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Recrystallization of Guaifenesin from Hot-Melt Extrudates containing Acryl-EZE® or Eudragit® L100-55

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Recrystallization of Guaifenesin from Hot-Melt Extrudates containing Acryl-EZE® or Eudragit® L100-55

by

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Dedication

To my parents, with joy.

To Joseph, with love.

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Recrystallization of Guaifenesin from Hot-Melt Extrudates containing Acryl-EZE® or Eudragit® L100-55

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The physical stability of guaifenesin in melt-extruded acrylic matrix tablets was investigated. The initial study found that recrystallization was caused by guaifenesin supersaturation in Eudragit®L100-55, and that the instability was confined to tablet surfaces. Drug release was not affected by crystal growth as guaifenesin is very water soluble. The addition of a polymer in which guaifenesin showed a higher solubility to the matrix blend decreased recrystallization on storage as supersaturation levels dropped.

The second investigation identified heterogeneous nucleation as an additional factor in guaifenesin recrystallization. A quantitative assay showed that talc in matrix tablets accelerated the onset and extent of the recrystallization due to a nucleating effect on guaifenesin. Storage under elevated humidity conditions promoted recrystallization as well, but crystal growth was not correlated with water uptake, which implied a nucleating effect of moisture on guaifenesin.

The third study investigated the effect of aqueous film-coating of the matrix tablets to stabilize amorphous guaifenesin using either hypromellose or ethylcellulose as coating polymers. The selection of the coating polymer influenced crystal morphology, and was a major factor in delaying the onset of crystallization, ranging from 1-3 weeks (ethylcellulose film-coatings) to 3-6 months (hypromellose film-coatings). Higher weight gains retarded recrystallization. Factors promoting drug and polymer diffusion, such as long curing times and elevated temperatures during both curing and storage, incomplete film coalescence and high core drug concentrations all resulted in an earlier onset of crystallization.

The effects of single-screw extrusion (SSE) and twin-screw extrusion (TSE) of diltiazem hydrochloride and guaifenesin-containing blends in Eudragit®L100-55 on drug morphology and dispersion were studied in the fourth project. Guaifenesin solubilized diltiazem hydrochloride, and plasticized Eudragit®L100-55. Extrusion temperature influenced the drug morphology in single-screw extrudates, while TSE rendered all formulations amorphous due to higher dispersive mixing capabilities. Drug distribution improved with extrusion temperature and by TSE over SSE. Homogeneous matrices showed the slowest drug release at pH 1.0. Recrystallization was inversely correlated to drug distribution.

In conclusion, the physical stability of guaifenesin in hot melt-extruded acrylic matrix tablets was shown to be affected by formulation, processing and post-processing factors.

Table of Contents

List of Tables

List of Figures

Chapter 1: The stability of composites made by thermal processing

1.1 INTRODUCTION

The stability of pharmaceutical products can be expressed in numerous forms, reflecting the many possible consequences of instabilities in pharmaceutical products [1]. The properties of thermally processed dosage forms are a combination of the effects of processing parameters, formulation components, storage conditions and possible interaction between these factors. The purpose of the following text is to give an overview over parameters affecting the chemical and physical stability of thermally processed formulations, and to show how the performance of a thermally processed dosage form can be influenced by processing and formulation factors. The discussion will center on hot-melt extrusion [2].

1.2 STABILITY ISSUES WITH DRUG SUBSTANCES

1.2.1 Chemical Stability of drug substances

Drugs are subject to degradation reactions based on their chemical structure and the environment they reside in. Drug degradation reactions are discussed in several books, for instance Carstenson [1], Yoshioka [3] and Baertschi [4]. Common degradation reactions are hydrolysis, dehydration, elimination reactions such as decarboxylations, and

oxidation reactions. Instabilities manifest themselves in a decreased drug concentrations and shifting content uniformity, changes in product appearance and performance parameters.

Decomposition reactions are often complex, with several reactions possible or competing, depending on the prevailing conditions. Byrn et al identify molecular mobility and mechanical stress as major factors influencing solid state reactivity [5], which prepare the environment for chemical reactions. Mechanical stress can increase the surface area, the number of defects and the amount of amorphous material present at the site. Molecular mobility is necessary for molecular rearrangement in connection with chemical or physical decomposition reactions. Temperature, pH, ionic strength, as well as the presence of moisture, oxygen and other compounds are then the main factors determining the type and extent of reactions taking place, manifesting the instability [3].

1.2.2 Influence of temperature on the stability of drug substances

One of the main factors in drug stability is temperature, and the Arrhenius equation has been traditionally used to describe the relationship between the temperature and the rate constant of degradation reactions [3]. Yoshioka discusses additional equations describing temperature-degradation rate relationships. As chemical reactions generally proceed faster at elevated temperatures, thermal processing inherently carries a higher potential for unwanted reactions. In addition, the prediction of events is

complicated by the state changes the blend components undergo during thermal processing. The substances may be solid for parts of the process. Some substances melt, others soften, components dissolve in one another, and the mixture experiences mechanical stress at the same time. The conditions for reactions change throughout the process, as the melt viscosity and the pressure in the barrel change. After extrusion, the return to a solid state varies with the cooling rate. Cooling after melt extrusion can trap metastable forms, which can then slowly transition to a more stable formation. The resulting reactions are complex. Carstensen [1] discusses solid state reactions, including the kinetics of instability reactions resulting in liquids and gases.

1.2.3 Oxidative stability of drug substances

Oxidation reactions depend on the presence of oxygen, and are often catalyzed by metal ions. Autoxidation involving reactive oxygen-species are often catalyzed by impurities, and may be hard to reproduce [6]. Oxygen susceptibility testing of the drug can yield mechanisms of degradation which can be used to predict the "natural" oxidation, to form the basis for preventive measures [6]. Stabilization can be achieved by restricting the amount of oxygen in contact with the dosage form, either by keeping the product in an inert gas atmosphere, or by using oxygen-barrier packaging and antioxidants. Metal ions can be neutralized by chelating agents such as EDTA.

Due to oxidation reaction kinetics, extrapolation of reaction rates can be difficult. Thermo-oxidative stability testing characterizes the behavior of materials when streesed by both heat and oxygen [7]. The presence of moisture will contribute to additional mechanisms of degradation.

1.2.4 Physical Stability of drug substances

The physical stability of a drug comprises several aspects [3]. Compounds can change between the amorphous and the crystalline state. Because the morphological states differ in their properties, the performance of the dosage form can be affected. Stresses involved in manufacturing unit operations can induce transitions in either direction (see discussion in section 6.3.). Excipients can be used to stabilize an amorphous state [8], and formulation components or impurities can induce nucleation and crystal growth. Crystallization from the amorphous state can be localized [9].

Polymorphic changes occur when the drug transforms from one polymorphic form into another. These transformations are driven by changes in the temperature and the pressure the substance is exposed to. For any combination of temperature and pressure, one polymorph is the most stable. Like crystalline-amorphous transitions, polymorphic change can be induced by pharmaceutical unit operations.

In addition to changes in the crystal structure, crystals can incorporate water or solvents, as hydrates or solvates, respectively. When the type or number of these associated molecules change, but not the crystal structure they are attached to, the alteration is known as a pseudopolymorphic transformation.

Crystals are not static, and changes in crystal dimensions present another physical instability. A wide particle size distribution is associated with Ostwald ripening, as smaller crystals dissolve, and the material is deposited onto larger crystals, which consequently grow further in size. The increase in average particle size is also known as coarsening.

The physical changes and stabilization strategies for amorphous pharmaceutical solids are discussed by Yu [8]. Excipients can stabilize the amorphous state by immobilization and isolation, and by direct interactions, for instance hydrogen-bonding, with the amorphous compound. The stabilizing excipients themselves may have to be protected from crystallization, and their stability against oxidation and hydrolysis is crucial in maintaining the integrity of the dosage form.

1.3 STABILITY OF POLYMERS

1.3.1 Chemical stability of polymers

Polymer stability is as crucial as API stability to arrive at stable formulations. Allen et al [10] and Bicerano [11] discuss the how the stability of polymers is related to their structure. Alexy et al [12] investigated the stability of poly(vinyl alcohols) during melt extrusion. The degree of hydrolysis, number of double bonds and heterogeneities increased the susceptibility to degradation during melt extrusion via an acid autocatalysis mechanism. Stability was increased by incorporating benzoic acid as a stabilizer.

Polymer composition and structure influence its stability. The strength of valence bonds between the elements making up the polymer backbone influence the chain stability. Common polymers can be grouped according to their relative stability based on the strength of valence bonds. Unsaturated bonds are susceptible to oxidation and bond strength is important for side chain stability as well. The weak carbon-chlorine bond contributes to thermal instability of PVC. While all carbon-hydrogen bonds are susceptible to oxidation, the carbon's hybridization state determines the degree of instability, as the hydrogen is abstracted more easily from a tertiary than a primary carbon. The backbone rigidity increases polymer stability. Polymers with aromatic rings, ladder or spiro structures are especially stable [11].

Depolymerization, or chain scission, is a major effect of polymer instability, which reduces the molecular weight of a polymer. As the molecular weight influences major polymer properties necessary for processing, product quality and performance, MW is a common experimental parameter. The practical significance of molecular weight reduction likely decreases for higher MW, since the reduction in MW is lower compared to the polymer chain length. However, there may be critical MW levels, at which the properties of a polymer change disproportionally. Depolymerization can occur during processing or in storage. Viljanmaa et al report depolymerization depending on storage temperature, with molecular weight decreasing 29% at -18˚C and 50% at room temperature after 56 days [13]. Stabilization was achieved by end-capping the polymers chains, which slowed degradation during storage. A polymer can also be changed by crosslinking, which increases the molecular weight.

Other degradation reactions are elimination and substitution reactions [10]. Elimination reactions result in small molecules which do not resemble the monomer, for instance water, or hydrochloric acid. The presence of these reaction products can in turn contribute further to instability. Substitution reactions change the side chains of a polymer, which can affect the polymer properties.

Degradation reactions depend on the immediate environment. In a processed polymer blend contains several phases, instabilities can vary by phase. Tocháček et al [14] were able to distinguish between different degradation reactions in different phases

of the polymer after multiple extrusions. Backbone cleavage was found in the polypropylene homopolymer phase, while crosslinking occurred in the rubbery phase containing ethylene-propylene rubber and polyethylene homopolymer. The effects of these reactions are the opposite of each other, as cleavage reduces the molecular weight while crosslinking increases it.

1.3.2 Oxidative stabilization of polymers

Oxidative reactions can be induced by impurities in the polymer, such as residual monomer, catalyst, metal ions, byproducts and structural irregularities. Preventive stabilization aims to reduce oxidation by removing these compounds from the bulk matter. Compendial purity standards take this approach, although practical limits apply.

