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Research paper

The influence of heterogeneous nucleation on the surface crystallization of guaifenesin from melt extrudates containing Eudragit® L10055 or Acryl-EZE®

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ABSTRACT

The objective of this study was to investigate the influence of talc and humidity conditions during storage on the crystal growth of guaifenesin on the surface of melt-extruded matrix tablets. Tablets consisted of the model drug guaifenesin in a matrix of either Acryl-EZE® or Eudragit® L10055 and either no talc, 25% or 50% talc. After processing, the hot-melt-extruded matrix tablets were supersaturated with amorphous guaifenesin, which resulted in the development of guaifenesin drug crystals on exposed surfaces of the tablet during storage (all tablets were stored at 24 °C). A previously developed, quantitative test was used to assay for surface guaifenesin. In tablets with a drug-to-polymer ratio of 19:81, talc-containing tablets exhibited an earlier onset of crystal growth (storage at 17% relative humidity). The presence of talc also increased the amount of surface crystallization and was independent of the talc concentration, since the talc levels used in this study exceeded the critical nucleant concentration. Additional non-melting components did not have an additive effect on surface crystal growth. High humidity during storage (78%) increased guaifenesin crystallization, but moisture uptake of tablets did not correlate with increased drug recrystallization. When storage at 17% relative humidity was interrupted for 3 days by storage at 78% relative humidity before the tablets were returned to their previous low RH storage conditions, crystal growth quickly increased during the high RH interval and remained at an elevated level throughout the remaining storage period. A similar intermediate period of low, 17% relative humidity in tablets stored before and after that time at 78% RH did not affect surface crystallization levels. The effects of humidity and talc on the crystallization of guaifenesin from melt-extruded dosage forms supersaturated with amorphous drug were ascribed to heterogeneous nucleation.

1. Introduction

Hot-melt extrusion [1,2] has been employed to incorporate drugs into polymeric matrices [3–5] and to convert crystalline drugs into the amorphous state [6–8]. Drugs in the amorphous state generally exhibit higher aqueous dissolution rates [9] and enhanced in vivo bioavailability [10]. During hot-melt extrusion, the drug powder, the matrix-forming polymer and other excipients are heated for a short period of time. The matrix former will soften or melt and the other components will be dispersed in the melt as the material moves through the barrel of the extruder. Depending on their melting point and solubility in the matrix, formulation components can be dissolved or dispersed in the polymeric carrier. Formulation components will be trapped in the hardening matrix as the extrudate cools. Hot-melt extruded products usually demonstrate good content uniformity due to intense mixing during processing [11].

The amorphous state of a drug is thermodynamically unstable compared to crystalline forms. Recrystallization from the amorphous state compromises the essential quality of the dosage form, a phenomenon that has been reported for several drugs [12,13]. Tablet properties such as disintegration time and dissolution performance depend on the physical state of the drug and can be negatively affected by recrystallization. Furthermore, pure drug crystals located on the tablet surface can be removed by shear forces, resulting in a diminished total dose of the drug.

In a previous study, we identified crystal growth as a sign of a physical instability of the matrix, resulting from supersaturation of guaifenesin in the polymer [14]. Fig. 1 illustrates the problem and depicts the changes in the state of guaifenesin during melt extrusion. Guaifenesin melts during processing, since its melting point is lower than the extrusion temperature. The solubility of guaifenesin in the polymeric matrix decreases at lower temperatures, consequently the matrix polymer can solubilize more guaifenesin at the higher extrusion temperatures than in the cooled extrudate, which results in a matrix supersaturated with guaifenesin, when the matrix contains more than 20% drug [15].

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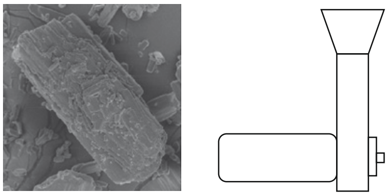
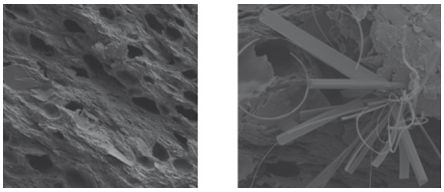


1. Crystalline Bulk Guaifenesin

2. Hot-melt Extrusion



3. Amorphous Guaifenesin in Matrix

4. Recrystallized Guaifenesin on Tablet Surface

Fig. 1. The development of physical instability.

Recrystallization occurred quickly and within 15 min, guaifenesin crystals were found to develop on tablets with a guaifenesin-to-polymer ratio of 37.5–62.5 at room temperature [14]. The same study demonstrated that crystals only developed on exposed surfaces of the extrudate. Our initial attempt to inhibit this crystal growth focused on enhancing the solubility of the drug in the matrix. The addition of selected hydrophilic polymers with higher solubility for guaifenesin decreased the supersaturation of the drug in the polymer, and hence reduced surface crystallization [14].

