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International Journal of Pharmaceutics 341 (2007) 162–172
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Crystal growth formation in melt extrudates

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Received 12 September 2006; received in revised form 8 February 2007; accepted 5 April 2007
Available online 19 April 2007

Abstract

The purpose of the study was to investigate the physical state of hot-melt extruded guaifenesin tablets containing either Acryl-EZE® or Eudragit L100-55® and to study the physicochemical factors influencing crystal growth of guaifenesin on the surface of the extrudates. The powder mixtures containing Acryl-EZE® were extruded on a single-screw Randcastle Microtruder at 20 rpm and at temperatures of 90, 95, 110 °C (zones 1, 2, 3, respectively) and 115 °C (die), before being manually cut into tablets (250 ± 5 mg). Extrudates containing Eudragit L100-55®, TEC and guaifenesin were extruded at temperatures ranging from 60 to 115 °C. Modulated differential calorimetry (DSC) was used to demonstrate the plasticizing effect of guaifenesin on Eudragit L100-55®. Powder X-ray diffraction (PXRD) showed that while the drug powder is crystalline, extrudates containing up to 25% drug exhibited an amorphous diffraction profile. Extrudates containing higher drug concentrations showed an amorphous profile with some crystalline peaks corresponding to guaifenesin, indicating that the limit of solubility of drug in the matrix had been exceeded. Scanning electron microscopy was used to demonstrate that drug crystallization was a surface phenomenon and dependent on the drug concentration. In vitro dissolution testing showed no effect of surface crystallization of guaifenesin on drug release rates of extruded matrix tablets. The influence of hydrophilic polymeric additives including PVP K25, polycarbophil, PEG 3350, poloxamer 188 or poly(ethylene oxide) as crystal growth inhibitors was investigated at a level of 10% based on the drug content. The extent of crystal growth was reduced for all additives. Complete drug release in pH 6.8 phosphate buffer was prolonged from 4 h in extrudates containing Acryl-EZE® and guaifenesin to 8 h in extrudates containing Eudragit L100-55®, TEC and guaifenesin. Drug release in extrudates containing Eudragit L100-55® and guaifenesin was not affected by the presence of hydrophilic additives present at 10% based on the drug content. In vitro drug release studies showed no significant change during storage for up to 6 months at 25 °C/60% relative humidity and 40 °C/75% relative humidity.

Keywords: Hot-melt extrusion; Eudragit® L100-55; Acryl-EZE®; Guaifenesin; Recrystallization; Matrix tablets; Physical stability

1. Introduction

Hot-melt extrusion (HME) has been demonstrated to be a simple and continuous one-step process to prepare dosage forms such as tablets (Fukuda et al., 2006; Liu et al., 2001), pellets (Young et al., 2005a) and films (Crowley et al., 2004; Repka and McGinity, 2000) as well as intermediates that can be further processed by milling or cryogenic grinding to yield a powder to be used in compression or powder coating. Hot-melt extruded formulations consist of drug that is either dispersed or dissolved in one or more thermal carriers, resulting in a matrix system. Thermal lubricants such as talc and glycerol monostearate facilitate the movement of the formulation through the barrel of the unit. The processing temperatures should be sufficiently high to soften or melt the thermal carrier and to allow mixing of the various components of the formulation. The residence times for blends in the extruder at elevated temperatures are short and usually in the range of 1.5–4 min. An extruded product typically displays excellent content uniformity due to the intense mixing and agitation in the barrel.

While preformulation, processing and the stability of drug release during storage of hot-melt extruded dosage forms have been investigated, less attention has been paid to the physical stability of hot-melt extrudates. To characterize extruded formulations, it is important to know how the drug loading and the processing conditions influence drug recrystallization from the dosage form, and how these factors affect drug release. The

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doi:10.1016/j.ijpharm.2007.04.008

Table 1
Composition of tablets prepared by hot-melt extrusion

Formulation	Guaifenesin (%, w/w)	Acryl-EZE® (g)	Eudragit L100-55® (g)	Guaifenesin (g)	TEC (g)	Crystallization inhibitor (g)
Guaifenesin in Acryl-EZE®	15	255	–	45	–	–
	20	240	–	60	–	–
	25	225	–	75	–	–
Guaifenesin in Eudragit	0	–	300	0	–	–
	5	–	285	15	–	–
	10	–	270	30	–	–
	15	–	255	45	–	–
	20	–	240	60	–	–
	25	–	231.1	57.8	11.1	–
	37.5	–	210.8	79.1	10.1	–
	50	–	193.8	96.91	9.3	–
	25 + 10[a]	–	207.5	75	10	7.5

[a] 25% guaifenesin and 10% crystallization inhibitor based on the guaifenesin content.

crystallization of drug substances from the amorphous state has been a concern in freeze dried products and with drug-containing transdermal matrix systems. Crystallization inhibition in these dosage forms as well as in hot-melt extrudates can be achieved by decreasing the amount of supersaturation driving the recrystallization or by interfering with the crystallization process. Many polymers, among them Eudragit RL PO, Eudragit E PO (Kotiyan and Vavia, 2001), polyvinyl pyrrolidone (PVP) (Yoshioka et al., 1995), and some low molecular weight compounds such as sodium chloride, boric acid and sodium tetraborate have been shown to inhibit recrystallization (Telang et al., 2003; Yoshinari et al., 2003; Izutsu et al., 2004). Poly(ethylene oxide) was shown to reduce recrystallization of amorphous indomethacin in compression (Schmidt et al., 2004). Additives can interfere with crystal formation and growth when incorporated into the growing crystal face (Myerson and Jang, 1995), thereby stunting crystal growth and affecting crystal habit. It has been proposed that intermolecular forces between the drug and the additive, such as hydrogen bonding, are responsible for this type of crystallization inhibition (Raghavan et al., 2001; Weuts et al., 2005). Drug concentration, processing conditions, storage time, humidity and temperature as well as additives have been found to affect recrystallization (van Laarhoven et al., 2002). Crystallization inhibition is very specific to the combination of drug and additive, and in some combinations additives were shown to promote crystallization rather than to inhibit crystal growth (Ma et al., 1996). Employing changes in processing, such as the rapid cooling of a melt or freeze drying without additives, usually will not provide long-term physical stability because the crystalline forms are usually more thermodynamically stable, and the amorphous forms may, over time, revert back to the more stable crystalline form under ambient conditions. Since the degree of supersaturation is related to the crystallization of drug, reducing the drug loading could reduce drug recrystallization, but this may not be a viable option.

