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ORIGINAL ARTICLE

Aqueous film coating to reduce recrystallization of guaifenesin from hot-melt extruded acrylic matrices

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Abstract

Objectives: This study investigated the effect of aqueous film coating on the recrystallization of guaifenesin from acrylic, hot-melt extruded matrix tablets. *Methods*: After hot-melt extrusion, matrix tablets were film-coated with either hypromellose or ethylcellulose. The effects of the coating polymer, curing and storage conditions, polymer weight gain, and core guaifenesin concentration on guaifenesin recrystallization were investigated. *Results*: The presence of either film coating on the guaifenesin-containing tablets was found to prolong the onset time of drug crystallization. The coating polymer was the most important factor determining the delay in the onset of crystallization, with the more hydrophilic polymer, hypromellose, having a higher solubilization potential for the guaifenesin and delaying crystallization for longer period (3 or 6 months in tablets stored at 40°C or 25°C, respectively) than the more hydrophobic ethylcellulose, which displayed a lower solubilization potential for guaifenesin (crystal growth on tablets cured for 2 hours at 60°C occurred within 3 weeks, whereas uncoated tablets displayed surface crystal growth after 30 minutes). Crystal morphology was also affected by the film coating. Elevated temperatures during both curing and storage, incomplete film coalescence, and high core drug concentrations all contributed to an earlier onset of crystal growth.

Key words: *Acryl-EZE®; curing; diffusion; Eudragit® L100-55; film coating; guaifenesin; hot-melt extrusion; matrix tablets; physical stability; recrystallization*

Introduction

The physical stability of drugs rendered amorphous in sold dispersions remains a challenging area of research[1]. Systems in which a drug is supersaturated are thermodynamically unstable, although the onset time of crystallization varies. Supersaturation results if the solubility of the drug in the matrix is exceeded, and for materials processed by hot-melt extrusion, the change in solubilities at the elevated processing temperatures, compared to storage temperatures, also contributes to supersaturation[2].

The recrystallization of guaifenesin in hot-melt extruded matrix tablets was reported earlier, and it was shown that the addition of hydrophilic polymers in which the drug had a high solubility could reduce the amount of crystal growth[2]. In addition, it was observed that crystal growth only occurred on the tablet surface. Random particulates and environmental moisture were shown to function as nucleating agents that accelerate nucleation and crystal growth.

Utilizing polymeric materials as barriers to diffusion is the basis of many applications in food products[3], packaging[4], membrane separations,[5,6] and sensors[7]. Commercial film coating systems have been developed to function as moisture barriers[8]. Relationships between water and gas permeabilities and membrane structure[9,10] have been described, and transport mechanisms and behavior of block copolymers have been reviewed by Jonquières et al.[11] Polymer morphology impacts diffusion through the matrix and polymer crystallinity has been reported to be a major factor in permeation[9,10]. Amorphous regions throughout a sample are known to differ in structure, resulting in heterogeneous molecular mobilities[12].

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The aim of this study was to investigate the properties of a hydrophobic and a hydrophilic film coating on the surface crystal growth of guaifenesin on tablets prepared by hot-melt extrusion. It was hypothesized that a film-forming polymer could stabilize the system either by impeding the diffusion of guaifenesin to the surface or by solubilizing guaifenesin, which would reduce the supersaturation of the API in the matrix polymer, which drives surface crystallization. Barrier membranes were reported to impede diffusion by using membrane materials with which the diffusing species did not interact. Ethylcellulose is a hydrophobic, film-forming polymer without polar functional groups as found on guaifenesin and was chosen to test the barrier membrane approach. In the second case, a film coating comprising a polymer that solubilizes guaifenesin was chosen to act as a sink for the drug, and based on prior studies, hypromellose was known to be able to solubilize higher amounts of guaifenesin for longer periods of time before crystal growth was observed. The effects of polymer type, polymer weight gain, curing, storage, and core drug-to-polymer ratio on the onset and extent of guaifenesin recrystallization were determined.