While the supersaturation of the drug in the tablet is the driving force for crystallization [16], other factors such as formulation composition and storage conditions can influence the onset and extent of crystallization. Formulation components can hinder or accelerate crystal growth [17] and change the crystal habit [18]. Talc is a common filler material and has been reported to affect the crystallization of matrix polymers [19,20]. An earlier film study [15] demonstrated a similar effect on guaifenesin for the present system. Storage conditions, mainly temperature [21–23] and humidity [24–29], have previously been shown to affect crystallization rates.

Formulation composition and storage conditions influence recrystallization by influencing the formation of nuclei which then grow into crystals. A supersaturated state can be sufficient for nucleation to occur. Such a spontaneous process is called homogeneous nucleation, since it is induced without the participation of other particles and is due only to the supersaturation of the nucleating species. This is considered a rare case due to the ubiquitous prevalence of impurities. In contrast, heterogeneous nucleation occurs when other particles or equipment surfaces induce nuclei formation at lower supersaturation levels or at lower supercoolings than observed in homogeneous nucleation. Thus, heterogeneous nucleation can induce and accelerate drug recrystallization from the amorphous state.

Acryl-EZE® is a commercially available powder blend that is generally used for aqueous film-coating. It contains the pre-plasticized, enteric acrylic polymer Eudragit® L10055 as well as non-melting components such as talc and titanium dioxide. In previous investigations [30], we reported that Acryl-EZE® may be readily processed by hot-melt extrusion, does not undergo die-swell and yields extrudates with smooth surfaces. It was used in this study as an extrusion blend containing several non-melting components.

The objectives of this study were threefold: to quantify the influence of talc on the recrystallization of guaifenesin from hot-melt extruded acrylic matrix tablets; to measure the impact of constant as well as cycling storage relative humidity on the recrystallization of guaifenesin from tablets containing different levels of non-melting components, and finally, to investigate if the composition of the crystalline material on the tablet surface was influenced by talc and relative humidity.

2. Materials and methods

2.1. Materials

Guaifenesin was purchased from Spectrum (Gardena, CA) and was used as the model drug. Acryl-EZE® was donated by Colorcon (West Point, PA). Eudragit® L10055 was provided by Evonik Degussa (Piscataway, NJ, particle size 95% below 250 μm). Triethyl citrate (TEC) was kindly donated by Vertellus (Greensboro, NC). The talc employed in the study (Imperial 500 USP, particle size 4.5 μm) was a gift from Luzenac (Centennial, CO). Drierite (Hammond, Xenia, OH), sodium chloride and ACS reagent (Sigma–Aldrich, St. Louis, MO) were purchased.

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, and component functions are listed in Table 2. Premixed powder blends were fed into a single-screw Randcastle extruder (Randcastle Microtruder® Model RCP-0750, Cedar Grove, NY) equipped with a Nitralloy 135 M 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 40 min before extrusion. The processing temperatures chosen for all extrudates were 65 °C, 75 °C, 85 °C (barrel heating zones 1, 2, 3, respectively) and 85 °C (extruder die). The screw speed was 20 RPM.

2.3. Storage conditions

Tablets were filled into open containers and placed in storage chambers, which were maintained at 24 °C. The desiccant Drierite® (anhydrous calcium sulfate containing an indicator) equilibrated the low humidity chambers to 17 ± 3.5% RH. Saturated sodium chloride solution was used in other storage chambers to create

Table 1
Composition of hot-melt-extruded tablets.

Formulation	Acryl-EZE® (%)	Guaifenesin (%)	Eudragit® L10055 (%)	TEC (%)	Talc (%)
With talc	–	9.3	39.8	1.9	49.0
No talc	–	18.3	77.9	3.8	–
Acryl-EZE®	85.0	15.0	–	–	–
0% talc	–	36.4	60.7	2.9	–
25% talc	–	27.5	45.9	2.2	24.4
50% talc	–	18.5	30.7	1.5	49.3

Table 2
Component functions.

Component	Function
Guaifenesin	Model drug
Eudragit® L10055	Polymeric matrix former
Triethylcitrate (TEC)	Plasticizer for Eudragit® L10055
Talc	Glidant
Acryl-EZE®	Complete matrix blend

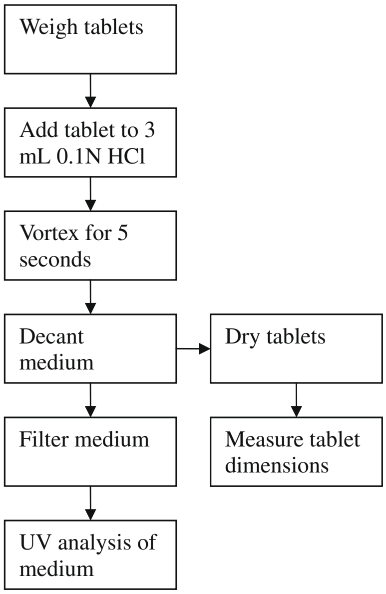


Fig. 2. Flow diagram of the quantitative analysis of surface guaifenesin levels.