Acryl-EZE® is a pre-formulated, dry enteric acrylic coating system for solid dosage forms and contains Eudragit® L100-55 plasticized with 4.8% triethyl citrate (TEC) along with talc and other components. Earlier work in our laboratories has highlighted the properties and applications of Acryl-EZE® as a thermal carrier in melt processing (Young et al., 2005b), resulting in matrix formulations. The use of Acryl-EZE® as a ready-made blend for melt extrusion is advantageous, as it can reduce formulation work while resulting in elegant extruded enteric dosage forms. During initial studies, the formation of crystals on the tablet surface was observed. We decided to investigate this phenomenon as it will impact the long-term physical stability of melt-extruded dosage forms containing Acryl-EZE®. Crystal growth on the tablet surface presents a change in the physical form of the drug. This is problematic for several reasons. Crystals can shear from the tablet, resulting in a lower dose of the active. Depending on the solubility of the drug, the dissolution properties of the dosage form may change as the tablet is enveloped in a layer of drug crystals which may change the interaction of the matrix with the medium. To simplify the present investigations, some studies were performed in melt extrudates containing only Eudragit L100-55®, rather than the entire blend. Guaifenesin forms needle-shaped crystals from solutions or melts and has a melting point of about 79 °C. It was chosen as the model drug since it melted under

Table 2
Processing conditions for extrudates containing Acryl-EZE®

Model drug	% Model drug	Barrel pressure (PSI × 1000)	Machine current (drive amps)	Extrusion temperatures
Guaifenesin	15	0.4	234	90–95–110–115
	20	0.2	157	90–95–110–115
	25	0.2	124	90–95–110–115

Table 3
Processing conditions for extrudates containing Eudragit L100-55®

Model drug	% Model drug	Barrel pressure (PSI × 1000)	Machine current (drive amps)	Extrusion temperatures
Guaifenesin	25	1.0	312	70–85–90–95
	37.5	0.8	335	60–80–80–90
	50	0.6	325	65–75–80–85

the processing conditions and is very water-soluble. The goal of this study was to investigate the factors influencing the growth of guaifenesin crystals on hot-melt extruded matrix tablets containing either Acryl-EZE® or Eudragit L100-55®. This study investigated the effects of guaifenesin recrystallization on the surface of melt-extruded tablets on drug release properties. The influence of hydrophilic polymeric additives on crystal growth inhibition and on drug release properties was also investigated.

2. Materials and methods

2.1. Materials

Guaifenesin was purchased from Spectrum (Gardena, CA), and was used as model drug. Acryl-EZE® was donated by Colorcon (West Point, PA). Eudragit L100-55® was given by Röhm GmbH (Darmstadt, Germany). Triethyl citrate (TEC) was kindly donated by Morflex (Greensboro, NC). Talc (Imperial 500, USP) was provided by Luzenac America (Centennial, CO). Hydrophilic polymers including Kollidon 25 (PVP K25), Pluracol E 3350 (PEG 3350) and Pluronic F68 (Poloxamer 188), were all donated by BASF (Florham Park, NJ). Noveon AA1 (Polycarbophil) was donated by Noveon (Cleveland, OH), and Polyox WSR 303 (Poly(ethylene Oxide)) was donated by Dow Chemical (Midland, MI). Ethanol (200 proof) was purchased from AAPER Alcohol and Chemical (Shelbyville, KY).

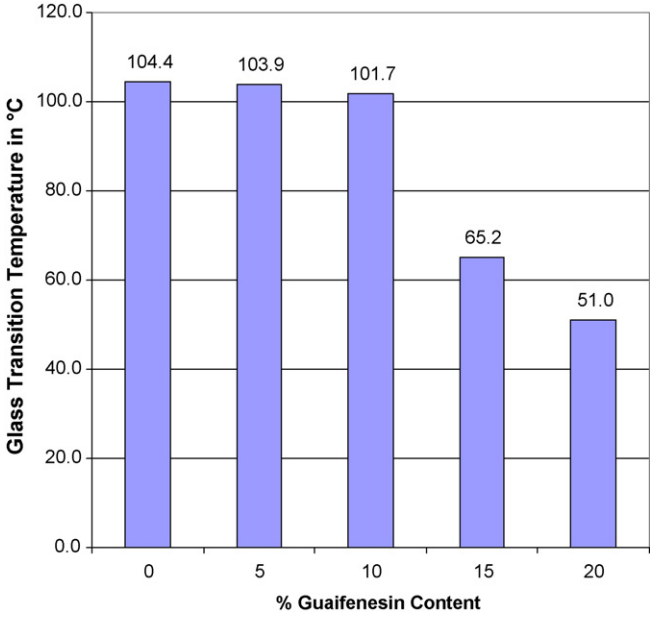

Fig. 1. Influence of guaifenesin content on the glass transition temperature of Eudragit L100-55®.

2.2. Tablet preparation

Tablets were prepared by hot-melt extrusion of the powder blends, followed by manual cutting of the extrudate strand. The formulations are presented in Table 1. Premixed powder blends were fed into a single screw Randcastle extruder (Randcastle Microtruder® Model RCP-0750, Cedar Grove, NY) equipped with a Nitralloy 135M screw (3:1 compression ratio with flight configuration containing feed, compression and mixing sections). The round die had a diameter of 6 mm. The three heating zones and the die were equilibrated at the processing temperatures for 30 min before extrusion. The extrudates were allowed to cool at room temperature for 24 h before manually cutting tablets weighing 250 ± 5 mg. For stability studies, the tablets were packaged with one desiccant bag (One gram silica gel Minipax, Impak, Los Angeles, CA) into HDPE containers (MoldRite Plastics, Plattsburgh, NY), which were induction sealed (Compak Jr, Enercon, Menomonee Falls, WI) and placed into appropriate storage chambers.

The processing temperatures chosen for extrudates containing Acryl-EZE® and guaifenesin were 90, 95, 110 °C (zones 1, 2, 3, respectively) and 115 °C (die). These temperatures were optimized in earlier studies investigating the suitability of Acryl-EZE® for hot-melt extrusion. Melt extrudates containing Eudragit L100-55® and guaifenesin were extruded at lower

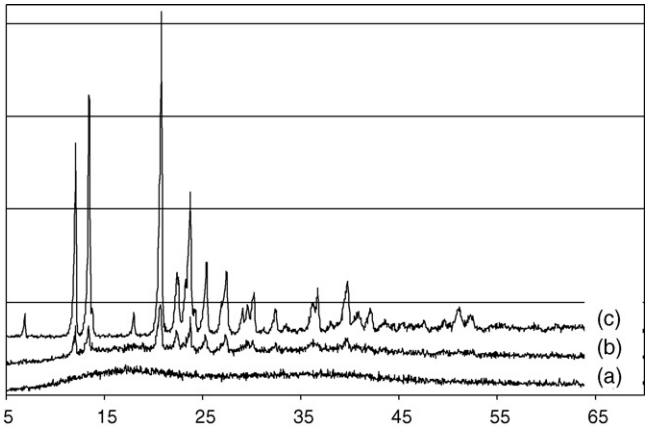

Fig. 2. Powder X-ray diffraction profiles of guaifenesin, Eudragit L100-55®, and their physical mixture. Scan range 5–70°, step size 0.05°, scan speed 0.05°/1.0 s. (a) Eudragit L100-55® (powder), (b) physical mixture 25% guaifenesin in Eudragit L100-55® (powder), and (c) guaifenesin (powder).

temperatures as shown in Table 3. Processing conditions were adjusted to obtain an acceptable extruded product at an adequate extrusion speed. Two in-process parameters, including the barrel pressure and machine current, were used to monitor the processability of the blends. The barrel pressure is the pressure exerted by the molten formulation inside the barrel; the machine current is the energy required to maintain the screw at a constant speed. The processing conditions for extrudates containing Acryl-EZE® and Eudragit L100-55® are shown in Table 2 and in Table 3, respectively.