Materials and methods

Materials

Guaifenesin was used as the model drug and was purchased from Spectrum (Gardena, CA, USA). Acryl-EZE® and Eudragit® L100-55 were donated by Colorcon (West Point, PA, USA) and Evonik (Piscataway, NJ, USA, particle size 95% below 250 μm), respectively, and were employed as matrix formers in the melt extruded tablets. The melt extruded tablets were film-coated using either Opadry® Clear YS-1-7006 (Polymer: hypromellose, donated by Colorcon) or Aquacoat® ECD 30 (Polymer: ethylcellulose, provided by FMC, Philadelphia, PA, USA). Dibutylsebacate (DBS) was used to plasticize ethylcellulose, and triethyl citrate (TEC) was used to plasticize Eudragit® L100-55, both were gifts from Vertellus (Greensboro, NC, USA). Ethocel Standard 7 Premium (NF grade) was donated by Dow Chemical (Midland, MI, USA) and was used to cast films containing ethylcellulose and guaifenesin. Alcohol (USP grade, 200 proof) was purchased from AAPER Alcohol and Chemical Co. (Shelbyville, KY, USA). Tablets were packaged in HDPE containers (MoldRite Plastics, Plattsburgh, NY, USA) containing a desiccant bag (1 g silica gel Minipax; Impak, Los Angeles, CA, USA). The desiccant Drierite® (Hammond, Xenia, OH, USA) was obtained from Fisher Scientific (Pittsburgh, PA, USA) to condition storage chambers.

Tablet preparation

Tablets were prepared by hot-melt extrusion of the powder blends, followed by manual cutting of the extrudate strand into cylindrical tablets (average weight 700 mg). Premixed powder blends were fed into a single-screw Randcastle extruder (Randcastle Microtruder® Model RCP-0750; Randcastle, Cedar Grove, NY, USA) 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. Tablets containing 19.1% guaifenesin, 79.4% Eudragit® L100-55, and 4.5% TEC were extruded at 70–85–90–95°C (temperature zones 1-2-3-die) at a screw speed of 20 rpm and 322 ± 9 amps. Tablets containing 35.8% API, 59.7% Eudragit® L100-55, and 4.5% TEC were extruded at 80–85–85–90°C, at a screw speed of 15 rpm and 157 ± 8 amps. The extruder was equilibrated at the processing temperatures for a minimum of 40 minutes before extrusion, and the extrudate strands were allowed to cool in a desiccator at room temperature for 1 day before being cut into tablets.

Film coating

Hot-melt extruded tablets were mixed with compressed placebo tablets in a 1:1 weight ratio, and 300-g batches (placebo plus melt extruded tablets) were placed into a perforated pan coater (HCT Mini HiCoater; Vector Corp., Cedar Rapids, IA, USA), equipped with a peristaltic pump (505S Watson-Marlow, Wilmington, MA, USA). The coating dispersions were kept under constant low-shear stir during preparation and during the film-coating process. To coat tablets with Aquacoat® ECD, the coating dispersion was sprayed at 1.5 g/min, the inlet air and outlet temperatures were 55–60°C and 41°C, respectively, and the pan rotated at 40 rpm. To coat tablets with Opadry®, the coating dispersion was sprayed at 2.0 g/min, the inlet air and outlet temperatures were 75°C and 42°C, respectively, and the pan rotated at 20 rpm. All tablets were coated to completion and were dried for 10 minutes at about 40°C in the rotating pan. Aquacoat® ECD-coated tablets were either uncured or cured for 2 hours at 60°C, while Opadry®-coated tablets were cured for 2 hours at 40°C. Tablets were packaged into labeled bottles, which were induction-sealed (Compak Jr; Enercon, Menomonee Falls, WI, USA) and placed into storage chambers either at 25°C/60% relative humidity or at 40°C/75% relative humidity.

Determination of guaifenesin solubilization in polymers

The solubility of guaifenesin in both polymers and in Eudragit® L100-55 was measured by casting films containing one of the polymers and dissolved guaifenesin

in increasing concentrations and by visually observing the physical stability during storage for 5 months at 24°C in a desiccator filled with indicating silica gel desiccant (relative humidity in chamber was measured to be 17% by a VWR Thermo-Hygro hygrometer; VWR, West Chester, PA, USA). Ethylcellulose films were cast using powdered ethylcellulose (Ethocel Standard 7 Premium, NF grade) rather than the Aquacoat® ECD dispersion, as the coating dispersion contained talc, which may have a nucleating effect on guaifenesin. The hypromellose-containing coating dispersion, Opadry® Clear, did not contain talc and was used to cast films. Films were prepared by dispersing 900 mg powder blend containing the polymer and different amounts of drug in 20–35 mL of 200 proof ethanol, DI water, or mixtures thereof to obtain clear dispersions. After stirring for at least 30 minutes under low shear until all components were dissolved or well dispersed, the solutions were cast into aluminum dishes (Fisher Scientific, Hampton, NH, USA) and were dried for 24 hours or until dry under a fume hood (alcohol-based films) or in a 55°C oven (water based films). Films were kept at 24°C in desiccators filled with indicating silica gel desiccant (relative humidity in chamber was measured to be 17% by a VWR Thermo-Hygro hygrometer; VWR) and were visually observed for crystal growth at regular intervals.