In arrestive stabilization, the sources of instability are inactivated or removed by adding compounds that possess reactive sites that preferentially react, or form reaction products that have greater stability than a product formed with the polymer. Antioxidants can be added to the formulation to stabilize the polymer. In addition to being pharmaceutically acceptable, the effects of specific antioxidant(s) on the polymer stabilization, the thermal process and the other formulation components have to be taken into consideration. Antioxidants can be combined, preferably to act synergistically. For a discussion of antioxidants in general, see Allen [10], Crowley discusses antioxidants in melt extrusion applications [15].

Polymer structure contributes to oxidative stability in polymers. Unsaturated bonds are prone to oxidation, and hydrogen is more reactive in radical reactions if bound to tertiary carbon, which is the result of branching. Higher crystallinity decreases oxidation due to the higher density of the samples [10]. Hoang et al [16] reported that initial vinyl unsaturation and short chain branch content correlated with induction times for oxidative instability in metallocene polyethylenes. In addition, multiple degradation reactions were detected, radical crosslinking reactions, formation of conjugated system, and discolorations due to catalyst residues, illustrating the complexity of degradations.

The chemical stability of PEO was investigated by Crowley et al [17]. The antioxidants, even when working by the same basic mechanism, had to be screened for their compatibility with the system and influenced the drug release rate. These results indicated that the choice of antioxidant for a formulation should be carefully considered.

1.3.3 Physical stability of polymers

Another aspect contributing to the stability and properties of polymers is their physical state. Some polymers are always amorphous, while others can exist in semicrystalline forms with varying degrees of amorphous material. In the semicrystalline state, parts of the polymer chains are arranged in ordered domains, which are interspersed with areas of amorphous structure. A single macromolecule will pass through many crystalline regions [18]. Morphological changes between amorphous and crystalline

polymers vary above the glass transition temperature. Solid amorphous polymers pass through rubbery, gumlike stages to the liquid state, while crystalline polymers retain their structure up to the melting temperature of the crystallites, where a rapid transition to a liquid state occurs [19]. If the temperature is raised further, polymers eventually undergo thermal decomposition. Thermal processing occurs above the Tg, at a temperature when the melt viscosity is low enough for processing. Consequently, crystalline polymers have a narrower window for processing, as they have to be heated not only above their Tg, but above their melting temperature as well, which brings the processing temperature closer to the decomposition temperature [20].

Both formulation and processing factors influence the crystallinity of polymers [21]. Nucleating agents decrease the surface free energy barrier to nucleation. Plasticizers enhance chain mobility and lower the energy required for the chain folding process. Processing conditions, especially process temperature and duration also influence polymer crystallization. Nucleating agents are diverse compounds, including low molecular weight organics that crystallize themselves before nucleating the polymer [22], and have been found to work by several mechanisms. Li et al describe classes of nucleating agents and their respective nucleating mechanisms for poly(lactic acid). The group reported that the combination of plasticizer and nucleating agent was necessary to maximize crystallization of poly(lactic acid) [21], but the processing temperature of the injection molding process continued to have a large influence on the product quality. The

effect of nucleating agents on crystallization kinetics of polymers was described by Aliotta et al [23].

Crystallinity of polymers can change with degradation [24]. Amorphous regions generally erode faster, increasing the percentage of crystallinity. Amorphous samples can recrystallize if water from the erosion medium lowers the glass transition temperature. One example is the recrystallization of the amorphous phase of a poly(L-lactide) and poly(ε-caprolactone) blend due to the low glass transition temperature of the blend. The recrystallization caused brittleness and shrinking of the films which decreased their adhesion properties [13]. Crystallinity influences many polymer properties, such as the response to mechanical stresses and the solubility.

1.4 STABILITY OF OTHER MATRIX FORMERS

Fats and waxes have been used in thermal processes [25]. Usually they are complex mixtures, and show changes during storage ("aging") in their physical structure, which manifests itself by increase in crystallinity, or polymorphic changes which affect the dosage form properties. The increase in melting point ("hardening") of triglyceride-containing suppositories has been associated with polymorphic changes of suppository bases [26], although concurrent amorphous-to-crystalline as well as polymorphic transitions are also possible [27]. Gelucires are mixtures of polyethylene glycol esters of fatty acids and glycerides, distinguished by melting points and HLB values, which have

been used to make solid dispersions [28]. Khan and Craig investigated the physical stability of these lipids in melt-derived tablets containing paracetamol and caffeine [29]. Crystals of fat ("blooming") developed on tablet surfaces, and their development was influenced by storage temperature and the type of drug. The physical integrity of the tablets rather than the molecular arrangement of the matrix former was altered, causing an increase in dissolution rate on storage. The effects of aging differed by Gelucire grade [30]. Choy et al replicated the increased dissolution due to aging, which lead to accelerated drug release in-vivo, but found that the extent of absorption was no affected [31].

1.5 FORMULATION DEVELOPMENT AFFECTING STABILITY

One approach to address potential changes should commence with the definition of the vulnerabilities of an active component. Which instabilities (degradation, crystallization, polymorphic changes) is the drug prone to in view of the intended processing methods, and to what extent? What is the desired form for the active? What are timescales involved? Does the desired form need to be stabilized? The excipients selection should assure processability of the blend as well as in-process and long-term stability of the dosage form in addition to the desired performance attributes.

In practice, performing preformulation studies [32], including the exposure to stresses encountered during processing, will characterize the drug well enough to set

limits, or at least a safety zone, within which the drug, excipients and the blend are stable. Important data to gather include decomposition temperatures (e.g. by TGA), melt and glass transition temperatures (DSC and MDSC), crystallization kinetics, the solubility of the drug (or other components) in the matrix former(s), including possible plasticization effects. Energy-temperature diagrams permit the prediction of relative physicochemical parameters of polymorphs [33].

Polymer degradation, and hence drug release, can be influenced by formulation [24, 34]. PH-regulating excipients influence matrix hydrolysis, low molecular weight compounds affect the hydrophilicity of the dosage form, and the matrix structure can be changed by copolymerization and the blending of several polymers.

1.5.1 Excipients influence API stability

Melt-extruded formulations commonly contain other components in addition to the active ingredient. The matrix former melts or softens during extrusion, encompassing all other components to form the matrix. Other components include plasticizers, often necessary to process the matrix former, excipients modulating the drug release or the stabilizing the drug's state, as well as thermal glidants, flow aids, pigments, stabilizers and others. The stability of the drug (or any formulation component) in the dosage form may be lower than in the bulk substance, and several decomposition reactions may occur

simultaneously, as demonstrated in compressed tablets by de Medeiros [35] and de Souza [36].

Other formulation components can interfere with a compound's stability by several mechanisms [3]. They can be reactants in chemical reactions, which is fairly specific to the substances involved. Excipients can also be a source of moisture, which contributes to many degradation reactions as discussed by Yoshika [3]. Hygroscopic excipients can increase the moisture content in the matrix on storage, unless this is prevented by packaging. Blends of ethylcellulose and hydrophilic polymers (hypromellose) to modify drug release were studied by de Brabander [37]. A high concentration of hydrophilic polymer in the ethylcellulose matrix correlated with lower storage stability over 12 months. Conversely, excipients (colloidal silica, silica gel) which bind water tightly may decrease the amount of free water able to participate in degradation reactions. Water can plasticize many substances, which increases the molecular mobility of the matrix. This is associated by a higher general reactivity of the matrix components. Consequently, limits for moisture levels of all blend components should be established and monitored to control this source of instability. Extensive studies on the effects of water and steam during extrusion have been collected by the food industry, where additional water is introduced as part of the extrusion process [38]. Excipients can reduce oxidation reactions by influencing the expansion of product at the die. Lower product expansion due to high fat and moisture levels resulted in lower oxidation [39].

1.5.2 Effects of formulation components on product performance

Formulations are designed to provide stability and protection for the active ingredient, among other guiding principles. Interactions between formulation components can stabilize the dosage form, while changes due to excipients can induce drug instabilities. Opposing effects on product quality by different components of the blend force the formulator to find a balance between conflicting objectives.

Drug-polymer interactions and incorporation into rigid matrices can increase the physical stability of amorphous drugs. Huang et al demonstrated that a 2 : 1 Eudragit RL to ethylcellulose blend containing 11% nifedipine stabilized the amorphous state of the drug by an antiplasticizing effect, which increased the glass transition temperature from 50˚C for the amorphous drug to 115˚C for the solid solution. In addition to reducing the molecular mobility, hydrogen bonding between nifedipine molecules was replaced by hydrogen bonding between the drug and polymers [40]. The combined effects of the immobilization in a rigid polymer glass as well as specific drug-polymer interactions stabilized the amorphous state [8]. However, even in the presence of drug-polymer interactions, stabilization of the amorphous state of the drug is not assured, and was influenced by the storage conditions. In particular, the amorphous state was maintained if the product was stored below 10% relative humidity [41].

Schachter et al [42] describe a melt-extruded ketoprofen-PEO system, and localized the drug in amorphous domains of the polymer. This localization of the drug

resulted in high molecular mobility of the drug (as detected with solid state NMR), which improved the drug's dissolution rates. Drug-polymer hydrogen bonding was found both in melt-extruded and non-processed physical mixtures. This interaction was used to explain the high miscibility and the storage stability of the blends, and enabled processing at lower temperatures.

Cooling after melt-extrusion can trap metastable forms, and drug instability can be induced by the polymer's transition to a more stable formation. Prodduturi et al [43] studied melt-extruded films containing clotrimazole and poly(ethylene oxide (PEO) and reported that the model drug was initially molecularly dispersed in the PEO matrix. After extrusion, PEO crystallized in metastable, folded-chain crystallites, but within one month the PEO chains transformed into the more stable extended-chain crystallites. This, in combination with the low glass transition temperature of PEO, resulted in the recrystallization of clotrimazole.

Several, sometimes conflicting, objectives guide the choice of polymers to be blended in a matrix. Adjusting the solubility of the drug in the matrix can be used to prevent amorphous drug from recrystallizing on storage. While optimizing the solubility of the drug in the matrix, the blends must be able to be processed by melt extrusion. In addition, the functionality, e.g. drug release characteristics, of the dosage form must be preserved. Bruce et al blended hydrophilic polymers with Eudragit L100-55 in order to extend the solubility of guaifenesin in melt-extruded matrix tablets [9]. The use of

polycarbophil provided the best solubility enhancement, but changed the dissolution profile [44]. Prodduturi et al blended PEO and hydroxypropyl cellulose (HPC) in order to stabilize clotrimazole in melt extruded films [45]. While the HPC raised the physical stability of both clotrimazole and PEO in the films, the bioadhesion and the flexibility of PEO films deteriorated with increasing HPC content. An optimum blend was found to consist of HPC : PEO : clotrimazole in a ratio of 55:35:10.