"high humidity" conditions at 78 ± 3.5% relative humidity. The relative humidity was measured in the chambers throughout the study by a Traceable humidity and temperature pen (Control Company, Friendswood, TX).

2.4. Scanning electron microscopy (SEM)

To enhance the conductivity of the samples, all tablets were coated with a 15-nm-thick platinum/palladium coating (80/20), applied by a Cressington Sputter Coater 208 HR equipped with a thickness controller MTM 20 at 2.5 kV, 20 mA under Argon. Images were taken in field emission mode at 5 kV using a Zeiss Supra 40VP electron microscope (Carl Zeiss SMT, Peabody, MA) equipped with a Gemini Column and SmartSEM software.

2.5. Assay for crystalline surface guaifenesin

The use of X-ray diffraction and DSC to quantify surface crystallization was investigated, but these techniques were not well suited to determine the surface crystallization on tablets for this study. The limit of detection for crystalline-in-amorphous samples by powder X-ray diffraction is 5–10% [31], and thus too high to capture early crystal growth. The sample preparation for DSC compromised the sample integrity, and sample size limits prevented analysis of the entire tablet surface area. Fig. 2 shows the flow diagram of the assay used to quantify the amount of recrystallized guaifenesin from the entire tablet surface. The assay was based on the differential solubility of guaifenesin and the matrix polymer in an aqueous medium during a short immersion period. While the assay was not specific for crystalline drug, the test captured only drug located on the tablet surface, where SEM examination confirmed the presence of crystalline guaifenesin. Using tablets without surface crystals, baseline values were established for each formulation to account for amorphous guaifenesin located on the tablet surface accessible to the medium.

Individual tablets were accurately weighed, and a single tablet was placed into a large test tube (25 mm × 150 mm) filled with 3.0 mL of 0.1 N HCl. While the matrix polymer was insoluble in this medium, the acid dissolved the model drug guaifenesin. The test tube was subjected to vortex mixing (SP vortex mixer, Baxter Diagnostic, Deerfield, IL) at level 5 for 5 s, as timed by a stop watch. Immediately after vortex mixing, the medium was decanted and filtered through a 0.45-μm nylon filter. The filtered medium containing the dissolved guaifenesin from the tablet surface was diluted in a 1-to-1 ratio with fresh medium. Two hundred microliters of the diluted sample was analyzed at 275 nm on a UV spectrometer (μQuant UV Spectrometer equipped with KC 4 software for data analysis, Bio-Tek Instruments, Inc, Winooski, VT). Linearity was established for drug concentrations between 8 and 200 ng/mL ($R^2 = 0.9999$). Concentrations of 2 ng/mL were below the limit of detection of the instrument. Residual liquid on the recovered tablets was blotted off, and the tablets were dried under ambient conditions. The dimensions of dry tablets (height and diameter) were measured using calipers (Starrett, Athol, MA). Test conditions, including immersion time, vortex intensity, vessel size and dilution for the UV test, were chosen to ensure discrimination between samples.

2.6. Moisture uptake of tablets

Moisture uptake of stored tablets was measured by observing the mass loss on drying (LOD) of samples using a moisture-analyzing balance (AND MF-50 Moisture Analyzer, A&D Instruments, Abingdon, UK). Two-gram samples were prepared by cutting the tablets with a utility knife into slices (thickness ca. 0.2–0.5 mm), which were then arranged in a single layer in a pre-dried aluminum weighing pan. The percent loss on drying was recorded after heating the sample for 30 min at 110 °C. In addition to any moisture taken up during storage, formulations contained substances which partially volatilized under the test conditions, triethylcitrate and guaifenesin. To differentiate between the mass loss due to moisture and the mass loss due to other components, excipient powders, extrusion blends and tablets, all stored at 17% RH as well as 78% relative humidity, were analyzed. The difference in the loss on drying results between tablets of the same formulation stored at either 78% or 17% RH was reported as the water uptake of the tablets.

2.7. Mass spectrometry (MS)

Mass spectrometry was employed to identify the surface crystals. The surfaces of stored tablets, which had developed surface crystallization, were scraped with a clean razor blade in several locations. The removed material was transferred to a capillary tube (Kimax-51, Kimble, Vineland, NJ), which was melted shut and analyzed on a Finnigan MAT TSQ 700 (ThermoFisher, Waltham, MA) using direct exposure probe desorption chemical ionization (DCI).