Powder X-ray diffraction

X-ray diffraction was used to study the morphology of coated tablet surfaces. A tablet containing 35.8% guaifenesin coated with hypromellose (10% polymer weight gain) was arranged on a glass slide and was analyzed using a Philips Vertical Scanning Diffractometer, Type 42273 (Philips Electronic Instrument, Mount Vernon, NY, USA), employing CuKα radiation, operating at 40 kV and 30 mA. The scan radius ranged from 10° to 60°, and the step size was 0.05° every 4 seconds.

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 coated hot-melt extruded tablets. Samples were mounted on stubs with carbon tape (Shintron Tape; Shinto Paint Co., Ltd., Tokyo, Japan). To enhance the conductivity of the samples for SEM, all tablets were coated with a 15-nm thick platinum/palladium coating (80%/20%), applied by a Cressington Sputter Coater 208 HR (Cressington, Watford, UK) equipped with a thickness controller (MTM 20; Cressington) at 2.5 kV, 20 mA under Argon. SEM images were taken in field emission mode at 5 kV using a Zeiss Supra 40VP electron microscope (Zeiss Supra, Minneapolis, MN, USA) equipped with a Gemini Column and SmartSEM software. The surface of the tablets was observed in numerous places, before selecting a typical part of the area for the micrograph.

Assay for surface guaifenesin

An assay was developed to quantify the amount of guaifenesin on the tablet surface (Figure 1). Briefly, individual tablets were accurately weighed and a single tablet was placed into a large test tube (25 × 150 mm) containing 5.0 mL of 0.1 N HCl. The test tube was subjected to vortex mixing (SP vortex mixer; Baxter Diagnostic, Deerfield, IL, USA) at a fixed agitation force for 5 seconds, dissolving surface guaifenesin. Immediately after vortex mixing, the medium was decanted and filtered through a 0.22-µm nylon filter (Puradics 25NYL syringe filter; Whatman, Maidstone, UK). The guaifenesin content of the filtered medium was analyzed by UV analysis. Residual liquid on the recovered tablets was blotted off and the tablets were dried at ambient conditions. The dimensions of dried tablets (height and diameter) were measured using calipers (Starrett, Athol, MA, USA). To study the effect of the procedure on the hypromellose coating, the coating thickness of tablets was determined before and after the assay.

UV analysis of guaifenesin

The guaifenesin content of samples from the surface guaifenesin assay was quantified at 273 nm in 400-µL

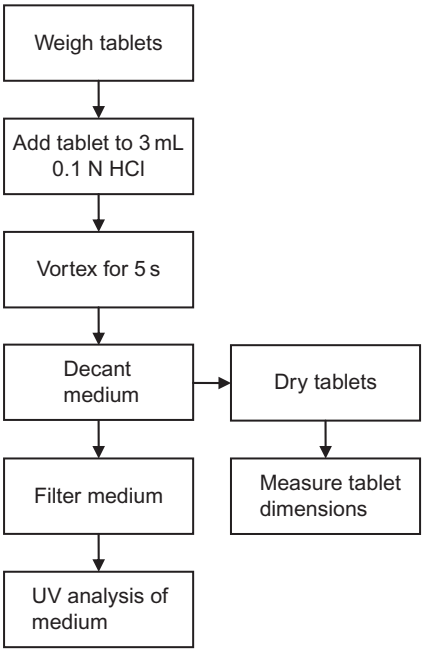

Figure 1. Diagram of the procedure to analyze the guaifenesin content on the surface of tablets.

samples by UV spectroscopy (μQuant UV Spectrometer equipped with KC 4 software for data analysis; BioTek Instruments, Inc., Winooski, VT, USA). Linearity was established for drug concentrations between 8 and 200 ng/mL (R^2 = 0.9968). Concentrations of 2 ng/mL were below the limit of detection of the instrument.

Results and discussion

Earlier studies provided an understanding of factors contributing to drug recrystallization. At a drug concentration exceeding the solubility limit, guaifenesin recrystallized from the amorphous state. In hot-melt extruded matrix tablets that contained Eudragit® L100-55 and guaifenesin, the drug concentration in the matrix, the presence of nucleating agents, and processing conditions influenced the recrystallization of guaifenesin. Crystal growth was observed only on tablet surfaces[2].