2.3. Film preparation

Films containing 900 mg solids were prepared by weighing out and blending the components on wax paper, which were then dispersed in 20–35 mL of 200 proof ethanol, DI water, or mixtures thereof. After stirring for at least 30 min under low shear until all components were dissolved, the solutions were cast into aluminum dishes (Fisher Scientific, Hampton, NH) and were dried for 24 h or until dry under a fume hood (alcohol based films) or in a 60 °C oven (water based films).

2.4. Glass transition temperature (T_g) determination

Modulated differential scanning calorimetry (MDSC) was used to characterize the thermal properties of the extrusion blends and extrudates. Power samples were prepared for mDSC by screening. Extrudates were thinly sliced and then crushed in a ceramic mortar and pestle. After weighing, the samples (10 ± 5 mg) were placed into aluminum pans (Kit 0219-0041 Perkin-Elmer Instruments, Norwalk, CT), fitted with a lid, and crimped. The analysis was conducted on a Thermal Advantage Model 2920 from TA Instruments (Newcastle, DE) equipped with Thermal Advantage Instrument Control Software and Universal Analysis 2000. Ultra pure nitrogen was used as a purge gas at a flow rate of 150 mL/min. The scan proceeded at a heating rate of 3 °C/min with a temperature modulation of ±1 °C every 30 s. The heating ranges were chosen to begin about 50 °C below the expected glass transition temperatures of the blends and run to approximately 30 °C after the end of the transition. Differential scanning calorimetry of physical blends of guaifenesin and polymers was performed on the same instrument on a heat-cool-heat cycle. The 1 to 1 mixtures were equilibrated at 10 °C, heated up to 110 °C at 5 °C per min, then cooled to 0 °C at 10 °C per min, and heated up to 110 °C at 5 °C per min.

2.5. Powder X-ray diffraction

Powder X-ray diffraction was used to study the crystalline or amorphous state of drug and polymer in the powder blends and the extrudates. All powder samples were screened prior to analysis, and deep bed sample holders were filled to a constant weight. Stored or freshly cut tablets (250 ± 5 mg) were arranged on a glass slide, while some extrudates were ground prior to analysis. Films were cut and placed as flat as possible on the sample holder. The samples were scanned using a Phillips Vertical Scanning Diffractometer, Type 42273, employing Cu Kα radiation,

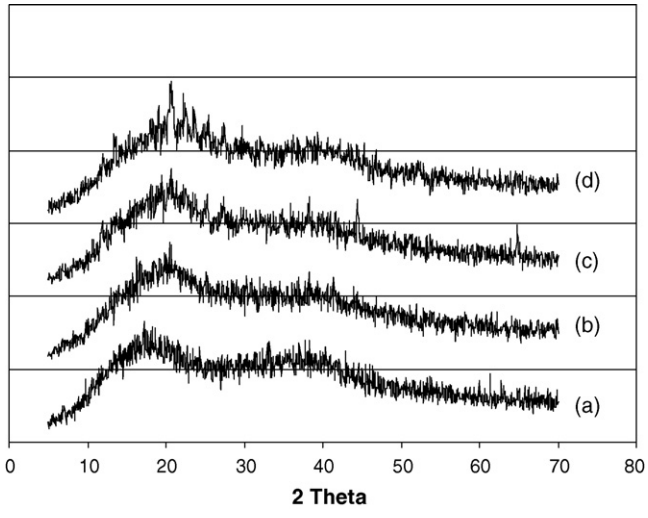

Fig. 3. Powder X-ray diffraction profiles of melt-extruded tablets containing Eudragit L100-55® and guaifenesin soon after extrusion. Scan range 5–70°, step size 0.05°, scan speed 0.05°/1.0 s. (a) No guaifenesin, (b) 25% guaifenesin, (c) 37.5% guaifenesin, and (d) 50% guaifenesin.

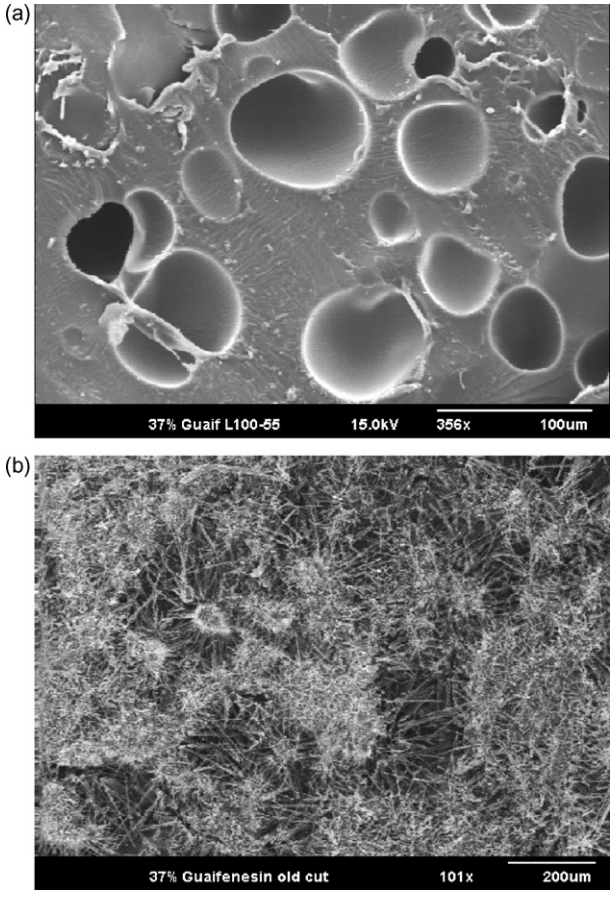

Fig. 4. SEM micrographs of the surface of a hot-melt extruded tablet containing 62.5% Eudragit L100-55® and 37.5% guaifenesin (based on total weight). (a) Soon after extrusion and (b) after 4 weeks of storage at 25 °C/60% relative humidity.

operating at 40 kV and 20 mA. The scan radius ran from 5° to 70° or 10° to 60°, and the step size was 0.05° every 1.5 or 2 s.

2.6. Scanning electron microscopy

Scanning electron microscopy (SEM) was used to study the surface morphology of the extrudates, and to investigate the recrystallization processes on the surface of the hot-melt extruded tablets. To determine the onset of crystallization, previously stored tablets were bisected and then either observed immediately or equilibrated at ambient conditions for predetermined time periods (5–30 min). Sputter-coating was performed at the end of the equilibration period. Samples were mounted on stubs with carbon tape (EMS, Fort Washington, PA) and dappled with silver adhesive (503, EMS, Fort Washington, PA). Sputter coating was performed in a Ladd Benchtop Sputter Coater (Ladd Research, Winston, VT) at 2.5 kV and 20 mA for 75 s under Argon with a gold/palladium mixture in a 60/40 ratio. The images were captured with a Phillips 515 SEM equipped with Semicaps 2000 software operating at 15 kV and 20 μA.

