citrate prepared with hot-melt extruded granules. Compression force: 2000 kg. Dissolution: USP 24 basket method, 100 rpm, 500 ml distilled water as the dissolution medium, 37 °C ($n = 3$). (△): 6% (w/w) chlorpheniramine maleate; (□): 10% (w/w) chlorpheniramine maleate; (○): 14% (w/w) chlorpheniramine maleate.

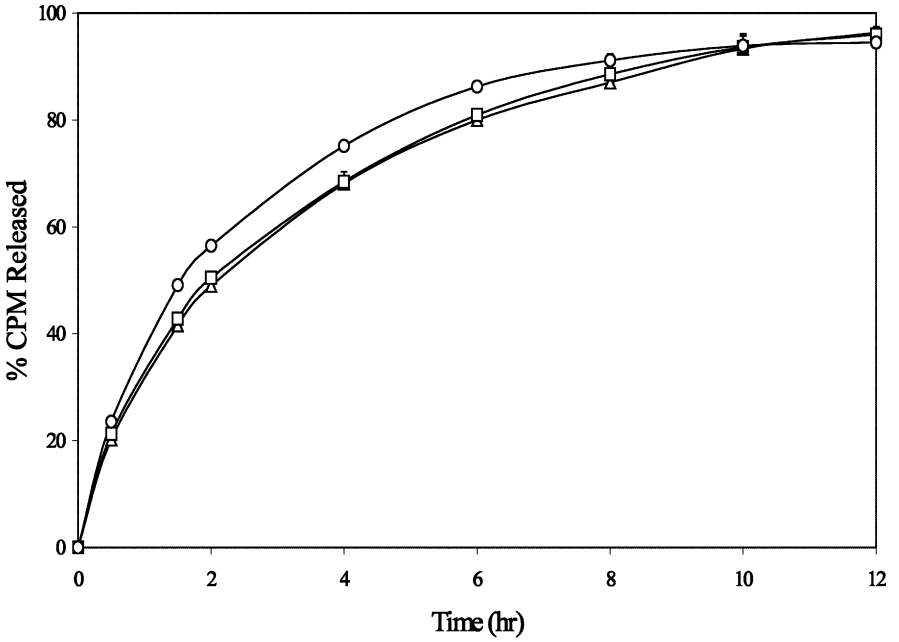

Fig. 6. Influence of chlorpheniramine maleate levels on the dissolution properties of chlorpheniramine maleate tablets containing Eudragit® RS PO and 4% (w/w) triethyl citrate prepared with high shear hot-melt granules. Compression force: 2000 kg. Dissolution: USP 24 basket method, 100 rpm, 500 ml distilled water as the dissolution medium, 37 °C ($n = 3$). (△): 6% (w/w) chlorpheniramine maleate; (□): 10% (w/w) chlorpheniramine maleate; (○): 14% (w/w) chlorpheniramine maleate.

In contrast, drug release from tablets prepared with granules made by the hot-melt granulation method, as seen in Fig. 6, was slower than from tablets prepared by hot-melt extruded granules, as in Fig. 5. The high shear hot-melt granules were more porous than the granules prepared from hot-melt extruded tablets, which contributed to the good adhesion properties of the granules prepared by high shear hot-melt granulation, resulting in harder tablets. Drug release rate from these tablets increased with increasing CPM concentration in the tablets.

3.2. Plasticization efficiency

The temperature and heat capacity calibration for MDSC was carried out utilizing indium as the standard prior to sample analysis (Coleman and Craig, 1996; Ferrero et al., 1999; Hill et al., 1998). For Eudragit® RS PO and the mixture of this acrylic polymer with either chlorpheniramine maleate or triethyl citrate, the transition temperature range was approximately 30 °C. With the heating rate of 5 °C/min, 6 cycles across the width of the transition were obtained. The glass transition temperature of Eudragit® RS PO was determined to be 67.4 °C using MDSC. A value of 61.5 °C determined by DSC using a scanning rate of 10 °C/min has been reported by other investigators (Lovrecich et al., 1996). The difference between the two T_g values may be due to the different methodologies used to experimentally determine this property. The data in Fig. 7 demonstrate that the glass transition temperatures of blends of Eudragit® RS PO and TEC decreased as a function of the percentage of TEC added to the formulations. Plasticizer efficiency is a function of the T_g of the plasticized polymer. A linear relationship between glass transition temperature and percent TEC in Eudragit® RS PO was observed within the TEC concentration range of 0–12%. The glass transition temperature decreased 2.70 °C for each percentage of TEC present in the polymer. Above 12% TEC in the

Eudragit® RS PO, the polymer agglomerated and could not be processed. A single glass transition temperature was observed for the mixtures of Eudragit® RS PO and TEC, indicating miscibility between the two materials.