The solubilization of guaifenesin in the coating polymers

The tablets were coated with either a hydrophobic or a hydrophilic polymer to investigate the influence of the film coatings on crystal formation on the tablet surface. The ability of these polymers to solubilize guaifenesin was determined to verify the hypothesis for the study, namely that ethylcellulose has a low solubilization potential for guaifenesin because of the differences in chemical structures, which would translate into barrier properties against the drug, and that hypromellose has a high solubilization potential for guaifenesin, which would enable this polymer to solubilize the API in the film coating. Recrystallization was observed over 5 months at 24°C and occurred within 1 week in ethylcellulose films containing 1% guaifenesin, whereas crystal growth in hypromellose films was observed only at 40% drug content and above and took several weeks to develop. Previous studies found that the matrix-forming acrylic polymer, Eudragit® L100-55, could dissolve about 20% guaifenesin during melt extrusion[13].

These results confirmed the assumptions and can be explained by the chemical structure of the materials. Guaifenesin is a hydrophilic molecule, with alcoholic and ether functional groups that enable it to hydrogen-bond to corresponding groups in the hydrophilic polymer, hypromellose, whereas ethylcellulose is a hydrophobic material, whose lack of hydrophilic groups offers little hydrogen bonding interaction potential. Studies on barrier membranes indicated that the rate of diffusion for small molecules depended on the interactions between the diffusing species and the polymer[12]. Earlier studies from our laboratory demonstrated that polymers with a higher solubility for guaifenesin than Eudragit® L100-55, such as hypromellose, were able to reduce guaifenesin recrystallization from a hot-melt extruded matrix when the polymers were coextruded with the guaifenesin[2]. The high solubility for the API suggested that a hypromellose film coating could solubilize excess guaifenesin from the matrix, whereas the low solubility of the drug in ethylcellulose indicated a dearth of polar interactions between the two molecules, possibly resulting in a barrier to the diffusion of guaifenesin.

Effects of the film-coating process on hot-melt extruded tablets

Coating parameters were chosen to promote complete film formation and to minimize sticking and twin formation. Film coating resulted in an amorphous coating layer. After 4 months of storage at 25°C/60% relative humidity, X-ray diffraction confirmed the amorphous nature of the coating and did not detect crystalline materials on the surface of tablets coated with hypromellose (Figure 2).

Influence of the film-coating layer on guaifenesin recrystallization

The recrystallization of guaifenesin from the amorphous state occurred within 30 minutes in uncoated tablets containing 35.8% guaifenesin, which were stored at 24°C in a desiccator (relative humidity in chamber was measured to be 17%). Crystal growth was delayed when the matrices were coated with either polymer. The polymeric film deposited on the extruded tablets separated the supersaturated matrix from exposure to the atmosphere. Particulate matter and moisture droplets present in air can function as nucleating agents. In particular, storage of tablets under high-relative humidity exposes the tablet surfaces to fine moisture droplets, which can function as nucleating agents. The coating process also exposed tablets to water droplets and moist air, but the exposure of tablets to humidity during the coating process differed from the exposure during storage under high humidity in several points. Although larger coating pans can apply similar film coatings in much shorter time frames, the coating process on the small-scale equipment was still short (less than 5 hours) compared to the duration of the storage (between 1 week and 6 months), and process water was removed first by drying of the tablets in the coating pan and then by curing at elevated temperatures. For droplets to act as nucleating agents, their size must be on the scale of the developing structure. While there was certainly an interaction of coating spray droplets and cores during coating, the coating dispersion or solution spray droplets are on a larger scale than moisture droplets in the air that account for atmospheric humidity and function as nucleating agents. The surface of the tablets constantly changed during the coating process as the coating layer was deposited, and the coating process