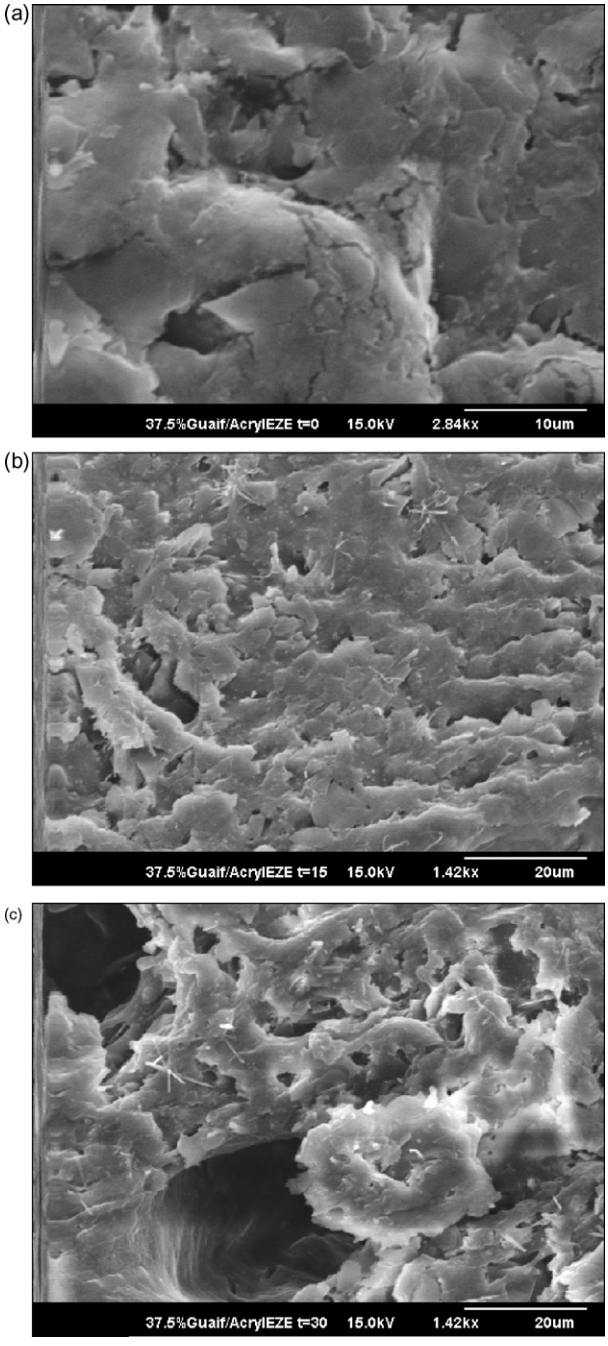

Fig. 5. SEM micrographs of hot-melt extruded tablets containing Acryl-EZE® and 37.5% guaifenesin. (a) $T = 0$ min, (b) $T = 15$ min, and (c) $T = 30$ min.

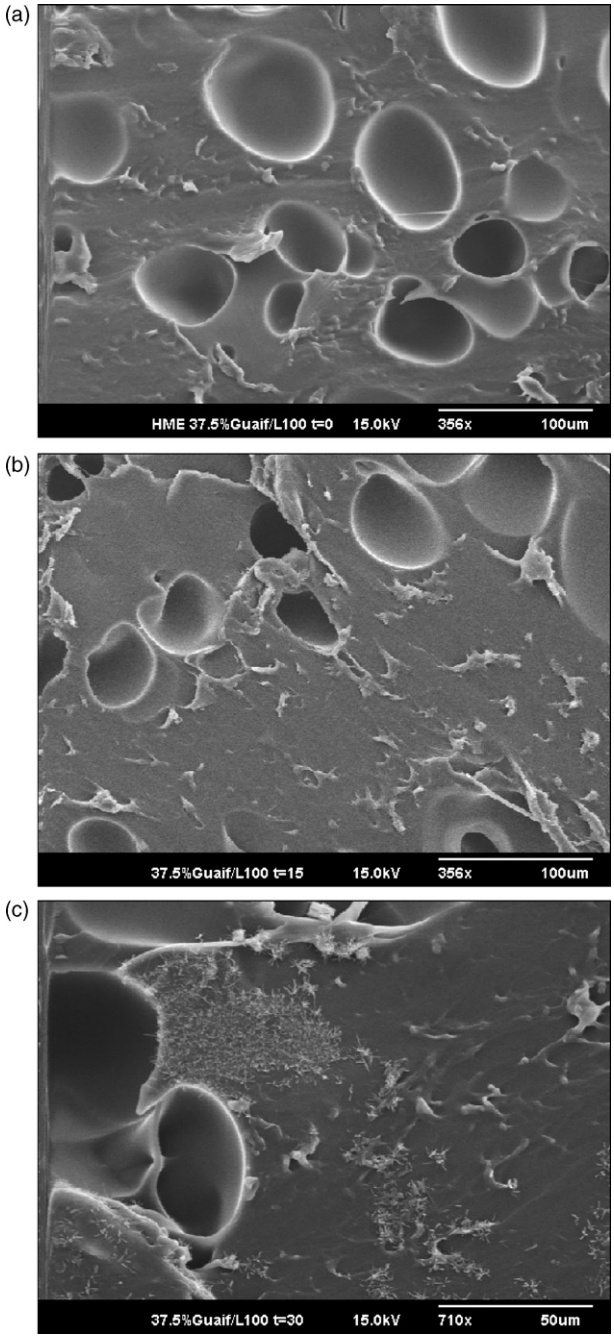

Fig. 6. SEM micrographs of hot-melt extruded tablets containing Eudragit L100-55® and 37.5% guaifenesin. (a) $T = 0$ min, (b) $T = 15$ min, and (c) $T = 30$ min.

The surface of the tablets was surveyed, and a representative area was chosen for the micrograph.

2.7. In vitro drug release testing

Dissolution testing was performed to study the drug release properties of the guaifenesin tablets using USP 27 Apparatus 2 (Varian Industries, Inc. VK 7000, Palo Alto, CA) equipped with an auto sampler (Varian Industries, Inc. VK 8000, Palo Alto, CA). Dissolution studies on melt-extruded tablets containing guaifenesin and recrystallization inhibitors were conducted via the basket method using USP apparatus 1, since the tablets swelled during the test, and the basket method showed less variability in the results than the paddle method. Both dissolution tests were conducted at 37 °C and 50 rpm in 900 mL 0.1N HCl for 2 h, followed by 8 h in 900 mL 0.05 M phosphate buffer pH 6.8 ($n = 6$). At the end of each dissolution test, complete drug release was obtained by mixing the vessel contents with a homogenizer for 2 min to ensure total disintegration of the tablets. Samples were filtered through a 0.45 or 0.22 nylon filter before HPLC analysis (Puradics 25NYL syringe filter, Lot Number R180 and Puradics 45NYL syringe filter, Lot Number S594; Whatman, Maidstone, GB) to remove insoluble excipients. The samples were filtered through a 0.45 nylon filter, switching to 0.22 nylon filters if the filtered samples still appeared cloudy.