As shown in Fig. 7, the glass transition temperature of the acrylic polymer decreased as the concentration of CPM in the sample increased. A single glass transition temperature was also observed for the blends of Eudragit® RS PO and CPM, indicating miscibility. The glass transition temperature decreased approximately 1.31 °C for each percentage of CPM in Eudragit® RS PO. These results indicated that the plasticization efficiency of CPM was approximately half that of the TEC. Both CPM and TEC exhibited a plasticization effect on Eudragit® RS PO, suggesting that lower processing temperatures can be used during hot-melt extrusion of a powder blend containing these materials.

3.3. Morphology studies on granules following thermal processing

The surface morphologies of drug and polymer physical blend as well as granules formed by the hot-melt processes are displayed in Fig. 8. A SEM of a physical mixture of CPM and Eudragit® RS PO in Fig. 8(A) shows that particles of CPM were adsorbed on the surface of Eudragit® RS PO particles. When 4% TEC was incorporated into the physical mixture, CPM particles adhered to

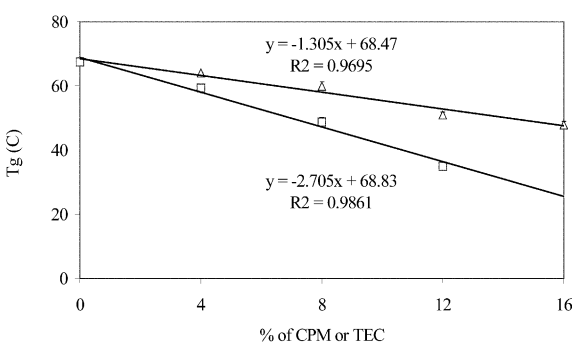

Fig. 7. Glass transition temperature of Eudragit® RS PO as a function of chlorpheniramine maleate and triethyl citrate level, determined by MDSC ($n = 3$). (△): chlorpheniramine maleate; (□): triethyl citrate.

the swollen surface of the Eudragit® RS PO as shown in Fig. 8(B). The binding of the CPM to the acrylic polymer contributes to the decrease in drug dissolution rate as the TEC concentration in the directly compressed tablet formulation was increased. Fig. 8(C) and (D) show the SEM photographs at two magnifications of granules containing TEC plasticized CPM and Eudragit® RS PO blends prepared by a high shear hot-melt granulation process. The lower magnification photograph (C) shows a typical porous granule formed after high shear hot-melt granulation. At higher magnification (D), the porous structure of granules formed from the fusing of drug and polymer particles following thermal processing is shown. Fig. 8(E) and (F) show the SEM photographs of hot-melt extruded granules of TEC plasticized CPM and Eudragit® RS PO powder blends at two magnifications. These two photographs display a fused granule containing drug and polymer following hot-melt extrusion. These SEMs suggest a homogeneous distribution of the CPM in the acrylic polymer and demonstrate that hot-melt extrusion technology is a thermal processing method that can be employed to prepare CPM-Eudragit® RS PO solid solutions.

4. Conclusions

Controlled release matrix tablets containing CPM and Eudragit® RS PO were successfully prepared using hot-melt extrusion and high shear hot-melt granulation techniques. The effects of TEC levels on drug release rates were dependent on the thermal processing method used to prepare the solid composite. As TEC levels increased, the drug release rates decreased for tablets prepared by either direct compression or from granules made by high shear hot-melt granulation. In contrast, drug release rates increased with increasing TEC levels for the hot-melt extruded tablets. The CPM content in the tablets influenced the drug release rates from tablet formulations, resulting in an increased drug release rate with increasing amounts of CPM irrespective of preparation method. Granules prepared via high shear hot-melt granulation formed a porous discontinuous