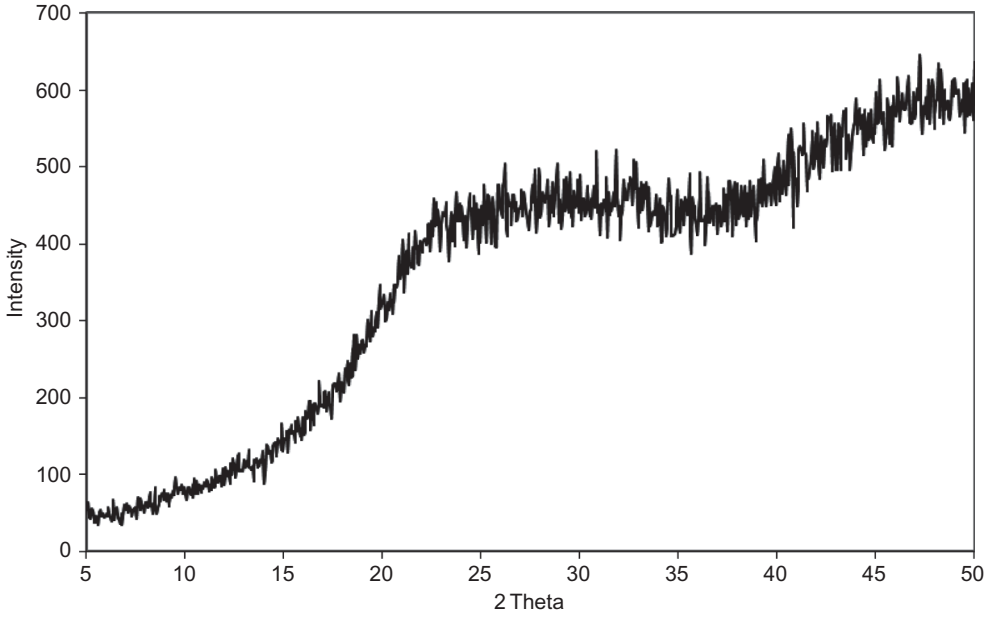

Figure 2. The influence of 4 months of storage at 25°C/60% relative humidity on the surface morphology of matrix tablet containing 35.8% guaifenesin coated with hypromellose (10% weight gain). (PXRD scan at 40 kV and 30 mA. The scan radius ranged from 10° to 60°, and the step size was 0.05° every 4 seconds.)

was very dynamic (rotation of the bed, constant airstream through the coating pan removing evaporated water). Water was present in the coating process in the form of the coating spray droplets, but those droplets were too big to affect nucleation, and in the form of evaporated water, which had a high turnover rate as it was constantly removed from the pan. However, during storage, the surface of tablets and the atmosphere around the tablets remained undisturbed, which facilitated crystal growth. Because of those differences in the exposure to water in different forms and under different conditions, the storage conditions of the tablets were considered to have a larger influence on the development of crystal growth than the coating process.

When crystal growth appeared on the surface of film-coated tablets, the crystal morphology was altered compared to the crystals on uncoated tablets (Figures 3 and 4). While needle-shaped crystals grew outward in uncoated tablets, crystals developed within the film coatings on coated tablets, and in hypromellose films, the crystal habit changed. The change in crystal habit in the presence of polymers[14] as well as in combinations of polymers and surfactants[15] has been reported and was explained by viscosity effects and the preferential adsorption of polymers to some crystal faces because of hydrogen bonding, which retards the growth at these sites. The faster relative development of other crystal faces then changes the appearance of the crystal. Katzhendler et al. described a detailed mechanism for the hydrogen bonding interaction of carbamazepine and hypromellose to explain the polymer's effect on the drug[16]. The change in the crystal habit of miconazole increased drug release from mucoadhesive patches[17],

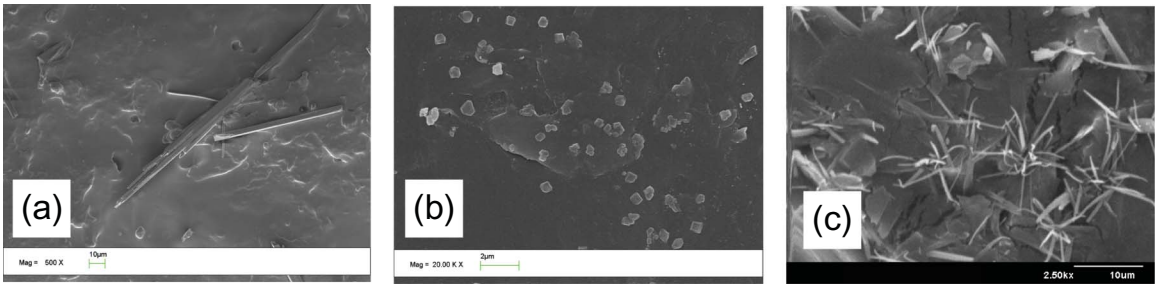

Figure 3. The influence of coating polymers on the growth of guaifenesin crystals: (a) ethylcellulose-coated tablets, (b) hypromellose-coated tablets, and (c) uncoated tablets.