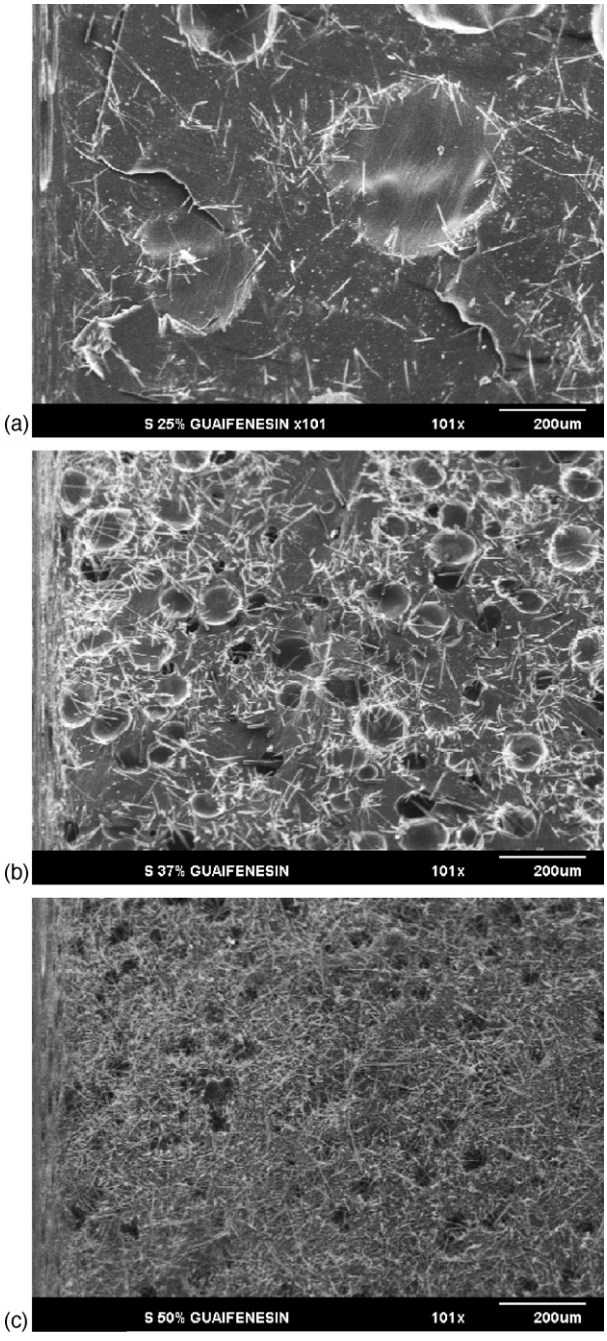

Fig. 7. Influence of drug concentration on surface crystallization (storage 25 °C/60% RH). SEM of hot-melt extrudate containing Eudragit L100-55® and various concentrations of guaifenesin. (a) 25% guaifenesin, (b) 37.5% guaifenesin, and (c) 50% guaifenesin.

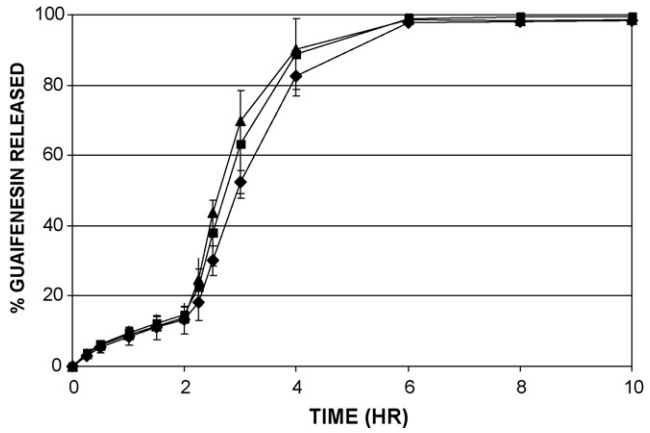

Fig. 8. Influence of guaifenesin content on the dissolution rate from tablets containing Acryl-EZE® (paddle, 900 mL, 37 ± 0.5 °C, 50 rpm, 2 h 0.1N HCl, 8 h pH 6.8 phosphate buffer, $n = 6$). (♦) 15% guaifenesin, (▲) 20% guaifenesin, and (■) 25% guaifenesin.

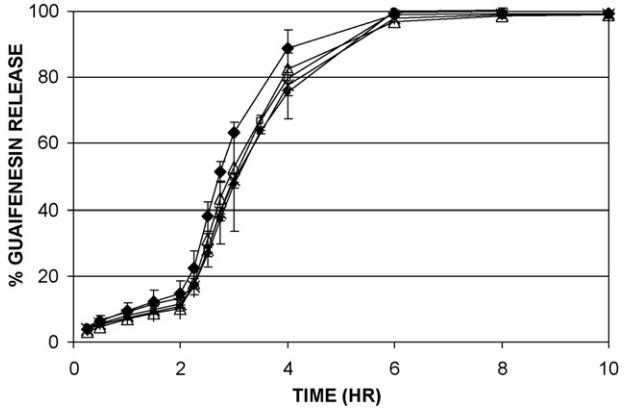

Fig. 9. Influence of storage for 3 weeks and 6 months on the dissolution rate of guaifenesin from melt-extruded tablets containing 25% guaifenesin and 75% Acryl-EZE® (paddle, 900 mL, 37 ± 0.5 °C, 50 rpm, 2 h 0.1N HCl, 8 h pH 6.8 phosphate buffer, $n = 6$). (♦) Initial ($T = 0$); (△) $T = 3$ weeks, storage 25 °C/60% RH; (×) $T = 3$ weeks, storage 40 °C/75% RH; (□) $T = 6$ months, storage 25 °C/60% RH; (◯) $T = 6$ months, storage 40 °C/75% RH.

2.8. Dissolution sample analysis

Samples were analyzed for guaifenesin content using a Waters high performance liquid chromatography (HPLC) system with a photodiode array detector (Model 996) extracting 276 nm for guaifenesin (Waters, Milford, MA). An auto sampler (Waters Model 717plus) was used to inject 10 μL. The data were collected and integrated using Empower® Version 5.0 software (Waters). The column used for guaifenesin analysis was an Alltech Versapack C18 10 μm, 250 mm × 4.1 mm (Alltech, Deerfield, IL). The mobile phase consisted of water, methanol and glacial acetic acid in the volume ratio 600:400:15, respectively. The retention time of the guaifenesin was 3.1 min. Both mobile phase solvents were vacuum filtered through