3. Results and discussion

The recrystallization of the model drug from the amorphous state was driven by the supersaturation of the drug in the polymeric matrix. However, other factors may influence the onset of crystal growth as well as the extent of crystallization. In addition, the crystal growth is localized and restricted to exposed surfaces of tablets [14], which has also been reported in glasses [32]. This localization has been attributed to catalytic effects of solid impurities present on the interface, as well as to faster surface diffusion rates, while thermodynamic barriers for nucleation (the interfacial energy or the chemical potential) were not altered [33]. Another possible factor influencing surface crystal growth are stresses created by the growing crystals, which accounted for higher nucleation rates on surfaces of selenium films [34].

3.1. The influence of talc on crystallization onset in melt extrudates with drug levels close to drug saturation solubility

Nucleants are able to induce nucleation at lower supersaturation levels than necessary for homogeneous nucleation. To investigate if talc functioned as a nucleating agent for guaifenesin in melt extrudates, powder blends with drug levels close to the saturation solubility were extruded, at lower drug levels than the other formulations in this study. Earlier film studies determined that Eudragit® L10055 could solubilize about 20% w/w guaifenesin [15], so the drug-to-polymer ratio of both formulations was chosen to be 19 parts guaifenesin in 81 parts Eudragit® L10055 to be close to saturation solubility. Both formulations contained the same drug-to-polymer ratio and TEC, based on the polymer weight. One formulation contained 50% talc, based on total weight, while the control formulation was talc-free. To obtain tablets from extruded rods, the samples were broken rather than cut. This was done to avoid particulate contamination stemming from the knife blade, which could introduce additional particles to the newly created surfaces which might act as nucleants, and therefore influence test results.

All samples were stored at 17% RH and were observed under SEM after 1 and 4 days. After 1 day, neither of the formulations showed crystal growth. After 4 days, the control formulation without talc showed no recrystallization, while tablets containing talc had developed surface crystals. The drug-to-polymer ratio of 19:81 was close to the solubility limit of the drug in the polymer. Thus, the driving force for nucleation was low, and kinetic effects, such as the induction of nucleation by nucleating agents, became apparent by the reduction in the onset time of crystallization. The observations were consistent with talc acting as a nucleating agent for guaifenesin. Talc [20] and oxides, such as titanium dioxide [35], have been reported to influence crystallization behavior. In the absence of talc, the melt extrudates only contained components which softened or melted during the process, and hence no formulation component was present which could induce nucleation. Instead, airborne particulates, impurities and other foreign particles could act as nucleating agents. Such contaminants could only be controlled by working in a clean room environment. Surfaces in talc-containing extrudates, on the other hand, were interspersed with talc particles, which presented readily available surfaces for heterogeneous nucleation and influenced how fast the onset of crystallization occurred.

3.2. The influence of talc content and storage time on the quantity of surface crystals

After determining that talc functioned as a nucleating agent for guaifenesin, it became necessary to quantify the effect of talc on surface crystal growth. A quantitative assay was developed to determine the amount of recrystallized guaifenesin on the surface of tablets. The assay measured the amount of guaifenesin present on the entire tablet surface, both in the crystalline and the amorphous state. To account for amorphous guaifenesin, baseline values were determined for each formulation in freshly made tablets, in which surface crystallization was still absent. In Figs. 3, 6 and 7, the baseline value is the "day 1" value on graphs. The baseline accounted for amorphous guaifenesin located in the matrix surface, where it was accessible to the medium during the test. When the measured guaifenesin amount in a sample exceeded the baseline value of this formulation, the additional amount of guaifenesin was considered to be crystalline guaifenesin which had developed up to this time point. This was a reasonable assumption, as electron microscopy confirmed the presence of crystalline material on tablet surfaces on storage.

Tablets used for this study contained a drug-to polymer ratio of 37.5:62.5, and hence the matrix polymer was supersaturated with guaifenesin. Tablet samples were analyzed every 3 days for 15 days to follow the increase in surface crystal growth. The drug-to-polymer ratio and the TEC content for all tablets in this study were identical, and all tablets were stored at low relative humidity, 17% RH, and 24 °C. Four formulations were investigated. The first formulation contained no talc. The second and third formulations contained 25% and 50% talc based on formulation weight, respectively, to test the concentration-dependence of the recrystallization on talc levels. The fourth formulation consisted of 15% guaifenesin in Acryl-EZE® as the matrix former, which was included to investigate the effect of more than one non-melting component on guaifenesin recrystallization.