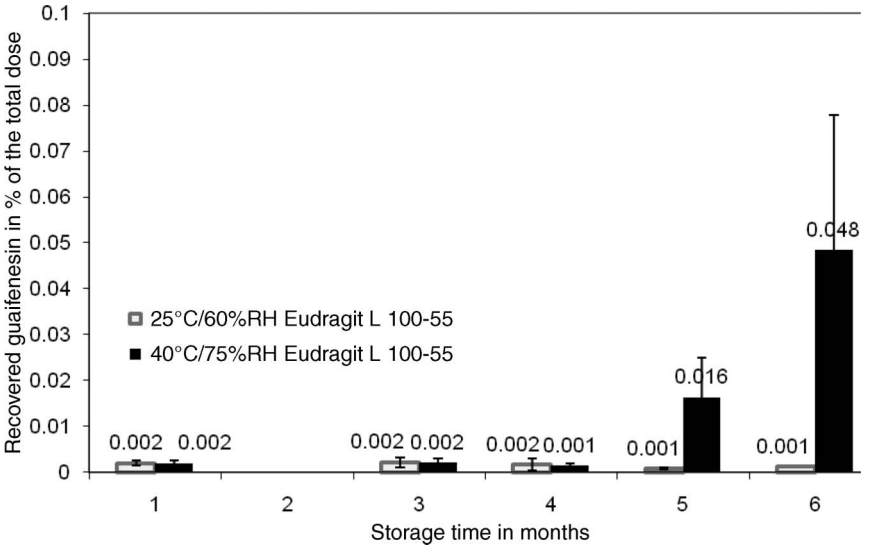

Figure 4. The influence of storage time on the amount of guaifenesin detected on the tablet surface in hot-melt extruded matrix tablets containing Eudragit L100-55 and 37.5% guaifenesin, film-coated with hypromellose (10% polymer weight gain, $n = 6$, tablets stored in induction-sealed HDPE containers).

although no effect of recrystallization on the drug release rate was found with the present system[2].

Effect of storage temperature and polymer type

Tablets coated with hypromellose to a 10% weight gain and stored at 40°C/75% relative humidity developed recrystallization after 5 months of storage, as compared to 6 months for tablets stored at 25°C/60% relative humidity (Table 1). Drug diffusion in polymers was investigated by Zhao et al. by molecular modeling of aspirin in polymer blends[18]. The movement of polymer chains was found to be more important for drug diffusion than the free volume of the polymer matrix. Free volume and average cavity size have been identified as a major factor in the diffusion of smaller gas molecules (carbon dioxide, oxygen) as part of the 'hopping diffusion mechanism'[19–21]. Zhao and coworkers proposed that because of the larger size of drug molecules compared to the gases, aspirin could not jump between different cavities of free volume in the polymer like the smaller gas molecules but rather moved forward with the diffusional motion of the polymer chains. Melt extrusion rendered the guaifenesin molecules dissolved and dispersed in the acrylic matrix, which resulted in a structure that was similar to the system investigated by Zhao et al. The change in crystallization rates of amorphous drugs with temperature was studied in detail by Aso et al.[22], who ascribed faster crystallization in part to higher molecular mobility. At elevated temperatures, molecules possess a higher mobility than at a lower temperature, and thus polymeric chains are more flexible. In our study, the higher molecular mobility of the polymeric chains of Eudragit L100-55 at the 40°C storage temperature resulted in a faster movement of guaifenesin through the matrix, as guaifenesin movement depended on the movement of the polymeric chains around the drug molecules. Crystal growth depends on mass transport of molecules to the growing crystal faces and was consequently accelerated when guaifenesin was more mobile.

Table 1. The effect of polymer weight gain and storage conditions on the onset time of guaifenesin recrystallization for melt extruded matrix tablets coated with hypromellose. (Tablets were cured for 24 hours at 40°C. Drug-to-polymer ratio of tablets containing 25% Acryl-EZE® or 37% Eudragit® L100-55 was identical.)

Coating polymer: hypromellose				
	Eudragit® L100-55 (guaifenesin concentration, 37%)		Acryl-EZE® (guaifenesin concentration, 25%)	
Core tablet matrix former				
Hypromellose weight gain	2%	10%	2%	10%
Onset at 25°C/60%RH	4 months	6 months	—	6 months
Onset at 40°C/75%RH	3 months	5 months	—	5 months

Curing in hypromellose-coated tablets was performed to remove process water after film coating. Hypromellose-coated tablets were cured for 24 hours at 40°C, and complete coalescence was observed in all cases. To investigate coalescence, SEM was used to examine the coated tablet for surface defects such as cracks, and the quality of the film coating on the tablet was studied. A film coating is considered to be fully coalesced if it exhibits a smooth surface over the entire tablet surface area and displayed no cracks or other surface defects.