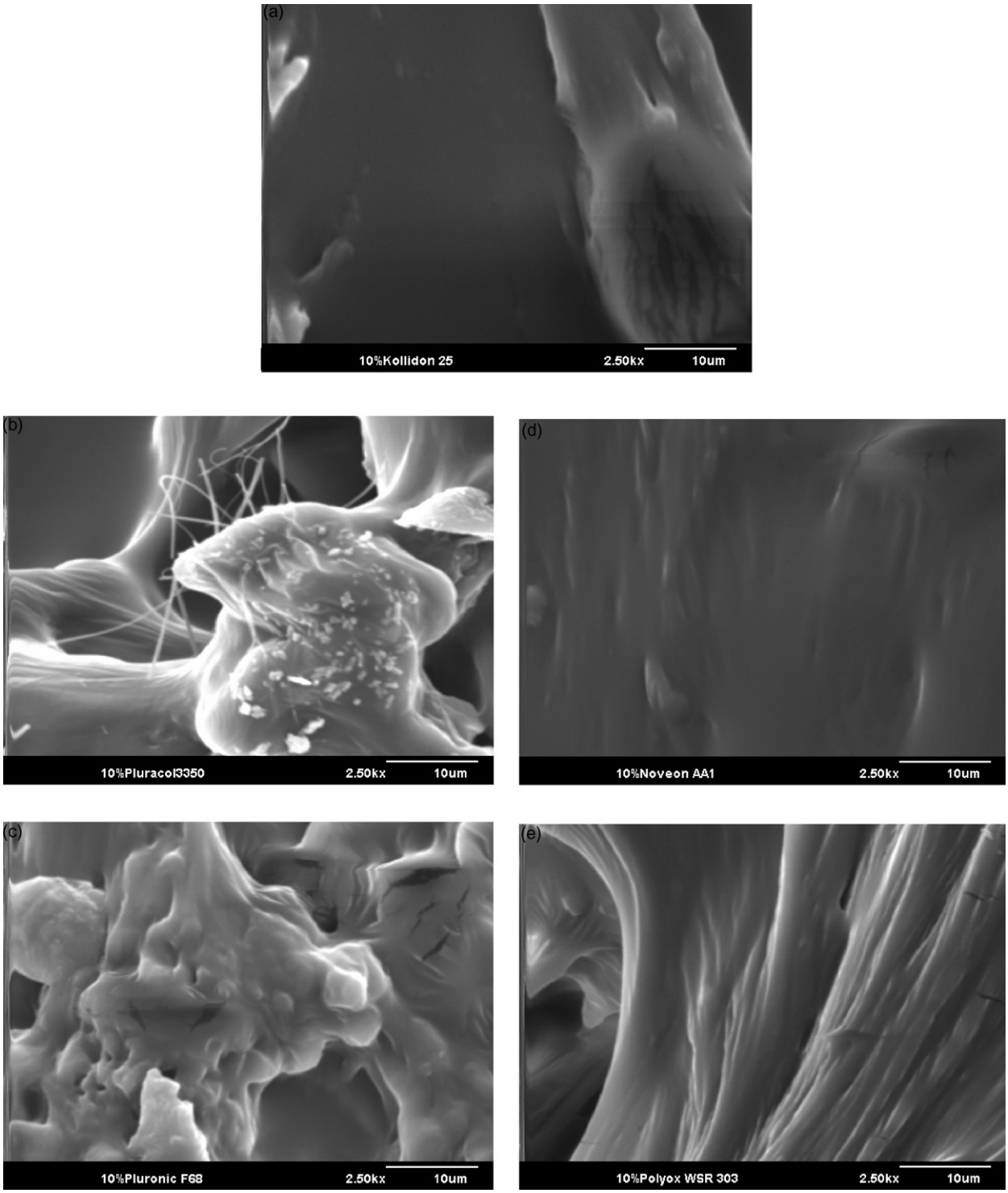

Fig. 10. SEM micrographs of melt-extruded guaifenesin tablets containing Eudragit L100-55® and 25% guaifenesin with 10% crystallization inhibitor, based on the amount of drug, soon after extrusion. (a) PVP K25, (b) PEG 3350, (c) poloxamer 188, (d) polycarbophil, and (e) poly(ethylene oxide).

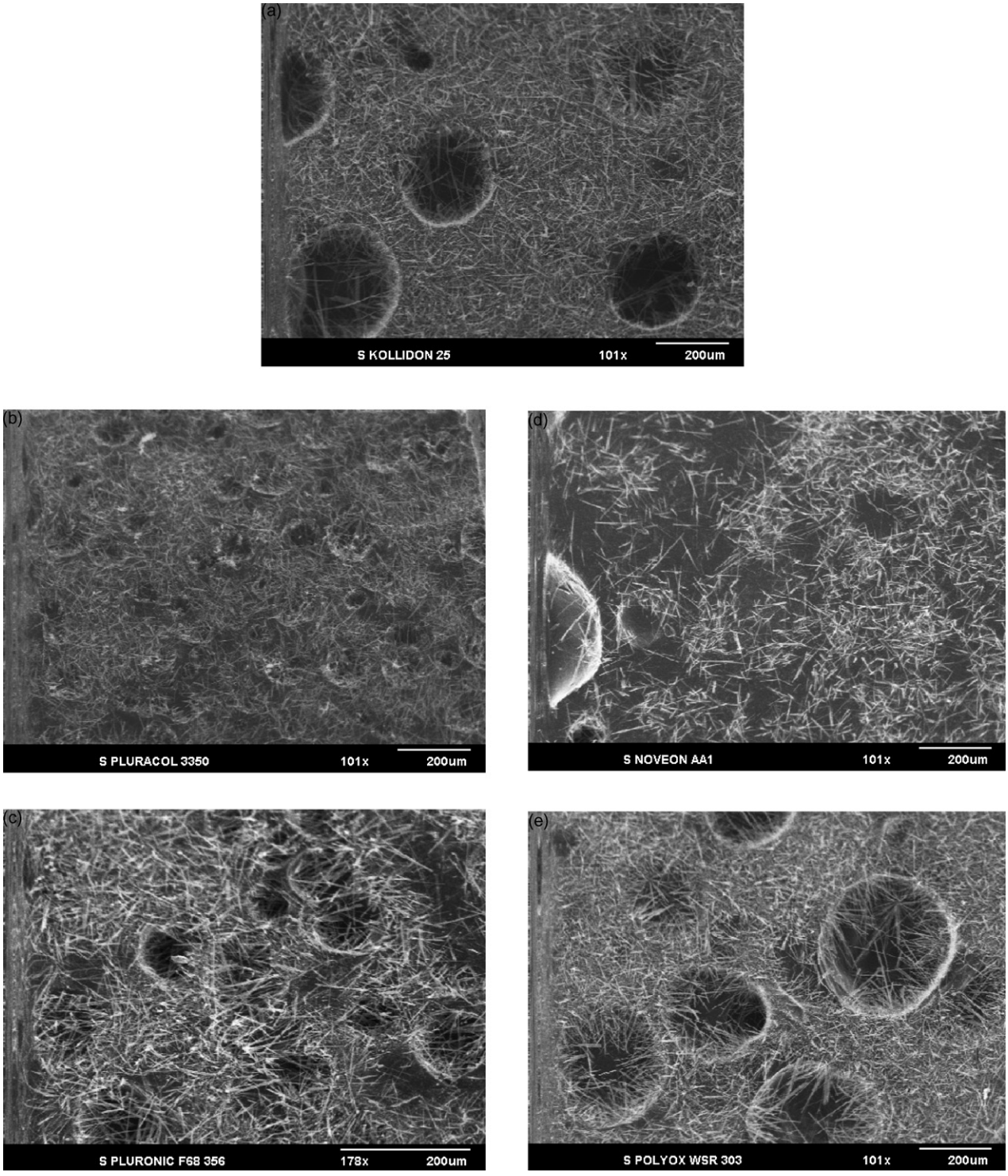

Fig. 11. SEM of melt-extruded guaifenesin tablets containing Eudragit L100-55® with 10% crystallization inhibitor, based on the amount of drug, after 4 weeks of storage at 25 °C/60% relative humidity. (a) PVP K25, (b) PEG 3350, (c) poloxamer 188, (d) polycarbophil, and (e) poly(ethylene oxide).

a 0.45 μm nylon membrane (0.45 μm nylon membrane filters by Whatman, Maidstone, GB) and degassed using a Waters In-Line Degasser AF. Linearity for guaifenesin was demonstrated from 2 to 80 mg/μL ($R^2 \geq 0.997$) and injection repeatability was 1% relative standard deviation for 6 injections.