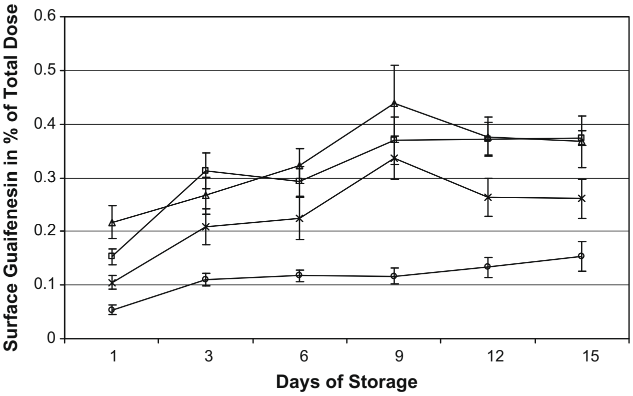


Fig. 3. The influence of talc content on the recrystallization of guaifenesin. All melt-extruded tablets contained the same guaifenesin-Eudragit® L10055 ratio and were stored at 24 °C and 17% relative humidity, $n = 6$. ○ No talc, Δ 25% talc, □ 50% talc, x Acryl-EZE®.

Fig. 3 follows the change in surface guaifenesin levels over 15 days. The amount of drug found with the assay was expressed as percentage of the total amount of guaifenesin in that tablet, which accounted for differences in weight between the samples. For tablets stored at 17% RH, the loss on drying values did not differ from those of the extrusion powder blend. This indicated that those tablets did not take up moisture during storage at low RH, and hence the results of the quantitative assay were not corrected for moisture uptake. Over 15 days, the amount of surface guaifenesin increased in all formulations, but the extent differed between formulations. Formulations containing no talc were found to have the lowest surface guaifenesin values after 15 days (0.15 ± 0.03% of the total dose of guaifenesin) compared to 0.37 ± 0.05% and 0.37 ± 0.02% in tablets containing 25% and 50% talc, respectively. These results show that the presence of talc increased surface crystallization of guaifenesin. However, doubling the talc concentration had no effect on guaifenesin recrystallization.

These results indicate that the use of a common excipient such as talc in melt extrusion can induce changes in the physical state of the drug, which should to be considered when formulating solid dispersions. Talc was beneficial during melt processing as well as product handling and appearance. During hot-melt extrusion, it acted as a glidant, and thereby improved the flow of the powder blend in the hopper, increased melt flow at the die and decreased undesirable die-swell and tackiness in the extrudate. The resulting tablets had smoother surfaces and could be readily cut into tablets. To function in this manner, however, the necessary talc levels were higher than the small percentages usually employed for nucleating agents. Kotek et al. found that adding 0.03 wt% nucleant to the formulation maximized the crystallization of isotactic polypropylene, demonstrating the critical nucleant concentration [36]. Other processes using high talc concentrations reported similar observations as in our study. For injection molding, the crystallization of the polymer was influenced by the nucleating effect of talc but did not depend on talc concentrations, which ranged from 10 to 40% [20]. Presumably, the high talc concentrations used in our study (25% and 50%) were well above the critical nucleant concentration, and thus no concentration-depended effect was found.

After 15 days, the surface guaifenesin assay detected 0.27% of the total guaifenesin dose on Acryl-EZE®-containing matrix tablets. Since the initial assay on tablets without surface crystallization had detected 0.11% of the total guaifenesin dose, it was concluded that the additional 0.15% of the total guaifenesin dose had recrystallized on the tablet. Surface crystallization for Acryl-EZE® matrix tablets was lower than expected based on its talc content. The efficacy of nucleating agents depends on both the system [35] as well as processing conditions [37]. Paxton et al. showed that good lattice matching of crystal and nucleant produced more crystals, and crystals attached to nucleant substrates had higher purity [38]. Presumably, the other components present in Acryl-EZE® did not have good lattice matching with guaifenesin, and thus reduced nucleation and subsequent surface crystallization on the tablet surface.

For all formulations, the amount of recrystallized guaifenesin was small compared to the total dose of the drug in the tablet. The relevance of these results will depend on whether the recrystallization can impact the performance of the tablets. In earlier studies, the recrystallization of guaifenesin had no effect on the drug release from the matrix tablet, since the high solubility of guaifenesin resulted in quick dissolution of the crystal layer on the tablet. However, a layer of hydrophobic drug crystals on a tablet surface could present a barrier to wetting the tablet, which could also slow the disintegration of the dosage form.

3.3. Loss on drying (LOD) – water uptake of tablets stored at 78% RH

Since the results of the surface guaifenesin assay were based on the mass of the tablet, the water uptake of tablets stored at 78% relative humidity was determined to correct for the weight of the moisture taken up during storage. The moisture content of tablets stored at 17% relative humidity did not differ from the moisture content of the melt extrusion powder blend; therefore, no correction was made for the tablets stored at low RH. Formulations contained components which partially volatilized during the loss on drying test (triethyl citrate and guaifenesin). The LOD values of tablets stored at 17% relative humidity were used to correct the LOD values obtained from tablets of the same formulation stored at 78% relative humidity.