In ethylcellulose-coated tablets, film coalescence and the prevention of recrystallization emerged as conflicting goals. Because film coalescence in uncured tablets was incomplete after coating (cracks in the film were visible under SEM directly after the coating process), a curing step was necessary to conclude film formation. Curing for 24 hours at 60°C was effective in attaining film coalescence, as verified by SEM observations.

The onset of crystallization in uncured, ethylcellulose-coated tablets varied, from a few hours to several days despite constant storage conditions of either 40°C or 25°C. For this reason, uncured, ethylcellulose-coated tablets were not investigated further. Crystal growth on these uncured tablets was observed in the vicinity of cracks or other film defects, which can be explained by the decrease in tortuosity of the ethylcellulose coating. Tortuosity describes the directness of a molecule's diffusion path through a film[23], which is affected among other factors by the degree of polymer coalescence. Aging effects typically result in a decrease in drug release during the storage of tablets film-coated with ethylcellulose[24]. Kucera and coworkers[25] ascribed the decrease in drug release to a decrease in free volume and an increase in film coalescence, which resulted in higher coating density and consequently higher tortuosity. Cracks in the film defects breach the coating layer, and hence decrease tortuosity, promoting the onset of crystallization by opening a channel through the coating material for drug molecules to reach the surface, where they are incorporated into the growing crystal faces.

Ethylcellulose-coated tablets cured at 60°C for 24 hours displayed a coalesced film coating, as verified by SEM analysis. After 24 hours of storage, no formulation had developed crystal growth. However, despite the intact film-coating layer, crystal formation was observed after 2 weeks in tablets containing 35.8% guaifenesin. Crystal growth on intact coatings was attributed in part to drug migration into the coating during the curing step due to higher molecular mobility of guaifenesin at the elevated curing temperature. It was concluded from these studies that ethylcellulose was an ineffective barrier coating in this application. Even though the solubility of guaifenesin in ethylcellulose was low, the small amphiphilic drug contains a benzene ring and short aliphatic chains in addition to its hydrophilic functional groups, which allow nonpolar interactions with ethylcellulose, and hence could enable diffusion through the coating. Insufficient film coalescence in uncured films and elevated temperatures during curing both promoted guaifenesin recrystallization. These results lead to the conclusion that ethylcellulose was an ineffective polymer to control the surface crystallization of guaifenesin from melt extruded tablets.

The hypromellose coating was shown to prolong the onset of crystal growth for 3–6 months (Table 1). Polar interactions of drug and polymer facilitated guaifenesin solubilization in the film coating and delayed the onset of crystallization. The effect of drug–polymer interactions on diffusion was investigated by Peppas and coworkers, who found that drug–polymer binding impeded drug diffusion in hydrogels[26].

Following the guaifenesin crystallization process using SEM alone was considered to be unsatisfactory, and a quantitative method was needed to determine the amount of recrystallized drug on the tablet surface. A wet-chemical assay was developed that quantified the amount of guaifenesin present on the tablet surface (Figure 1), which was based on dissolving guaifenesin from the surface of tablets in a medium under standardized conditions and then quantifying the drug content in the liquid by UV analysis. The test itself did not distinguish between different states of guaifenesin on the tablet, but it was useful when combined with SEM observations. SEM micrographs before and after the test showed that surface crystals present before the test had been removed after the procedure (pictures not shown). Determinations of the surface drug concentration were restricted to tablets coated with hypromellose, as this polymer was shown to be successful in retarding crystal growth for extended periods of time, and the onset of crystallization in ethylcellulose-coated tablets was more variable.

Tablets coated with hypromellose were stored either at 25°C/60% relative humidity or at 40°C/75% relative humidity in induction-sealed containers and were analyzed at regular intervals to follow the increase in surface guaifenesin content during storage (Figure 4). As hypromellose was soluble in the medium, the coating thickness was determined before and after the assay (Figure 5), and it was found that only the upper coating layer was dissolved because of the short immersion time (5 seconds) in the medium. This confirmed that the assay captured only guaifenesin present in the coating layer and not from the matrix tablet.