Plasticizer influence formulations by their presence as well as their loss from the dosage form. The use of carbon dioxide as a plasticizer has been shown to enable the extrusion of heat-labile drugs by substantially lowering the necessary extrusion temperatures. Verreck et al [46] reduced the percentage of p-aminosalicylic acid decomposition by injecting liquid carbon dioxide into the barrel. CO_2 functioned as a plasticizer in-situ, and evaporated from the melt at the die as the product equilibrated to atmospheric pressure. The transient presence of the plasticizer is an advantage, since it allows for higher drug loadings, and prevented changes in the matrix due to the loss of plasticizer on storage. The CO_2 evaporation shaped the melt into a foam, which eased the post-processing milling step, according to Verreck et al.

Plasticizers condition polymers to enable extrusion, and influence the mechanical properties of films. If plasticizers volatilize, migrate, leach or otherwise leave the melt-extruded system, then the properties of the dosage form change. Bruce et al reported an influence of plasticizer level on drug dissolution from hot-melt extruded tablets [47].

Repka et al [48] demonstrated the effects of plasticizer loss from hot-melt extruded films. The effects of plasticizer loss on dissolution have also been investigated in film coating applications [49]. As the plasticizer loss depends on the specific polymer-plasticizer combination used, this is another area open for formulation optimization.

Practical consequences of instabilities differ. Ghebremelski et al studied the use of surfactants as plasticizers in hot-melt extrudates. The poorly water-soluble compound recrystallized during storage in some formulations. Despite this instability, no effect on the dissolution rate was observed over 6 months. Bruce et al [9] reported similar results for the well water-soluble compound guaifenesin.

1.6 PROCESSING AFFECTING THE STABILITY

Thermal processing will affect the stability of a drug by shaping the environment for the compound during extrusion, and by influencing the product quality, which determines the environment of the drug for long-term stability. Riaz expounds that a host of primary equipment factors (processing temperature, die geometry, extruder type, screw speed and configuration) and formulation factors (composition, moisture level and particle size) will determine a set of secondary factors: specific mechanical energy, melt temperature and pressure. The resulting viscosity and shear values shape the product properties [38]. Henrist et al detail effects of process parameters on melt extrudates, and

conclude that the maximum barrel temperature was the most critical parameter for their study [50].

For process development, it is useful to define a processing temperature window, including the highest temperature the compound can be exposed to without degradation, as well as which elevated temperatures it can tolerate for sustained periods, both by itself and in the processing blend. Preformulation studies, as discussed above, help to set limits for process parameters.

To maximize the stability in processing, several strategies can be explored. Processing at low temperature reduces the thermal stress the blend is exposed to, which can also be achieved by shortening the exposure time to high temperatures. Excluding known factors of instability from the process will also increase drug stability. This can be extended to design a process such as to avoiding process-induced changes of the active as well as the excipients.

1.6.1 Processing at lower temperatures.

The processing temperature presents a compromise between the ability to manufacture the dosage form using a given process and the short-term as well as the long-term stability of the product. For melt extrusion, the temperature must be high enough to process the matrix former at a reasonable viscosity, but limit any unwanted

reactions such as the degradation of the drug and other thermo-labile formulation components.

The addition of a plasticizer enables processing at lower temperatures, at reduced pressures and with lower melt viscosities, by lowering the glass transition temperature of the polymer. Liquid plasticizers, such as citrate esters, have been employed in hot melt extrusion. In addition to excipients, drugs such as chlorpheniramine maleate [51, 52], ibuprofen [53], guaifenesin [9], indomethacin [52, 53] and excipients such as methyl paraben [54] and tartaric acid [55] can plasticize polymers. Transient plasticization was achieved by carbon dioxide, which was injected into an extruder during extrusion [13]. Preformulation studies should identify the existence and extent of a plasticizing effect on any blend component. It is suggestive of additional instability risks, because the plasticizing effect is connected to the solubility of a compound on a polymer. Since the drug's solubility is likely to be higher at the elevated extrusion temperature than at the storage temperature, the product incorporating a drug that is soluble in the thermal binder is at risk for supersaturation-related instabilities. A drug rendered amorphous by the process, but is supersaturated in the matrix at the storage temperature can recrystallize on storage [9].

Using matrix formers with low melting or softening points reduces the necessary processing temperatures. This approach should be carefully weighed against the long-term stability of the melt-extruded dosage form. Reactions leading to instability depend

on the molecular mobility of the components in the matrix at the storage temperature. The glass transition temperature (Tg) marks the transition of the polymer from the "glassy" state to the "rubbery" state, and can be measured by several methods, for instance by DSC [56]. Mobility dramatically increases above the glass transition temperature, and decreases below it. Mobility below the Tg, however, is not reduced to zero, and can contribute to instabilities of all matrix components. A larger difference between the storage temperature and the matrix Tg(s) translates into less mobility in the system. The T_0 or Tg-50 K rule refers to the temperature at which the molecular mobility in the system goes towards zero. It has been proposed to base the selection of storage temperatures on the temperature T_0, not the Tg, to minimize instability [8].

1.6.2 Minimizing exposure time to high temperatures

In twin screw extruders, materials can be added further downstream in the barrel. This can be used to shorten the exposure of the drug to the processing temperatures. The matrix blend can be melted and blended without regard to the limitations imposed by the drug's thermal or mechanical stability. The active is then added to the conditioned and compounded matrix just upstream enough to achieve a uniform blend.

1.6.3 Effects of processing on blend components

Thermal processing impacts the stability of the polymer. Both melt-extrusion as well as injection molding caused a decrease in molecular weight of poly(lactic acid) from

9096 dalton to below 6000 dalton [57]. The heat treatment of polyanhydride implants made by injection molding caused a drop in the molecular weight from 48,485 (control) to 7,120 dalton [58]. The selection of polymer grades for thermal processing must take that into account.

Processing can cause instability by inducing phase transformations in drugs. Morris et al review how solids can change in processing, and consider the time scales of transformations relative to time scales of process-induced stress [59]. Zhang et al discuss practical approaches to identify and prevent problems associated with in-process conversions, and discusses the impact on product quality [60]. In melt-extrusion, the potential for process-induced transformations lies in the temperature gradients as well as the mechanical stress during extrusion and should be considered during process development. Processing and post-processing conditions can be used to stabilize the extrudate. Duclos et al demonstrated that a slower cooling rate resulted in the emergence of a stable progesterone polymorph in solid dispersions with poly(ethylene glycol) 6000, which was physically stable for at least one year [61].

In melt-extrusion, the effect of oxidation reactions on the polymer depends on the processing conditions. High levels of oxygen can result in chain scission and lower the melt viscosity, while low levels of oxygen can lead to cross-linking, raising the melt viscosity [10]. Al-Malaika report that in addition to temperature and shear, the structure

of co-monomers determined whether crosslinking reactions or chain scission dominated oxidation reactions of polyethylene polymers [62].

1.6.4 The effects of thermal processing on the product performance

The type of processing directly affects the performance of the product. The surface morphology resulting from the processing method was correlated to the integrity of the product during long-term dissolution of implants. Rothen-Weinhold et al [57] investigated the effect of melt extrusion and injection molding on the in vitro degradation of implants containing a somatostatin analogue. No interactions of drug and polymer were observed in either sample. The implants differed in molecular weight, degree of crystallinity of the polymer, density and surface structure, which resulted in different rates of matrix degradation. While slightly more protein degradation occurred during injection molding, higher matrix integrity could sustained drug release for longer periods of time in injection-molded implants. This was explained by the absence of surface defects in injection molding. Gray et al present another study demonstrating that the surface morphology of the extrudate directly influences product stability. Initial lipid oxidation in starch extrudates containing linoleic acid started near the surface, as expected. However, the highest oxidation rates were observed not in the rubbery samples, but in glassy extrudates with surface micro-cracks [63].

Properties directly related to the processing method influenced the performance of powders derived by thermal processing. Melt-extrusion resulted in powders with a lower surface area than powders made by solvent co-precipitation (0.13 m^2/g versus 6.19 m^2/g, respectively, measured by multipoint BET). When the powders were suspended in water, melt-extruded powders were physically stable for longer than the co-precipitates. The lower surface area of melt-extruded powders decreased its exposure to the aqueous medium, since water plasticized the system and consequently destabilized the matrix [64].

Melt extrusion can create products with a wide range porosities, which vary from very low-porosity structures [65] to foams [66]. Fukuda et al developed porous tablets for gastroretentive systems. The carbon dioxide generated by thermal decomposition of sodium bicarbonate in the softened acrylic polymer resulted in the porous, buoyant structure [67]. Riscanu et al describe the development of microporosity in extruded thin films during cooling, and subjected the films to cold stretching to develop surface porosity [68].

The micro-structure of extrudates contributes to product stability. Qi et al [69] used ATR-FTIR and microthermal analysis to characterize solid dispersions of paracetamol in Eudragit E. They found that drug crystals were preferentially located in the center, rather than the surface, of extrudate strands. Such localized distribution of drug can influence the stability by creating concentration gradients in the extrudates. The

authors commented that several analytical techniques were necessary to properly characterize the drug distribution in the extrudates.

Post-processing operations likewise affect product stability. Post-processing heat treatment of injection-molded polyanhydride implants containing gentamicin sulfate was studied by Deng [58]. Nitrogen protection during the heat treatment correlated with an intact implant shape after 25 days of in-vitro dissolution and more delayed drug release. The cracking and disintegration of the implant had been correlated with osmotic pressure generated by the gentamicin as it dissolves and leaves the implant. The lower stiffness and higher flexibility of implants stored under a nitrogen atmosphere resulted in a matrix able to accommodate the increased osmotic pressure without cracking, enabling a longer drug release from the dosage form.

1.7 CONCLUSION

Thermal processing inherently carries a higher potential for unwanted reactions, which are often complex. Degradation reactions of drugs or excipients are based on their chemical structure and the environment they reside in, and the chemical stability is influenced by temperature, moisture, mechanical stress, other formulation components and impurities. Often, the combined impact of several factors determines degradation reactions and rates. The physical stability of drugs extends to amorphous-crystalline changes, polymorphic and pseudopolymorphic transformations as well as changes in

existing crystals. Polymers undergo degradation as well; chain scission and crosslinking are the most common manifestations of instability. Semicrystalline polymers undergo changes in the ratio of amorphous-to crystalline domains, and generally possess a narrower temperature window for processing between their melting point and their degradation temperature. Nucleating agents induce and maximize crystallization, either controlled as part of the formulation, or as an unwanted effect of blend components or impurities. Other matrix formers are fats and waxes, whose main stability problem are polymorphic transitions which manifest themselves in the properties of the dosage form. Preventive stabilization aims to reduce instability-inducing factors by purifying the bulk materials, and arrestive stabilization, generally by using antioxidants, is designed to stop degradation reactions as they occur.