Fig. 4 shows the water uptake of melt-extruded tablets. At 78% relative humidity, extrudates containing 25% and 50% talc took up 2.74% and 1.98% moisture, respectively, while tablets without talc took up 4.36% moisture. Thus, at high relative humidity after 15 days, tablets containing more polymer took up more moisture.

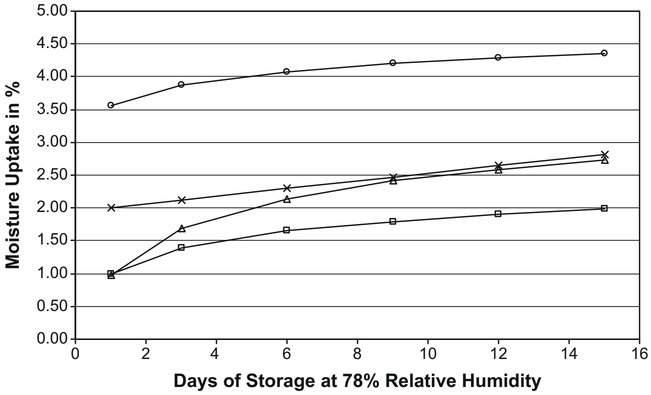


Fig. 4. The influence of talc content on the water uptake of melt-extruded tablets. All melt-extruded tablets contained the same ratio of guaifenesin to Eudragit® L10055, storage at 24 °C, $n = 3$. ○ No Talc, △ 25% talc, □ 50% talc, × Acryl-EZE® tablets.

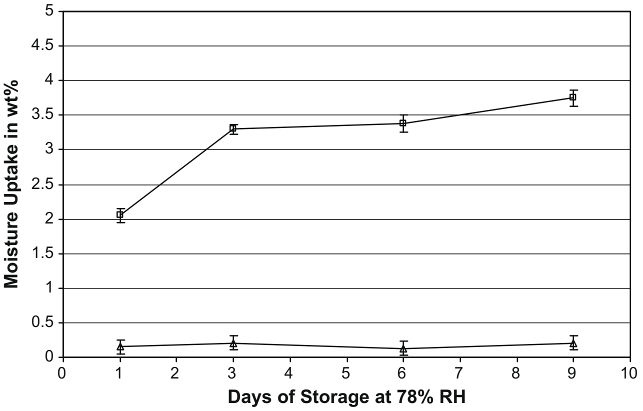


Fig. 5. The influence of storage at 24 °C and 78% relative humidity on the moisture content of excipient powders, $n = 3$. □ Eudragit® L100-55; Δ Talc.

The correlation between polymer content and moisture uptake was further investigated by storing powder samples of Eudragit® L10055 as well as the talc used in this study at 17% as well as 78% relative humidity. Fig. 5 depicts the moisture uptake of excipient powders. After 9 days, the polymer powder absorbed 3.4% moisture, while the talc took up 0.13% water. Thus, the moisture uptake of tablets was determined by the behavior of its components.

3.4. Influence of relative humidity on guaifenesin recrystallization – continuous storage

To investigate the influence of relative humidity during storage, tablets containing Eudragit® L10055, 37.5% guaifenesin and no talc were stored in open containers for 15 days. Fig. 6 demonstrates the influence of elevated atmospheric moisture on the amount of guaifenesin surface crystallization under constant relative humidity conditions. After 15 days of storage, tablets stored at 17% relative humidity had an average of 0.15 ± 0.0275% surface guaifenesin, compared with an average of 0.42 ± .01390% on tablets stored at 78% relative humidity. Relative humidity has been known to induce crystallization in many amorphous systems, including natural products such as sugars [29], whey powder [28] and milk powder [39], as well as drugs such as griseofulvin [40], indomethacin [41] and acadesine [42]. Several mechanisms have been found to explain this phenomenon. Acadesine absorbs moisture to form an intermediary

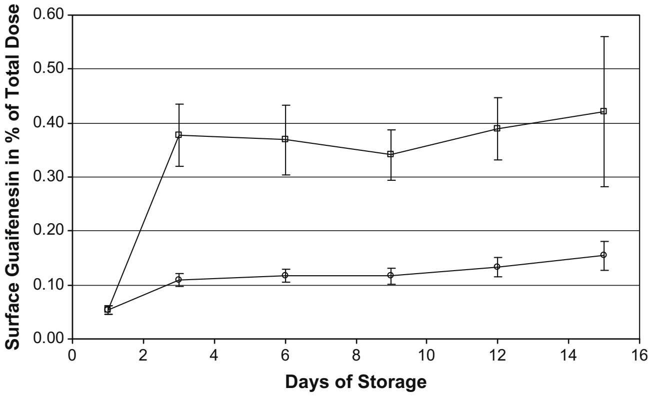


Fig. 6. The influence of relative humidity conditions during storage on the recrystallization of guaifenesin on the surfaces of tablets containing 36.4% guaifenesin, 2.9% TEC and 60.7% Eudragit® L10055, storage temperature 24 °C, $n = 6$. ○ Storage at 17% relative humidity, □ storage at 78% relative humidity.