Drug levels on tablets stored at 40°C increased faster than the amount of drug found on tablet surfaces stored at 25°C (Figure 4). As outlined above, elevated storage temperature accelerated drug diffusion. Levels remained very low and started to increase after 5 months for tablets stored at 40°C. After 6 months, crystals were visible under SEM analysis. These results indicate that the film coating was able to solubilize guaifenesin, which prevented drug surface levels from building up past the solubilization capacity of the coating for the first 4 months. This capability was eventually exhausted, and guaifenesin reached surface levels that were high enough for nucleation and crystal growth, although the overall amount of drug on the surface compared to the total dose of guaifenesin in the tablet remained low.

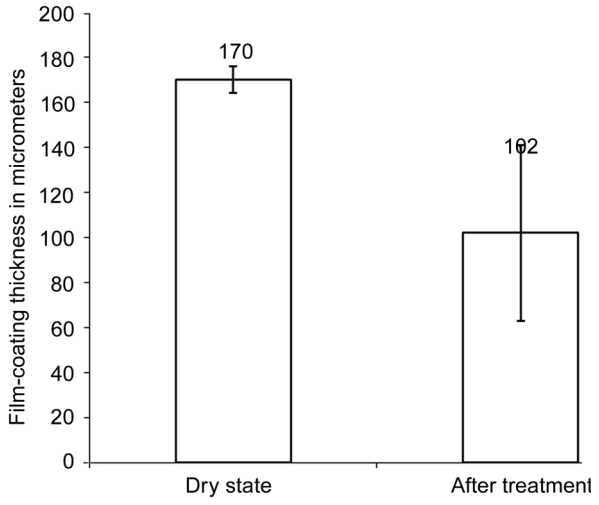

Figure 5. Influence of the quantitative analysis process on the film thickness of hypromellose-coated tablets (n = minimum of six individual measurements on at least two tablets).

Effect of weight gain, polymer film thickness, and core drug concentration

For both ethylcellulose and hypromellose, a higher polymeric weight gain was demonstrated to prolong the onset of crystallization (data not shown for ethylcellulose). Increasing the hypromellose weight gain from 2% to 10% resulted in an increase in film thickness from 191 to 358 μm and a delay in the onset of crystal growth from 3 to 5 months in tablets stored at 40°C, and from 4 to 6 months for tablets stored at 25°C (Table 1). A thicker hypromellose film involved longer diffusion paths and had a higher polymeric volume to solubilize higher amounts of guaifenesin. The higher volume of a thicker film delays the development of a supersaturated state, especially because the polymer can solubilize up to 40% guaifenesin as was the case with hypromellose. However, an increase in weight gain from 7% to 15% did not delay crystallization if the coating polymer was unsuitable, as demonstrated in ethylcellulose-coated tablets, which developed crystals earlier than hypromellose-coated tablets (2% or 10% weight gain). Thus, the polymer type had a much larger influence on crystal growth than the polymer weight gain.

The guaifenesin content in tablet cores affected the onset time of crysallization on the tablet surface. After 2 weeks, crystals appeared on the surface of tablets containing 35.8% guaifenesin and coated with 15% ethylcellulose (curing time 2 hours at 60°C), while similar tablets containing 19.1% guaifenesin showed crystal growth after 3 weeks. The core drug concentration determined the concentration gradient between the tablet core and the coated tablet surface, and a higher gradient resulted in a faster onset of crystallization. Similar observations were made with hypromellose-coated tablets.

Conclusion

The film coating of hot-melt extruded acrylic matrix tablets containing guaifenesin was investigated. Film coating delayed the onset of crystallization over uncured tablets regardless of the polymer used for the coating, which was ascribed to the protection from ubiquitous nucleating agents present in the environment by covering the tablet surface. The choice of coating polymer was the most important factor affecting the onset time of crystallization, and hypromellose, a polymer able to solubilize up to 40% guaifenesin, and thus acting as a sink for excess surface drug, delayed recrystallization for up to 6 months. The drug morphology of guaifenesin crystals was altered because of the presence of polymers, and thicker coatings (higher polymer weight gain) retarded the onset of crystal growth, while a high drug-to-polymer ratio in the core promoted crystal growth. Elevated storage temperature resulted in an earlier onset of recrystallization. An assay detecting surface drug levels showed that despite crystal growth, surface guaifenesin levels remained low compared to the total dose of drug in the matrix. In conclusion, the film coating of hot-melt extruded, acrylic matrix tablets successfully delayed the onset of guaifenesin recrystallization for up to 6 months.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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