Preformulation studies are used to discover vulnerabilities of an active, so that formulation and process development can preclude the instabilities. Formulation components as well as processing are additional sources of instability. Excipients can impact formulation stability by being reactants in degradation reactions, by being a source of moisture or by increasing the formulation moisture content. Drugs can be stabilized by drug-polymer interactions, and by incorporating them into a rigid matrix, which reduces their molecular mobility, and thus reduces their reactivity. Nevertheless, in addition to formulation, storage conditions and packaging are an important part of dosage form stability by controlling instability-inducing factors such as oxygen, moisture levels and temperature. Instability in the formulation can be due to inhomogeneous distribution

of the drug as well as by a change in the polymer state during storage. Often, a formulation has to fulfill objectives which conflict with the goal of stabilizing the stability, and a compromise between stabilizing the drug and other factors has to be found. Plasticizers affect formulation stability and influence its performance, especially drug release, and a reduction in plasticizer levels on storage can destabilize the formulation. The impact of instabilities on dosage form performance has to be determined on an individual basis.

Processing shapes the environment for the compound during processing, and influences the product quality. To lower thermal stress on the product, processing can occur at lower temperature by plasticizing the matrix, using a low-melting matrix former, or adding thermally labile compounds late in the process, if possible. However, long-term stability can be negatively affected if the storage temperature is too close to the Tg of the formulation (T0 or Tg-50 K rule). Thermal processing impacts formulation stability by decreasing the molecular weight of the polymer or by process-induced transformations of either drug or excipients. The thermal processing as well as post-processing operations shape the surface morphology, surface area, porosities and micro-structure of products, which has been shown to impact product performance and quality.

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Chapter 2: Research Objectives

2.1.1 Overall Objective

The objective of this study was to investigate the physical stability of hot-melt extruded acrylic matrix tablets containing either Eudragit® L100-55 or Acryl-EZE®. The instability manifested itself by the recrystallization of the model drug, guaifenesin, from the amorphous state. This type of instability is a general concern in solid solutions, and a limiting factor in the wider utilization of solid solutions to formulate poorly water-soluble drugs. The causes and contributing factors of guaifenesin crystal growth formation were investigated to devise strategies to contain and eliminate this source of physical instability for this specific model drug, but are applicable to solid solutions in general. To meet the overall goal, the study was divided into several supporting objectives.

2.1.2 Supporting Objectives

2.1.2.1 Crystal Growth Formation on Melt-Extrudates

To provide the basis for subsequent investigations, the factors influencing the growth of guaifenesin crystals on hot-melt extruded matrix tablets containing either Acryl-EZE® or Eudragit L100-55® were determined. The first sub-objective was to examine the influence of guaifenesin as a model drug on the processing conditions during hot-melt extrusion. The second sub-objective characterized the causes, the onset and the localization of guaifenesin crystal growth as well as the effect of recrystallization on the

drug release properties of melt-extruded tablets. The third sub-objective studied the use of hydrophilic polymeric additives as crystal growth inhibitors and their influence on the drug release properties of the blended matrix tablets.

2.1.2.2 The Influence of Heterogeneous Nucleation on the Surface Crystallization of Guaifenesin from Melt Extrudates Containing Eudragit® L100-55 or Acryl-EZE®.

The second objective was to identify additional factors influencing the physical stability of guaifenesin in melt extrudates. The first sub-objective quantified the influence of talc on the recrystallization of guaifenesin from hot-melt extruded acrylic matrix tablets. Secondly, the impact of relative humidity levels during storage on the recrystallization of guaifenesin from tablets containing different levels of non-melting components was studied, both at constant and cycling relative humidity values. The last sub-objective concerned the identity and composition of the crystalline material on the tablet surface, and whether it was influenced by talc and relative humidity.

2.1.2.3 The Influence of Aqueous Film-Coating on the Recrystallization of Guaifenesin from Hot-Melt Extruded Acrylic Matrix Tablets

The effect of aqueous film-coating of hot-melt extruded matrix tablets on the physical stability of guaifenesin was investigated. Two coating polymers were selected based on their solubility for guaifenesin, ethylcellulose as a hydrophobic polymer was

expected to provide a barrier to the diffusion of hydrophilic guaifenesin due to their structural differences. A hypromellose film was thought to slow guaifenesin diffusion through the film as it was able to interact with guaifenesin via hydrogen bonding.

The objectives of this study were to investigate the influence of aqueous film-coating of hot-melt extruded matrix tablets on the physical stability of guaifenesin. The effects of polymer type, weight gain, curing time and temperature, storage conditions and core drug-to polymer ratio the onset and extent of guaifenesin recrystallization were determined.

2.1.2.4 Properties of extruded tablets produced by either single-screw or twin-screw melt extrusion

The reciprocal influence of two model drugs and their effect on melt extrusion, as well as the extrusion of pre-mixed powder blends on either a single-screw or a twin-screw extruder and the consequences of mixing efficiency for tablet performance were investigated in the final objective.

The sub-objectives were to characterize thermal properties of blends containing diltiazem hydrochloride and guaifenesin, to examine drug morphology and drug distribution in melt-extruded tablets produced by either single-screw or a twin screw extrusion, and to determine the effect of extruder type on the drug content of the

extrudates, their dissolution rate, and the recrystallization of guaifenesin from the amorphous state on storage.

Chapter 3: Materials and Methods

3.1 MATERIALS

The following materials were used in all studies. Guaifenesin was purchased from Spectrum (Gardena, CA), and was used as model drug. Eudragit® L100-55 was donated by Evonik Degussa (Piscataway, NJ, particle size 95% below 250 micron).

Hydrophilic polymers employed in supporting objective I, 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). Acryl-EZE® was donated by Colorcon (West Point, PA). Ethanol (200 proof) was purchased from AAPER Alcohol and Chemical (Shelbyville, KY). The talc (Imperial 500 USP, particle size 4.5 micron) was a gift from Luzenac (Centennial, CO). Triethyl citrate (TEC) was kindly donated by Vertellus (Greensboro, NC).

The talc employed in the supporting objective II (Imperial 500 USP, particle size 4.5 micron) was a gift from Luzenac (Centennial, CO). Drierite® (Hammond, Xenia, OH) and sodium chloride, ACS reagent (Sigma-Aldrich, St. Louis, MO) were purchased.

Acryl-EZE® was donated by Colorcon (West Point, PA). The desiccant Drierite® (Hammond, Xenia, OH) was obtained from Fisher Scientific.

In supporting objective III, the melt-extruded tablets were film-coated using Opadry® Clear YS-1-7006 (Polymer: hypromellose) and Surelease® (Polymer: ethylcellulose), which were donated by Colorcon (West Point, PA). FMC (Philadelphia, PA) provided Aquacoat® ECD 30 (Polymer: ethylcellulose). Dibutylsebacate (DBS) was used to plasticize ethyl cellulose, and triethylcitrate (TEC) was used to plasticize Eudragit® L100-55, both were gifts from Vertellus (Greensboro, NC). Films to investigate the solubility in polymers were cast using Ethocel standard 7 Premium (NF grade) by Dow Chemical (Midland, MI). 200 proof alcohol (USP grade) was purchased from AAPER Alcohol and Chemical Co (Shelbyville, KY). The desiccant Drierite® (Hammond, Xenia, OH) was obtained from Fisher Scientific.

Diltiazem hydrochloride (DIL) was used as additional model drug in supporting objective IV, and was purchased from Spectrum (Gardena, CA). Colloidal silicon dioxide (Cab-O-Sil M-5P, Cabot Corporation, Alpharetta, GA, average particle size 0.2-0.3 micron) was kindly donated by Cabot. The desiccant Drierite® (Hammond, Xenia, OH) was obtained from Fisher Scientific.

3.2 METHODS

3.2.1 Tablet Preparation

Tablets were prepared by hot-melt extrusion of the powder blends, followed by manual cutting of the extrudate strand. 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 at least 30-40 minutes before extrusion. The extrudates were allowed to cool at room temperature for 24 hours in a desiccator before manually cutting tablets.

The processing temperatures chosen for extrudates containing Acryl-EZE® and guaifenesin were 90°C, 95°C, 110°C (zones 1, 2, 3, respectively) and 115°C (die), and between 65 and 95°C for extrudates containing Eudragit® L100-55 (supporting objective I). In supporting objectives II and III, formulations were extruded at 65, 75, 85 (zones 1, 2, 3, respectively) and 85°C (die). In supporting objective IV, the first temperature zone (feeding section) was set to 65°C for all extrusions, and the remaining two temperature zones (melting and metering sections) and the die were set to the same temperature for any given extrusion. To extrude guaifenesin-containing tablets, separate extrusions were carried out at 65, 75, 85, 95 and 125°C. Tablets for containing guaifenesin and DIL were extruded at either 75, 95 or 125°C. Identical powder blends were processed at the same

temperatures on a twin-screw extruder, (Haake Minilab II Microcompounder, ThermoScientific, Waltham, MA) equipped with a single heating zone, a conical flighted screw (L/D ration 7.82-21.9), a water-cooled force-feeder and a round die (diameter 2 mm). The melt was not circulated through the back-flow channel.

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.

3.2.2 Film Coating (supportive objective II)

Film coating was applied to study the effect of the film coating on the physical stability of guaifenesin in melt-extruded matrix tablets. Hot-melt extruded tablets were mixed with compressed placebo tablets up to a 1:1 weight ratio, and 300 gram batches (placebo plus melt-extruded tablets) were placed into a perforated pan-coater (HCT Mini HiCoater, Vector Corp, Cedar Rapids, IA), equipped with a peristaltic pump (505S Watson-Marlow, Wilmington, MA). The coating dispersions were kept under constant low shear stir during preparation and the film-coating process. The tablets were coated to completion, and were dried for 10 minutes at the processing temperature in the rotating pan. Some tablets were cured by placing them on open containers into ovens for the prescribed time. All tablets were stored in desiccators at 17% relative humidity until they were packaged.

3.2.3 Storage conditions

For stability studies in supportive objective I and III, 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.

In supportive objective II and IV, tablets were filled into open containers and placed in storage chambers, which were maintained at a constant ambient temperature. The desiccant Drierite® (anhydrous calcium sulfate containing an indicator) equilibrated the low humidity chambers to 17±3.5% RH. For supportive objective II, saturated sodium chloride solution was used in storage chambers to create "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).

3.2.4 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 milliliters of 200 proof ethanol, DI water, or mixtures thereof. After stirring for at least 30 minutes under low shear until all components were dissolved, the solutions were cast into aluminum dishes

(Fisher Scientific, Hampton, NH) and were dried for 24 hours or until dry under a fume hood (alcohol based films) or in a 60 °C oven (water based films).

3.2.5 Thermal analysis

Differential scanning calorimetry (DSC) was used to determine the melting points of drugs in powder blends and modulated DCS (MDSC) was used to determine the glass transition temperature of polymers alone or in mixtures. A ceramic mortar and pestle was used to prepare powder mixtures and to crush melt extrudates. All powder blends were prepared in a ceramic mortar and pestle. Three to twenty milligram samples were analyzed in crimped aluminum pans (Kit 0219-0041 Perkin-Elmer Instruments, Norwalk, CT) on a calorimeter (Thermal Advantage Model 2920, TA Instruments, Newcastle, DE) equipped with Thermal Advantage Instrument Control Software for instrument control and Universal Analysis 2000 for data analysis. Ultra pure nitrogen was used as a purge gas at a flow rate of 150 mL/min.