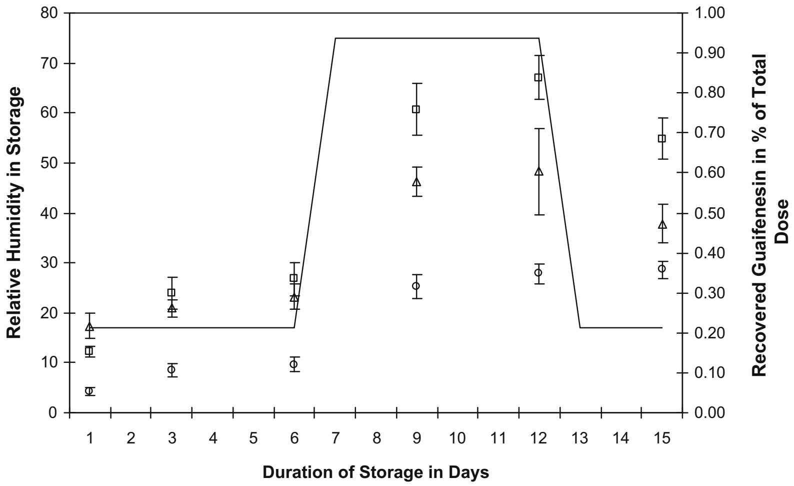


Fig. 7a. The effect of a temporary increase in relative humidity conditions on the surface crystallization of guaifenesin. The storage relative humidity was indicated by the dashed line and the left *y*-axis. The individual symbols mark a guaifenesin amount, which can be read on the right *y*-axis. All melt-extruded tablets contained the same ratio of guaifenesin to Eudragit® L10055, storage temperature 24 °C, *n* = 6. ○ No talc, Δ 25% talc, □ 50% talc.

hydrate, which decomposes into the anhydrous form [42]. Crystallization can occur after absorbed water acts as a plasticizer and depresses the glass transition temperature of the matrix below the ambient temperature [29,39]. Relative humidity can also be a cause of heterogeneous nucleation as water droplets function as nucleating agents. Guaifenesin does not form hydrates, and the moisture uptake into the matrix was inversely correlated to surface crystallization. Therefore, the third possibility was considered to be the most likely explanation for the increased surface crystallization at high relative humidity. At high atmospheric humidity, more minute moisture droplets were present, which functioned as nucleating agents for guaifenesin on the tablet surface. It was the presence of droplets on the matrix surface, not the uptake of moisture into the matrix, which resulted in the nucleation-enhancing effect.

Under constant relative humidity, the largest change in surface crystallization occurred over the first 3 days. After that time, the amount of surface crystallization increased more slowly. This is consistent with nucleation and initial growth taking place within the first 3 days, which quickly elevate the amount of recrystallized material on the tablet surface. The continuing crystal growth adds new guaifenesin to the surface more slowly.

3.5. Influence of relative humidity – RH cycling

Relative humidity cycling is characterized by changing relative humidity conditions during storage. This is of practical importance, since intermediates or unpackaged products may be moved around facilities and could encounter uncontrolled humidity conditions. The impact of changing storage conditions on guaifenesin recrystallization is presented in Fig. 7a and b. In study A, tablets stored under low relative humidity for 6 days were moved to a chamber with high RH for the next 6 days, before being returned to the original low relative humidity conditions for the remaining 3 days. In the complementary protocol, study B, tablets stored at high RH for the initial 6 days were transferred to low RH conditions for 6 days before being returned to the high RH chamber for the last 3 days.

Under all conditions studied, tablets containing talc were found to have higher levels of surface crystallization than the talc-free tablets, for reasons presented in Sections 3.2 and 3.3. In study A, surface drug levels remained low and stable for 6 days but rose about fourfold when transferred to the high-humidity chamber. The surface drug levels remained high even after the tablets were transferred back to the low humidity environment.