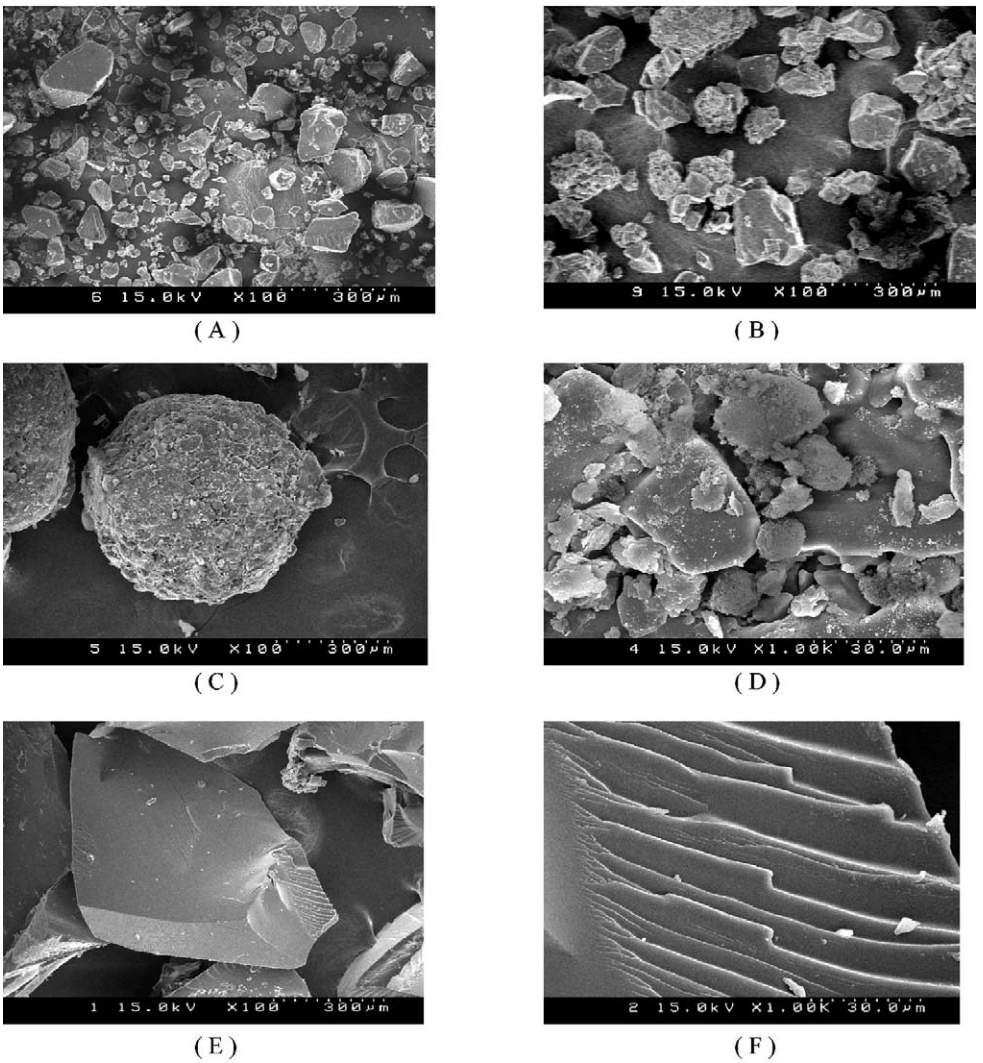

Fig. 8. SEM photographs. (A) Physical mixture of chlorpheniramine maleate and Eudragit® RS PO; (B) physical mixture of chlorpheniramine maleate, Eudragit® RS PO, and triethyl citrate; (C, D) high shear hot-melt granules containing triethyl citrate plasticized Eudragit® RS PO and chlorpheniramine maleate at two magnifications; (E, F) hot-melt extruded granules containing triethyl citrate plasticized Eudragit® RS PO and chlorpheniramine maleate at two magnifications.

matrix structure, thus resulting in faster drug release rates. In comparison, CPM was homogenously dispersed in the hot-melt extruded tablets resulting in a slower and more controlled release of drug. The acrylic polymer was plasticized in situ by both the CPM and the TEC during thermal processing, and the plasticization efficiency of TEC was shown to be twice that of CPM. The influence of both CPM and TEC levels on the drug release rate from these polymeric drug delivery systems was shown to be a function of whether the granules or tablets were formed by either hot-melt granulation or hot-melt extrusion, as well as the plasticization effects of both TEC and CPM on the acrylic polymer.

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