For supporting objective I, 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 at a heating rate of 3°C/min with a temperature modulation of ±1°C every 30 seconds. DSC was used to investigate guaifenesin solubility in hydrophilic polymers using a heat-cool-heat cycle. The 1:1 mixtures were equilibrated at 10°C, heated up to 110 °C at 5°C per minute, then cooled to 0°C at 10°C per minute, and heated up to 110 °C at 5°C per minute.

For supporting objective IV, DSC of powder samples determined the melting points of guaifenesin and diltiazem in binary powder blends and in the extrusion blend. The temperature ranged from 50 to 230°C at a heating rate of 10°/minute. MDSC determinations of blends containing guaifenesin, diltiazem hydrochloride and Eudragit® L100-55 were analyzed at a heating rate of 15°C/minute from 50 to 170°C, with a temperature amplitude of 0.5° every 40 seconds.

3.2.6 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 sample holders or glass slides were filled to a constant weight. Stored or freshly cut tablets 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 (Phillips Electronic Instruments, Mahwah, NJ), employing CuKα radiation, operating at 40kV and 20-30 mA. The scan radius ran from 5° to 70° or 10° to 60° degrees, and the step size was 0.05° every 1.5 or 2 seconds (supporting objective I). The scan radius ranged from 10° to 60° degrees, and the step size was 0.05° every 4 seconds (supporting objective III). The scan radius ran from 10° to 40° degrees, and the step size was 0.02° every 2 seconds (supporting objective IV).

3.2.7 Scanning Electron Microscopy and Energy-Dispersive Spectroscopy

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 (supporting objective I), previously stored tablets were bisected and then either observed immediately or equilibrated at ambient conditions for predetermined time periods (5-30 minutes). 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 as needed (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 sec under Argon with a gold/palladium mixture in a 60/40 ratio. The images were captured with an electron microscope (Phillips 515, Phillips Electronic Instruments, Mahwah, NJ) equipped with Semicaps 2000 software (Semicaps, San Jose, CA), operating at 15 kV and 20 μA. The surface of the tablets was surveyed, and a representative area was chosen for the micrograph.

For supporting objectives II-IV, all tablets were coated with a 15 nm thick platinum/palladium coating (80/20), applied by a Cressington Sputter Coater 208 HR (Watford, UK) equipped with a thickness controller MTM 20 at 2.5 kV, 20 mA under Argon. For supporting objectives II and III, 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.

SEM imaging and EDS mapping for supporting objective IV were carried out using a LEO 1530 electron microscope (LEO Electron Microscopy, Thornwood, NY) equipped with a Gemini field emission column and a Gresham Sirius 10 detector (e2v scientific instruments, Woburn, UK) for EDS. SEM micrographs were captured at 10 kV using LEO-32 software. EDS mapping of carbon, oxygen and chlorine present in the sample was carried out using EDS2006 software (IXRF systems, Houston, TX). Each sample was investigated in both cross-sections as well as longitudinal sections through the extrudate strand in at least 3 distinct locations to ensure that the scans were representative.

3.2.8 Moisture Uptake of Tablets

Moisture uptake of stored tablets was measured for supporting objective II 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 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 minutes 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.

3.2.9 Mass Spectrometry (MS)

Mass spectrometry was employed to identify the surface crystals in supporting objective II. 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).

3.2.10 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 0.1 N hydrochloric acid for two hours, followed by eight hours 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 minutes to ensure total disintegration of the tablets. Samples were filtered through a 0.45 or 0.22 micron nylon filter before HPLC analysis (Puradics 25NYL syringe filter and Puradics 45NYL syringe filter; Whatman, Maidstone, UK) to remove insoluble excipients.

In supporting objective IV, dissolution studies of guaifenesin tablets were conducted in 900 mL 0.05 M phosphate buffer pH 6.8 (n=3) at 37°C and 50 rpm for 8 hours. Dissolution studies on melt-extruded tablets containing DIL and guaifenesin were conducted in 900 mL simulated gastric fluid without pepsin (n=3) at 37°C and 50 rpm for 8 hours. At the end of each dissolution test, complete drug release was obtained by mixing the vessel contents with a homogenizer for one minute to ensure total disintegration of the tablets. The dissolution samples were filtered through a 0.22 micron nylon filter (Puradics 25NYL syringe filter, Whatman, Maidstone, UK) to remove insoluble excipients before quantifying the drug by UV testing.

3.2.11 Drug Content Determination

The drug content was determined to study the drug distribution in the extrudates. Thin sections of the extruded rods were accurately weighed and placed in volumetric flasks containing 100.0 mL of phosphate buffer pH 6.8 (n=3). After the sections had

dissolved, the medium was filtered through a 0.22 micron nylon filter (Puradics 25NYL syringe filter, Whatman, Maidstone, UK). The drug content of each sample was analyzed by UV testing as described in section 2.8.

3.2.12 Assay for Crystalline Surface Guaifenesin

Melt extruded tablets containing guaifenesin were assayed for surface crystallized drug substance using the procedure described in Figure 5.2. Briefly, individual tablets were accurately weighed and a single tablet was placed into a large test tube (25x150 mm) filled with either 3.0 or 5.0 mL of 0.1 N hydrochloric acid. The test tube was subjected to vortex mixing (SP vortex mixer, Baxter Diagnostic, Deerfield, IL) at a fixed agitation force for 5 seconds. Immediately after vortex mixing, the medium was decanted and filtered through a 0.22 micron nylon filter (Puradics 25NYL syringe filter, Whatman, Maidstone, UK). The filtered medium containing the dissolved guaifenesin from the tablet surface 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). Test conditions, including immersion time, vortex intensity, vessel size and dilution for the UV test, were chosen to ensure discrimination between samples.

3.2.13 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 microliter. 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 micrometer, 250 x 4.1mm (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 minutes. Both mobile phase solvents were vacuum filtered through a 0.45 micron nylon membrane (0.45 micron 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/microliter ($R^2 \geq 0.997$) and injection repeatability was 1% relative standard deviation for 6 injections.

The drug content in samples from dissolution testing, drug content analysis and recrystallization testing was determined by UV analysis (supporting objectives II-IV). The guaifenesin content was quantified at 273 or 275 nm in 200 or 400 microliter samples by UV spectroscopy (μQuant UV Spectrometer equipped with KC 4 software for data analysis, BioTek Instruments, Inc, Winooski, VT). 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.

DIL was analyzed at 230 nm using the same instrument. For drug content analysis, 50 microliter samples were diluted with 350 microliter of 0.05 M phosphate buffer pH 6.8. Dissolution test samples were diluted with simulated gastric fluid without pepsin in a 1 to 1 ratio. Linearity was established for drug concentrations between 10 and 200 mg/mL (R^2=0.9994).

Chapter 4: Crystal Growth Formation in Melt Extrudates

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°C, 95°C, 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 hours in extrudates containing Acryl-EZE® and guaifenesin to 8 hours 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.

4.1 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 (Christopher R. Young, 2005) and films (Crowley et al., 2004, Repka, 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 to 4 minutes. 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 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, 1995), and some low molecular weight compounds such as sodium chloride, boric acid and sodium tetraborate have been shown to inhibit recrystallization (Telang, 2003, Yoshinari et al., 2003, Izutsu et al., 2004). Poly(ethylene oxide) was shown to reduce recrystallization of amorphous indomethacin in compression (Schmidt, 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., 2005), 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 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.

4.2 MATERIALS AND METHODS

4.2.1 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).

4.2.2 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 4.1. 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 minutes before extrusion. The extrudates were allowed to cool at room temperature for 24 hours 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°C, 95°C, 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 temperatures as shown in Table 4.3. 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 4.2 and in Table 4.3, respectively.

4.2.3 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 milliliters of 200 proof ethanol, DI water, or mixtures thereof. After stirring for at least 30 minutes under low shear until all components were dissolved, the solutions were cast into aluminum dishes

(Fisher Scientific, Hampton, NH) and were dried for 24 hours or until dry under a fume hood (alcohol based films) or in a 60 °C oven (water based films).

4.2.4 Glass Transition Temperature (Tg) 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 seconds. 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 minute, then cooled to 0°C at 10°C per minute, and heated up to 110 °C at 5°C per minute.

4.2.5 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±5mg) 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 CuKα radiation, operating at 40kV and 20mA. The scan radius ran from 5° to 70° or 10° to 60° degrees, and the step size was 0.05° every 1.5 or 2 seconds.

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

4.2.7 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 0.1 N HCl for two hours, followed by eight hours 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 minutes to ensure total disintegration of the tablets. Samples were filtered through a 0.45 or 0.22 micron 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 micron nylon filter, switching to 0.22 micron nylon filters if the filtered samples still appeared cloudy.

4.2.8 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 x 4.1mm (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 minutes. Both mobile phase solvents were vacuum filtered through 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.

4.3 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 (Figure 4.1). 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 Figure 4.2, 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 (Figure 4.3). 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 (Figure 4.4). To determine the onset time of crystallization, previously stored tablets containing

Acryl-EZE® (Figure 4.5) or Eudragit L100-55® (Figure 4.6) 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 minutes. No crystals were observed on the newly exposed matrix surface of tablets (Figure 4.5 (a) and Figure 4.6 (a)). SEM micrographs of the tablets which were sectioned and exposed to the environment 15 minutes (Figure 4.5 (b) and Figure 4.6 (b)) or 30 minutes (Figure 4.5 (c) and Figure 4.6 (c)) 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 (Figure 4.7). 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 Figure 4.7 a-c were taken under the same magnification (x101). 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 Figure 4.8. Eudragit L100-55® is an enteric polymer that starts to dissolve above pH 5.5. In 0.1 N hydrochloric acid, the polymer matrix remained intact although more than 10% drug was released after 2 hours. 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 hours in phosphate buffer pH 6.8. The results in Figure 4.9 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 4.1). 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 (Figure 4.10) and after 4 weeks of storage at 25°C and 60% relative humidity (Figure 4.11). The extrudates containing PEG 3350 showed crystal growth under high magnifications soon after extrusion and was similar to the extrudates without additive. After four 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 (Figure 4.11 a 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 hours in pH 6.8 phosphate buffer (Figure 4.12), as opposed to extrudates containing Acryl-EZE® and guaifenesin, which showed complete drug release after 4 hours in pH 6.8 phosphate buffer (Figure 4.9). 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 release is due only to the dissolution of the polymer, which slowes 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 four weeks of storage at 25°C and 60% relative humidity (Figure 4.13), indicating that the formulations were stable.