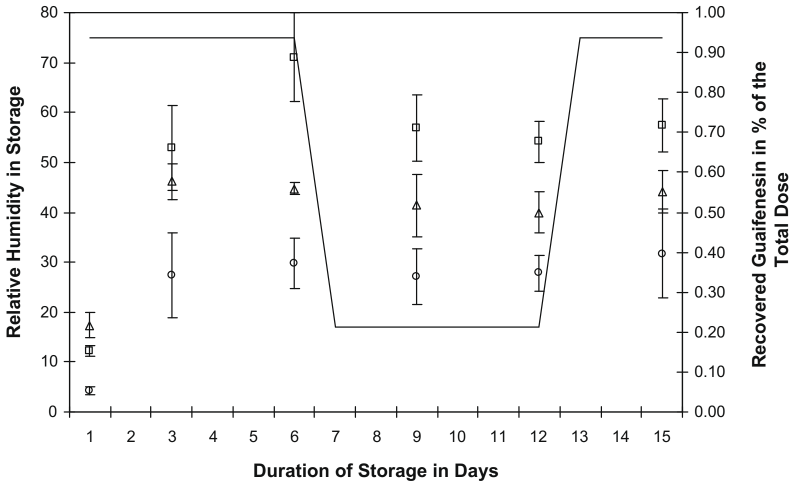


Fig. 7b. The effect of a temporary decrease in relative humidity conditions on the surface crystallization of guaifenesin. The storage relative humidity was indicated by the dashed line and the left *y*-axis. The individual symbols mark a guaifenesin amount, which can be read on the right *y*-axis. All melt-extruded tablets contained the same ratio of guaifenesin to Eudragit® L10055, storage temperature 24 °C, *n* = 6. ○ No talc, Δ 25% talc, □ 50% talc.

In study B, the tablets containing talc had not yet reached the surface drug levels that were observed in the continuous storage experiment after 15 days when the tablets were switched to the low humidity environment. During the 6 days at low RH, no further increase in surface drug levels was observed, indicating that further drug recrystallization was either stopped or slowed. After returning to high RH storage, recrystallization levels quickly reached those of tablets stored continuously at high RH. Tablets containing no talc experienced the largest increases in surface crystallization within the first 6 days, and a change in storage RH did not affect surface drug levels.

The surface drug levels in study A parallel the results of the continued storage at low RH for the first 6 days. The increasing surface drug levels can be attributed to additional surface crystallization induced by the storage humidity. The crystals, once present, were permanent, which is the reason that the surface drug levels remained high after the tablets were returned to the low RH chamber. So a transitory exposure to higher RH conditions can permanently alter the tablets by inducing surface crystal growth. The difference between surface drug levels at low and high RH can be a function of other formulation components, as shown here with talc content.

3.6. Identity of surface crystals

Mass spectrometry was employed to determine whether the composition of the surface crystals was affected by the agents that stimulate crystal growth. All talc-containing formulations investigated in Section 3.2 were evaluated. The mass spectra obtained from surface samples containing the drug crystals were compared to the mass spectrum of bulk guaifenesin. In all spectra, the base peak was detected at 199 m/z, which corresponded to the molecular mass of ionized guaifenesin. A peak detected at 397 m/z was due to dimer formation resulting from ion–ion interactions after ionization. The consistent presence of the guaifenesin base peak in all samples and the existence of identical lower incidence peaks shared between all samples identified the samples as guaifenesin. No additional peaks were observed in any of the samples, indicating the absence of other components in the samples. The matrix polymer was not detected by MS since its molecular mass, about 250,000 g/mol, was outside the scanned mass range. These results verified that the relative humidity during storage and talc in the formulation did not alter the chemical nature of the developing crystals.

4. Conclusion

This study investigated the influence of heterogeneous crystallization due to relative humidity in storage and talc as a formulation component on the amount of guaifenesin recrystallizing on the surface of melt-extruded matrix tablets. Tablets contained a constant guaifenesin-to-polymer ratio in a matrix of either Acryl-EZE® or Eudragit® L10055 and either no talc, 25% or 50% talc. Even at low supersaturation levels, talc-containing extrudates developed recrystallization earlier, as talc induced nucleation as nucleating agent. At higher drug levels (37.5:62.5 drug-to-polymer ratio), the presence of talc increased the quantity of drug crystals on tablet surfaces after 15 days (storage at 24 °C and 17% RH). No concentration-depended effect of talc on the drug recrystallization was found, probably because both talc levels were above the critical nucleant concentration. Lower than expected crystal growth on Acryl-EZE®-containing matrix tablets demonstrated that the effects of several non-melting components were not additive. Relative humidity increased guaifenesin crystallization in tablets with and without talc, but recrystallization did not correlate with increased moisture uptake, indicating heterogeneous nucleation as a probable cause for this observation. Results from tablets stored transiently under high or low humidity conditions demonstrated the effect of relative humidity in storage on guaifenesin recrystallization was due to its effect on nucleation. The guaifenesin crystals, once they were induced, remained on tablet surfaces regardless of subsequent changes in storage relative humidity. This is an important consideration when working with intermediates and finished products containing amorphous components which might recrystallize. Formulation components and relative humidity conditions had no effect on the composition of surface guaifenesin crystals. Mass spectrometry indicated all crystalline samples recovered from stored tablets were identical to guaifenesin bulk material. In conclusion, both talc in the formulations and humidity during storage increased surface crystallization of guaifenesin by heterogeneous nucleation.

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