3. Results and discussion

The processing temperature of a melt extrusion process is selected based on the melting or softening temperature of the thermal carrier or the extrusion blend. The drug may or may not melt under these conditions. Guaifenesin has a melting point

of 79 °C, and formed a melt during extrusion at the processing conditions used. Mani et al. reported on the properties and solubilities of guaifenesin (Mani et al., 2003). An extrusion blend that is well plasticized and contains thermal lubricants can be extruded at lower temperatures and pressures, and such a blend will extrude faster and result in a better product. To study the effect of the molten drug on the processing conditions, extrudates containing Acryl-EZE® and guaifenesin were prepared. These blends flowed well in the hopper, extruded fast, and yielded smooth, regular extrudates without die swell. The barrel pressure and the torque decreased with higher guaifenesin content.

To distinguish between the lubricant properties of the guaifenesin melt and a plasticizing effect of the drug on the polymer, the glass transition temperatures of melt extrudates containing 5%, 10%, 15% and 20% of guaifenesin in Eudragit L100-55® were determined, and a concentration-dependent decrease was found (Fig. 1). The glass transition temperature of Eudragit L100-55® decreased from 104.4 °C without any guaifenesin to 51 °C with 20% drug. Extrudates containing Eudragit L100-55® were employed for this purpose instead of Acryl-EZE®-containing product as Acryl-EZE® contains of other components which complicate the determination of the glass transition temperature. The sharp decrease in the glass transition temperature with increasing guaifenesin content indicated that the favorable processing conditions were mainly due to the plasticizing effect of the drug on the polymer. In previous studies, solid state compounds such as ibuprofen (Wu and McGinity, 1999) and methylparaben (Wu and McGinity, 2003) were shown to plasticize acrylic polymers during processing, demonstrating that actives and excipients can be used as non-traditional plasticizers in hot-melt formulations.

The effect of hot-melt extrusion on the aggregate state of guaifenesin was investigated by powder X-ray diffraction. Eudragit L100-55® rather than Acryl-EZE®-containing formulations were employed because crystalline components in Acryl-EZE® obscured small changes in the amorphous part of the spectrum. As seen in Fig. 2, the thermal carrier Eudragit L100-55® was amorphous as the powder X-ray diffraction profiles show an amorphous profile without crystalline peaks. The unprocessed guaifenesin powder was crystalline, and the physical mixture of guaifenesin with Eudragit L100-55® exhibited partial crystallinity, showing peaks corresponding to guaifenesin, but at lower intensities. The powder X-ray diffraction profiles of ground extrudates containing 25%, 37.5% and 50% guaifenesin in Eudragit L100-55® were similar to the amorphous profile exhibited by the pure polymer (Fig. 3). Crystalline peaks corresponding to guaifenesin started to appear in extrudates containing higher concentrations of drug (37%, 50%). These results demonstrated that there was an upper limit to the amount of drug that could dissolve in the molten polymer matrix and remain in an amorphous state as a solid solution in the extrudate on cooling and storage.

Scanning electron microscopy of tablets stored for 1 month at 25 °C and 60% relative humidity showed that the polymeric surface was obscured by crystals (Fig. 4). To determine the onset time of crystallization, previously stored tablets containing Acryl-EZE® (Fig. 5) or Eudragit L100-55® (Fig. 6) with a guaifenesin content of 37.5% were bisected and then either observed immediately, or stored at ambient conditions for predetermined time periods. The formation of crystals was observed over 30 min. No crystals were observed on the newly exposed matrix surface of tablets (Figs. 5a and 6a). SEM micrographs of the tablets which were sectioned and exposed to the environment 15 min (Figs. 5b and 6b) or 30 min (Figs. 5c and 6c) before observation showed crystal growth for both thermal binders. Since no crystals were present when a new cut was first made, guaifenesin recrystallization on both Acryl-EZE®- and Eudragit L100-55®-containing extrudates was demonstrated to be a surface phenomenon which only occurred on the outside faces of the tablets. A possible explanation for these results is that the matrix exerted a restraining pressure large enough to prevent internal crystal growth, as the growing crystals would have to displace the matrix to accommodate their growth. This phenomenon was recently discussed by other researchers (Chatterji, 2005).

SEM also demonstrated dependence of crystal growth on the drug concentration (Fig. 7). Tablets containing higher guaifenesin levels were observed to have a higher level of drug recrystallization after storage for the same time period. SEM micrographs for Fig. 7a–c were taken under the same magnification (101×). The concentration-dependent drug recrystallization indicated that the drug solubility in the polymeric matrix had been exceeded. Higher drug loading resulted in a higher degree of supersaturation in the matrix, causing recrystallization on the surface of the tablet when equilibrated at ambient temperatures.

The influence of surface crystallization of guaifenesin on the in vitro dissolution properties of both freshly extruded and aged extrudates was investigated. For initial samples, guaifenesin content had no influence on the drug release rate as seen in Fig. 8. Eudragit L100-55® is an enteric polymer that starts to dissolve above pH 5.5. In 0.1N hydrochloric acid, the polymer matrix remained intact although more than 10% drug was released after 2 h. When the pH of the media was changed to phosphate buffer (pH 6.8), the polymer started to dissolve. For extrudates containing Acryl-EZE® and either 15%, 20% or 25% guaifenesin, complete drug release was achieved after 4 h in phosphate buffer pH 6.8. The results in Fig. 9 show that the drug release rate did not change significantly for tablets stored for either 3 weeks or 6 months at 25 °C and 60% relative humidity as well as at 40 °C and 75% relative humidity. This can be explained from the observation that guaifenesin crystals were only present on the tablet surface and the total amount of recrystallized drug was small compared to the amount in an amorphous state inside the matrix. Guaifenesin is highly soluble in both the amorphous and in the crystalline form. The drug release rates of extruded matrix tablets stored in induction-sealed containers showed no change and the performance of melt extruded tablets was not influenced by the formation of drug crystals on the tablet surface. Melt-extruded products tend to show good long-term stability (Hülsmann et al., 2001). Long-term stability can be influenced by the storage conditions. Remon and coworkers found that drug release can be increased after storage under high humidity conditions since the molecular

mobility within the matrix was increased (De Brabander et al., 2003).