4.4 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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4.6 TABLES

Table 4.1 Composition of tablets prepared by hot-melt extrusion

Formulation	Guaifenesin % wt/wt	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*	-	207.5	75	10	7.5

*25% guaifenesin and 10% crystallization inhibitor based on the guaifenesin content

Model Drug	% Model Drug	Barrel Pressure (PSI x 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 4.2 Processing conditions for extrudates containing Acryl-EZE®

Model Drug	% Model Drug	Barrel Pressure (PSI x 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

Table 4.3 Processing conditions for extrudates containing Eudragit L100-55®

4.7 FIGURES

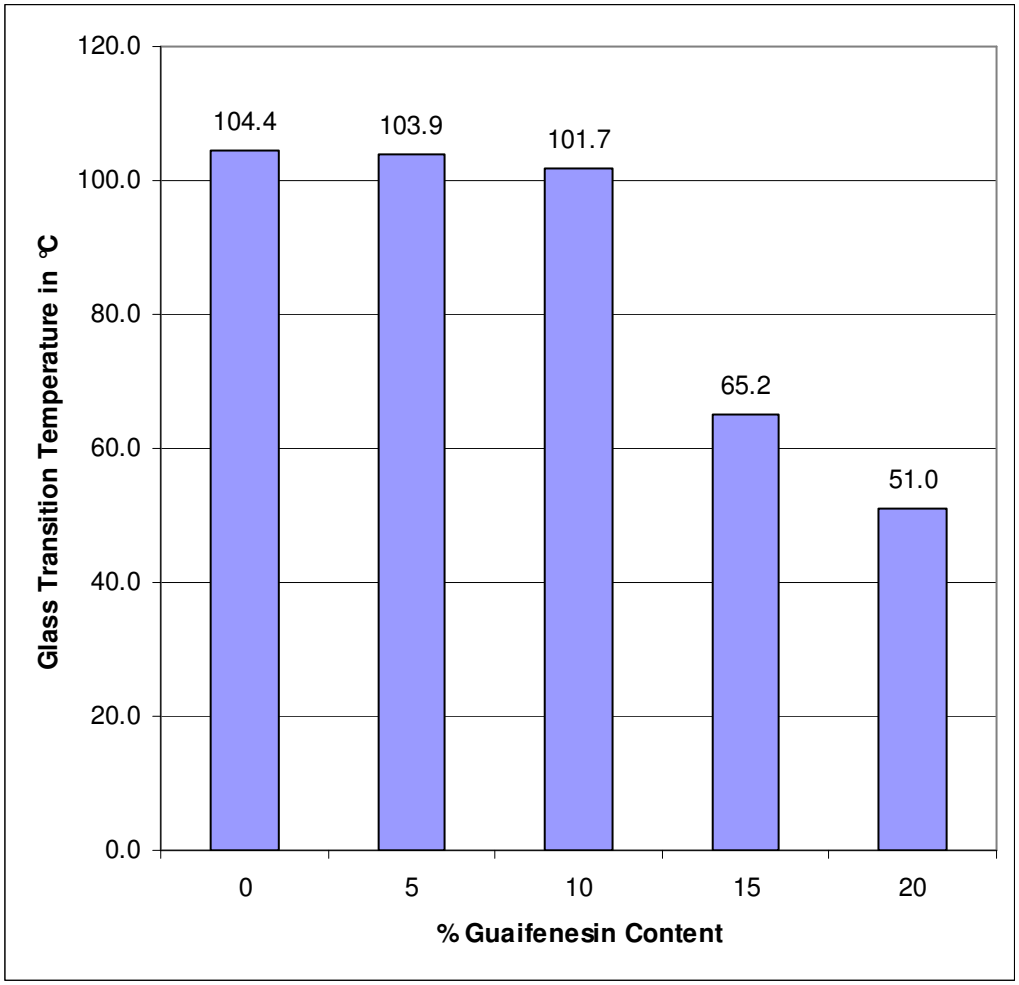


Figure 4.1 Influence of guaifenesin content on the glass transition temperature of Eudragit L100-55®.

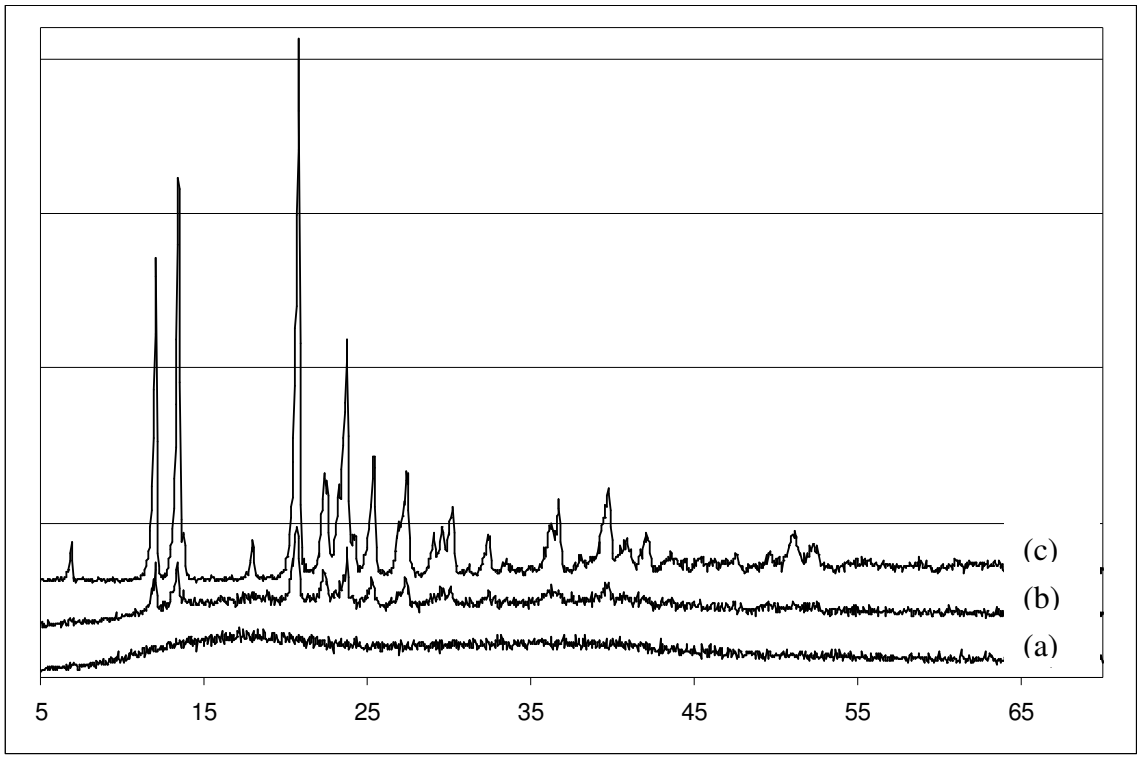


Figure 4.2 Powder x-ray diffraction profiles of guaifenesin, Eudragit L100-55®, and their physical mixture.

Scan Range 5 to 70 degrees, Step size 0.05 degrees, Scan Speed 0.05 degrees/1.0 second.

(a) Eudragit L100-55® (powder), (b) Physical mixture 25% guaifenesin in Eudragit L100-55® (powder), (c) guaifenesin (powder).

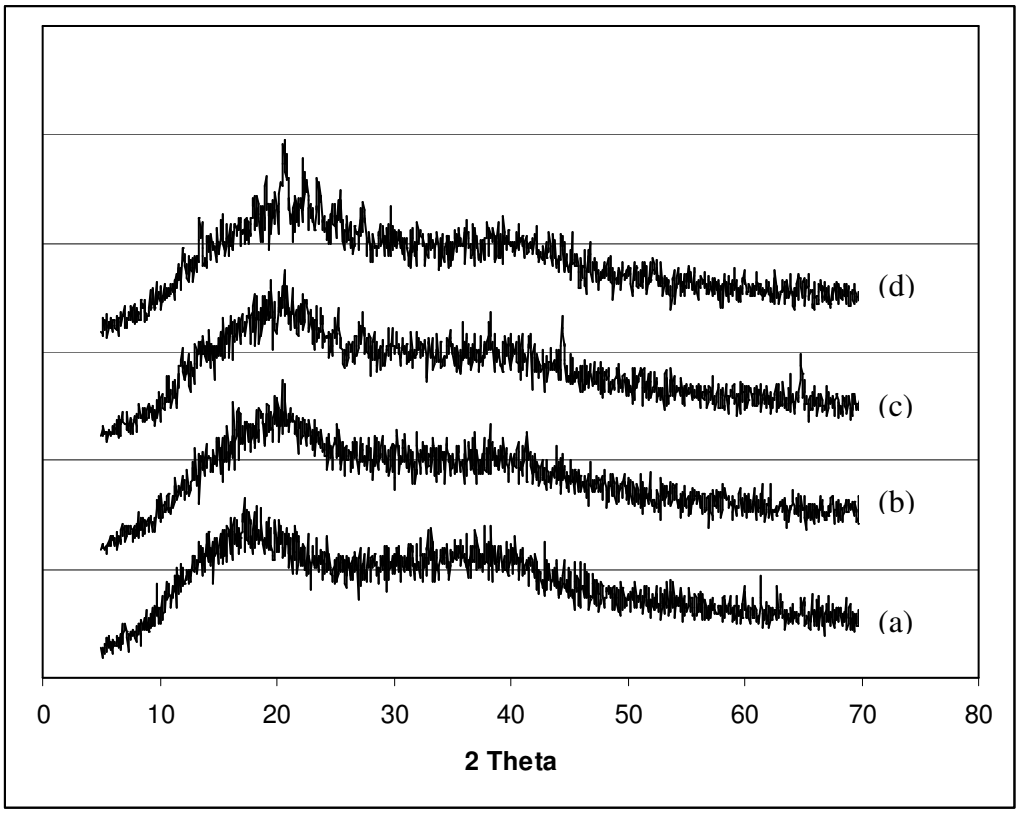
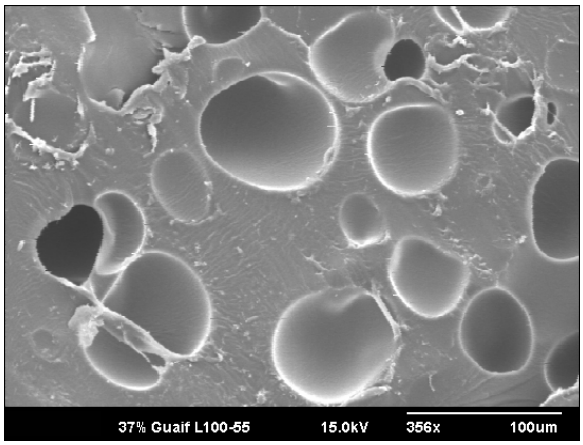


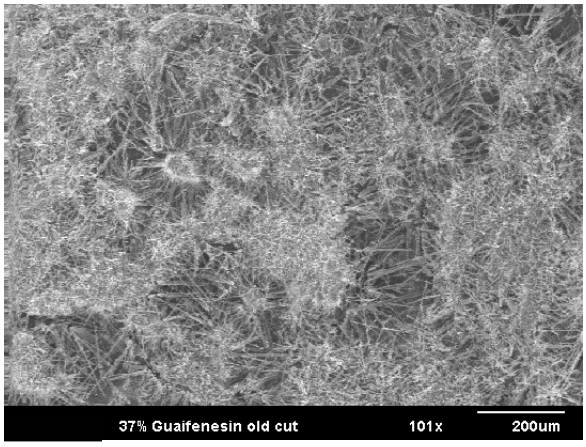
Figure 4.3 Powder x-ray diffraction profiles of melt-extruded tablets containing Eudragit L100-55® and guaifenesin soon after extrusion.

Scan Range 5 to 70 degrees, Step size 0.05 degrees, Scan Speed 0.05 degrees/1.0 second.

(a) No guaifenesin, (b) 25% guaifenesin, (c) 37.5% guaifenesin, (d) 50% guaifenesin.



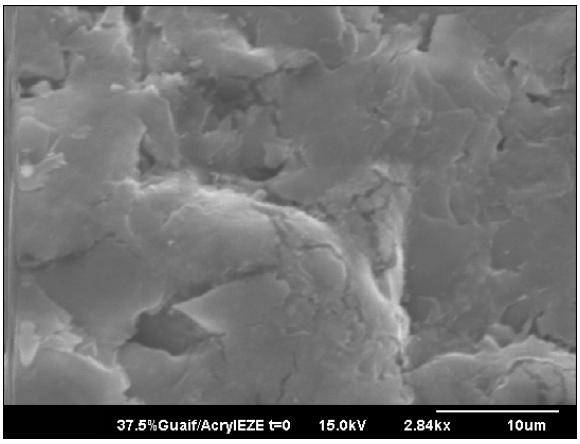
(a)



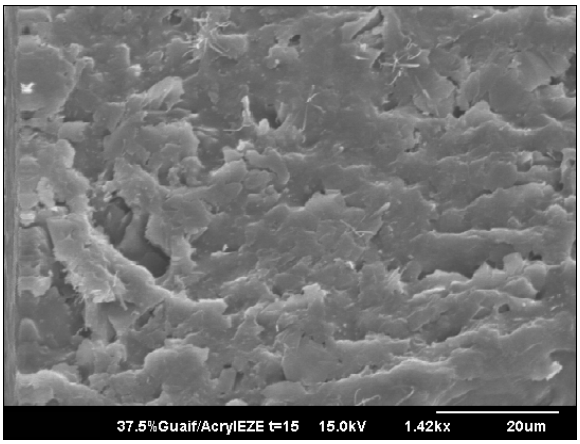
(b)

Figure 4.4 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)

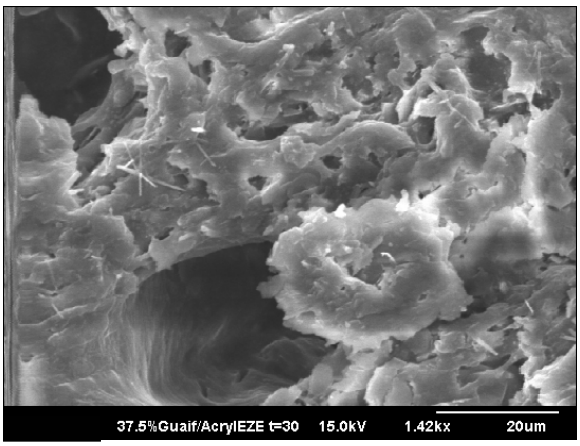
(a) soon after extrusion, (b) after four weeks of storage at 25°C/60% relative humidity.



(a)

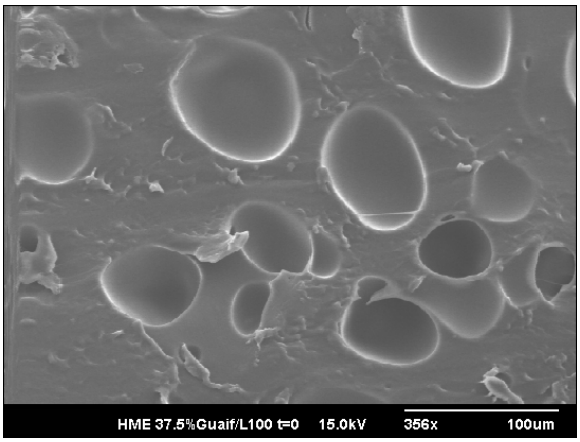


(b)

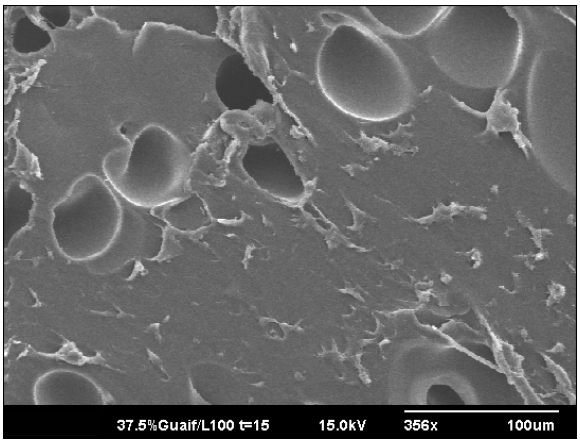


(c)

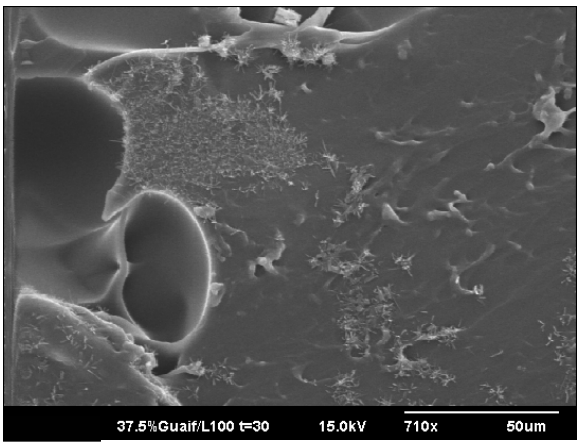
Figure 4.5 SEM micrographs of hot-melt extruded tablets containing Acryl-EZE® and 37.5% guaifenesin.
(a) T=0 min, (b) T=15 min, (c) T=30 min.



(a)

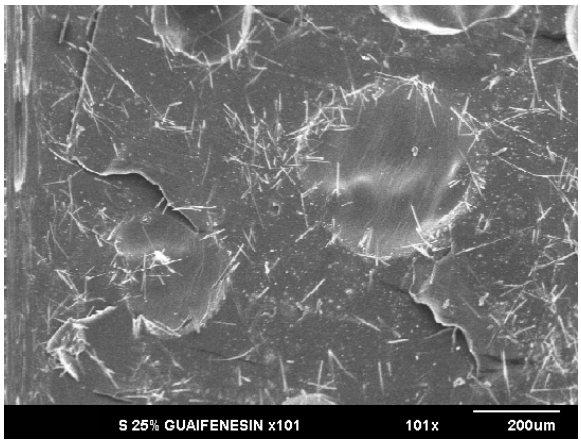


(b)

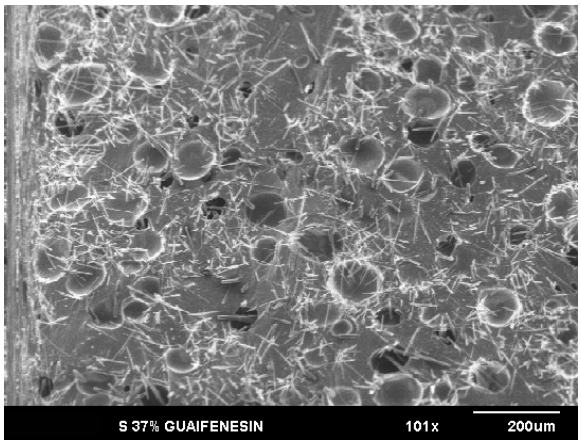


(c)

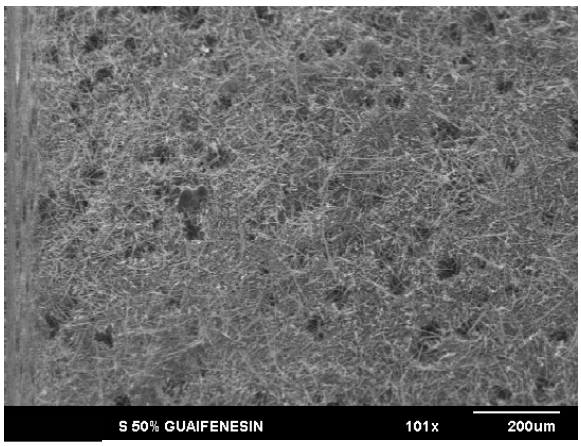
Figure 4.6 SEM micrographs of hot-melt extruded tablets containing Eudragit L100-55® and 37.5% guaifenesin.
(a) T=0 min, (b) T=15 min, (c) T=30 min.



(a)



(b)



(c)

Figure 4.7 Influence of drug concentration on surface crystallization (storage 25ºC/60% RH). SEM of hot-melt extrudate containing Eudragit L100-55® and various concentrations of guaifenesin.
(a) 25% guaifenesin, (b) 37.5% guaifenesin, (c) 50% guaifenesin.

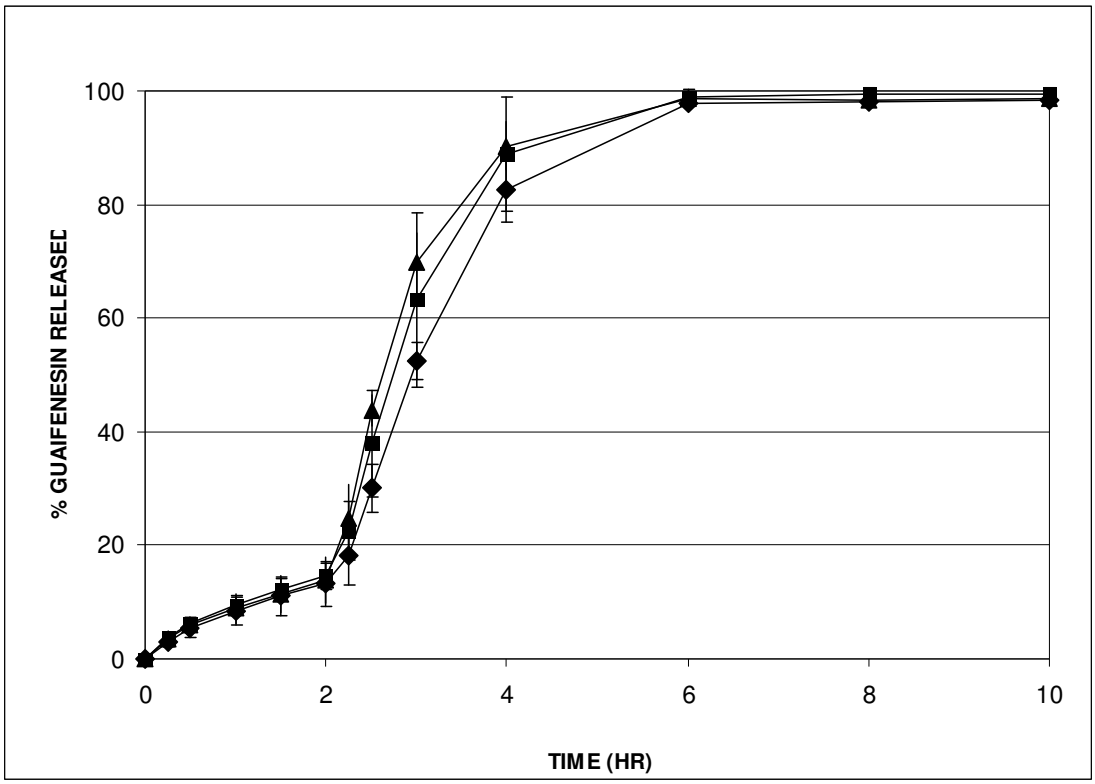


Figure 4.8 Influence of guaifenesin content on the dissolution rate from tablets containing Acryl-EZE®.