In order to test the ability of five hydrophilic polymers to act as crystallization inhibitors, PVP K25, PEG 3350, poloxamer 188, poly(ethylene oxide) or polycarbophil were incorporated into the formulation (Table 1). Each blend contained one of the polymers and 25% guaifenesin in Eudragit L100-55®. The additives were employed at a level of 10%, based on the amount of guaifenesin in the formulation and were incorporated into the initial powder blend for extrusion before processing. These additives were selected either because they are well-known solubilizers (PVP), because guaifenesin was known to have solubility in similar lower molecular weight polymers (Mani et al., 2003) (PEG, poloxamer 188), or because of structural similarity to these polymers (polycarbophil, poly(ethylene oxide)). DSC performed on the physical mixtures of drug and each of the polymers revealed that in the second heating cycle of the heat-cool-heat program the heat of fusion of guaifenesin was absent or reduced for all polymers. This indicated that the drug was solubilized by the polymer in the first heating cycle, and either did not recrystallize on cooling or a reduced amount recrystallized. Therefore, the drug exhibited either no or a reduced peak for the heat of fusion in the second heating run, indicating at least some solubility of the drug in the polymers (data not shown). The use of a DSC method to select crystallization inhibitors was used by Lipp in the formulation of a transdermal matrix system (Lipp, 1998).

Scanning electron micrographs were taken soon after extrusion (Fig. 10) and after 4 weeks of storage at 25 °C and 60% relative humidity (Fig. 11). The extrudates containing PEG 3350 showed crystal growth under high magnifications soon after extrusion and was similar to the extrudates without additive. After 4 weeks of storage, surface crystallization had occurred in all formulations and the extent of crystallization observed on the tablets with each hydrophilic additive was less than on tablets without any additives. Extrudates containing polycarbophil and PVP K25 exhibited reduced drug recrystallization compared to the other formulations containing an additive after 4 weeks of storage (Fig. 11a and d, respectively). None of the additives changed the crystal habit of the re-crystallized guaifenesin. This indicated that the crystallization inhibitors did not interfere with the growing crystal face. Together with the DSC results, the decrease in crystallization of the API can thus result from the increased solubility of the guaifenesin in the matrix containing both the acrylic polymer and the hydrophilic carrier.

Extrudates containing Eudragit L100-55® released 100% of drug after approximately 8 h in pH 6.8 phosphate buffer (Fig. 12), as opposed to extrudates containing Acryl-EZE® and guaifenesin, which showed complete drug release after 4 h in pH 6.8 phosphate buffer (Fig. 9). In extrudates containing Eudragit L100-55® and guaifenesin, the presence of additives had no effect on the in vitro drug release rates, and release properties of all extrudates were very similar. The difference in the release rates was due to the presence of other excipients present in Acryl-EZE®, which accelerate the break-up of the matrix, and thus speed up drug release. In extrudates consisting of Eudragit L100-55®, TEC and guaifenesin, the drug

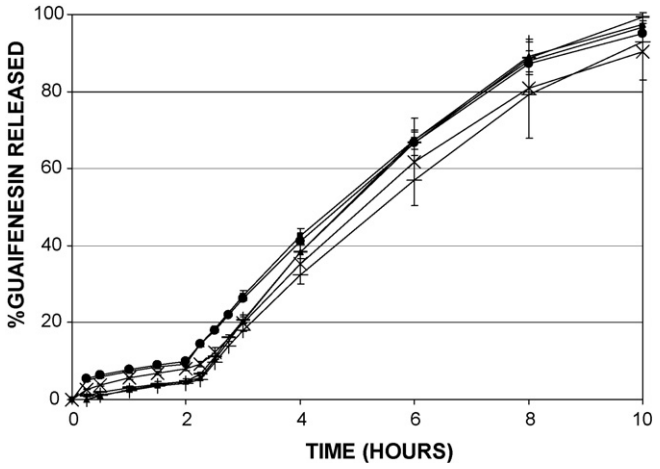

Fig. 12. Influence of 10% crystallization inhibitor (based on drug content) on the dissolution of guaifenesin from tablets containing 25% guaifenesin and Eudragit L100-55®; soon after extrusion (basket, 900 mL, 37 ± 0.5 °C, 50 rpm, 2 h 0.1N HCl, 8 h pH 6.8 phosphate buffer, $n = 6$). (▲) Polycarbophil, (×) PEG 3350, (◯) poloxamer 188, (■) PVP K25, (−) no additive, and (+) poly(ethylene oxide).

release is due only to the dissolution of the polymer, which slows the drug release. All hydrophilic additives tested were water-swellable polymers, whose hydration and erosion is a function of molecular weight. The melt-extruded tablets containing guaifenesin, Eudragit L100-55® and each of the hydrophilic additives swelled during dissolution testing. Formulations not containing the hydrophilic additives did not swell during dissolution testing. Drug release in formulations containing the hydrophilic additives was thus a function of the pH-depended solubility of Eudragit L100-55® and the swelling/erosion caused by the hydrophilic additive. Due to the low levels of hydrophilic additive, the drug release rates were not affected. The release rate did not change following 4 weeks of storage at 25 °C and 60% relative humidity (Fig. 13), indicating that the formulations were stable.

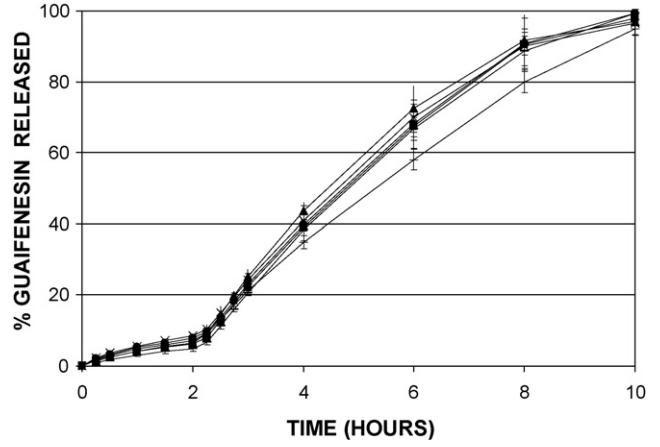

Fig. 13. Influence of 10% crystallization inhibitor (based on drug content) on the dissolution of guaifenesin from tablets containing 25% guaifenesin and Eudragit L100-55®; after 3 weeks of storage at 25 °C/60% relative humidity (basket, 900 mL, 37 ± 0.5 °C, 50 rpm, 2 h 0.1N HCl, 8 h pH 6.8 phosphate buffer, $n = 6$). (▲) Polycarbophil, (×) PEG 3350, (◯) poloxamer 188, (■) PVP K25, (−) no additive, and (+) poly(ethylene oxide).

4. Conclusion

Acryl-EZE® and Eudragit L100-55® were successfully extruded with guaifenesin as the model drug and guaifenesin had a plasticizing effect on the acrylic polymer. Preliminary results demonstrated that guaifenesin formed a solid solution in the acrylic polymer during processing and that at a 25% drug loading the saturation solubility of the guaifenesin in the Eudragit L100-55® was exceeded after the extrudate was cooled to ambient conditions, resulting in crystal formation at the surface of the tablet. The addition of hydrophilic polymers to the matrix reduced the onset and the extent of drug recrystallization. Future studies will further address the solubility of guaifenesin in hydrophilic additives and the role of other formulation components on guaifenesin recrystallization from melt extrudates containing either Acryl-EZE® or Eudragit L100-55®.

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