Paddle, 900 mL, 37±0.5°C, 50 rpm, 2 hours 0.1N HCl, 8 hours pH 6.8 phosphate buffer, n=6.

♦ 15% guaifenesin, ▲ 20% guaifenesin, ■ 25% guaifenesin.

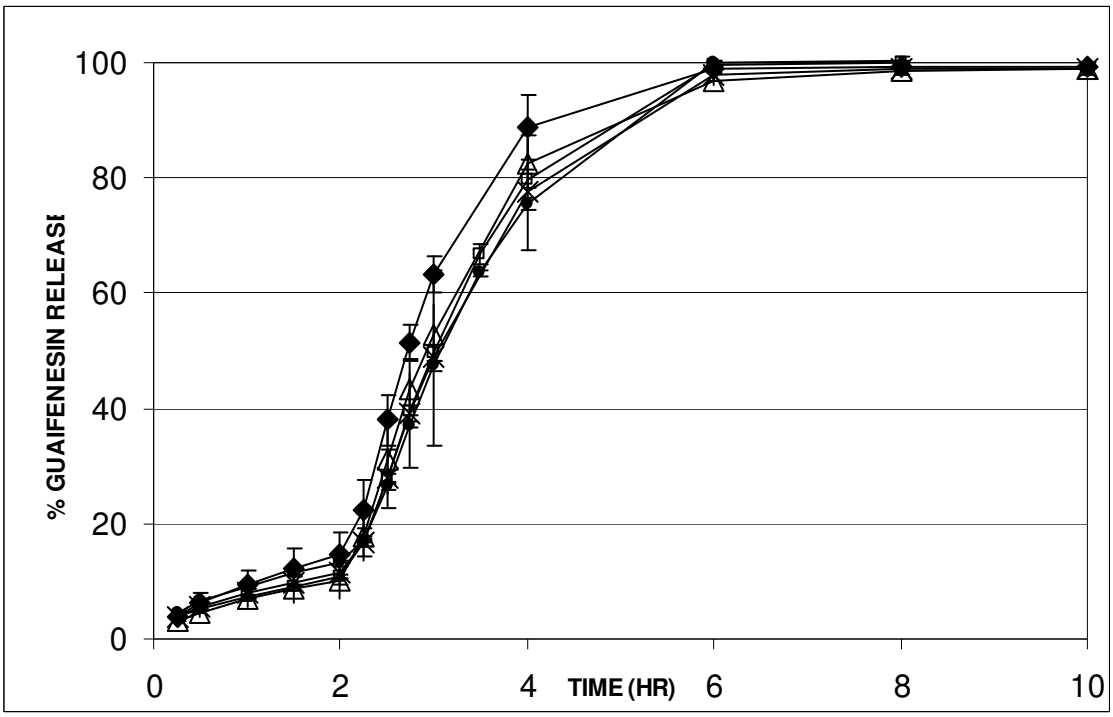
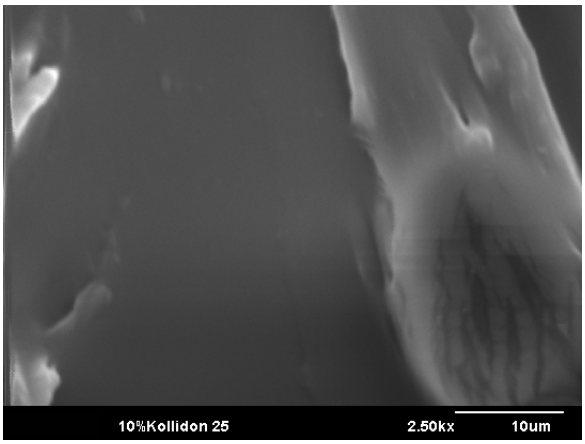


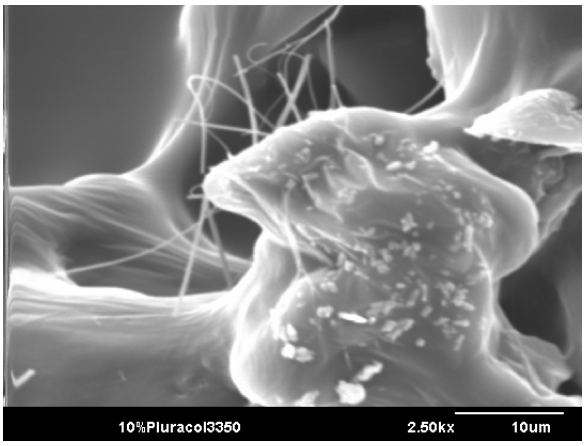
Figure 4.9 Influence of storage for 3 weeks and 6 months on the dissolution rate of guaifenesin from melt-extruded tablets containing 25% guaifenesin and 75% Acryl-EZE®.

Paddle, 900 mL, 37±0.5°C, 50 rpm, 2 hours 0.1N HCl, 8 hours pH 6.8 phosphate buffer, n=6.

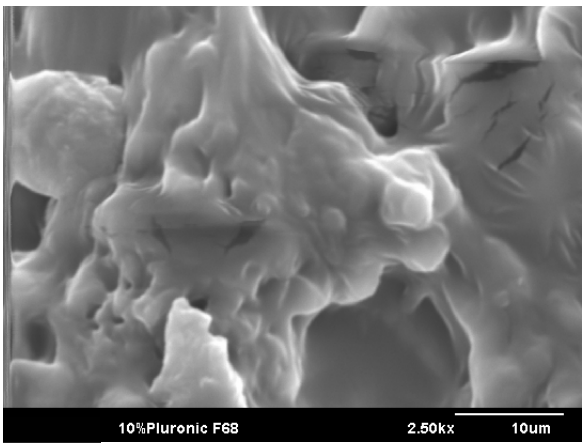
♦ Initial (T=0);
Δ T=3 weeks, storage 25°C/60% RH;
X T=3 weeks, storage 40°C/75% RH;
□ T=6 months, storage 25°C/60% RH;
○ T=6 months, storage 40°C/75% RH.



(a) PVP K25



(b) PEG 3350



(c) Poloxamer 188

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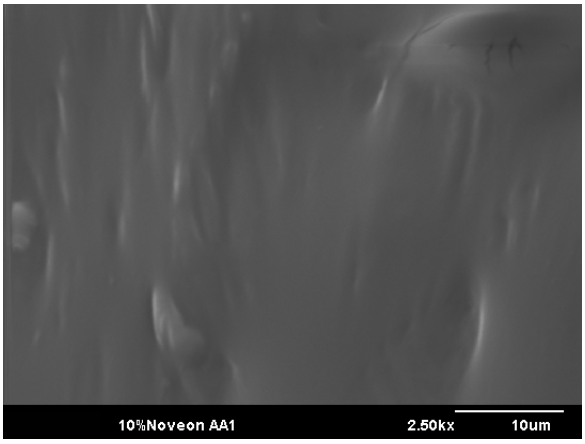
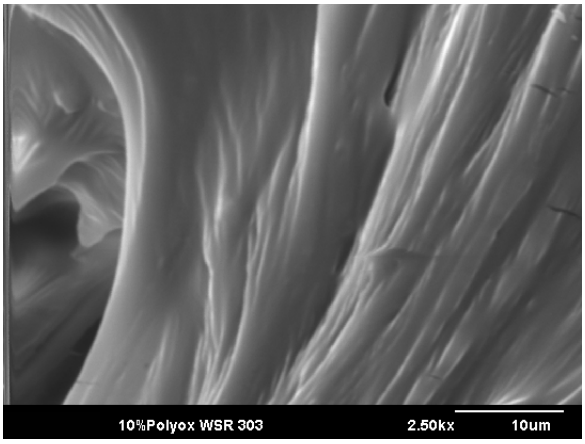


(d) Polycarbophil

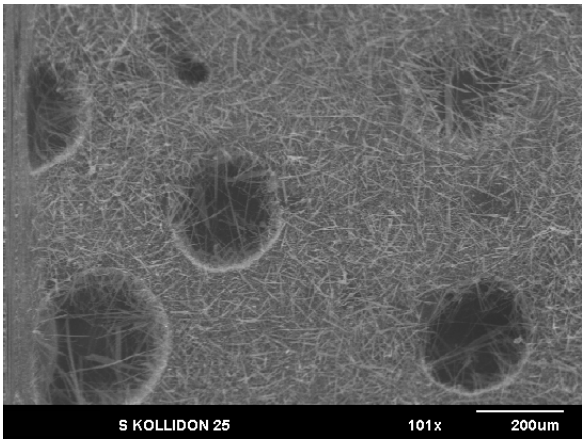


(e) Poly(ethylene oxide)

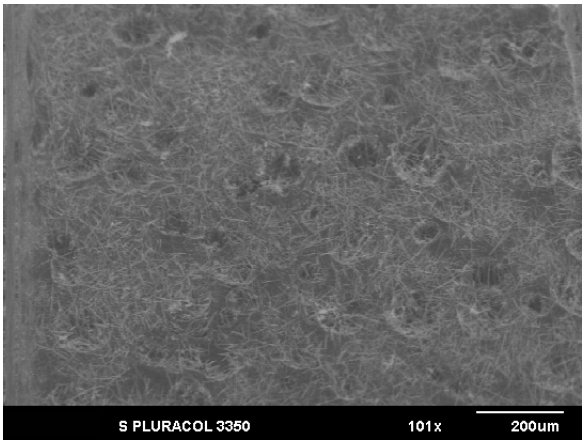
Figure 4.10 SEM micrographs of melt-extruded guaifenesin tablets containing Eudragit L100-55® and 25% guaifenesin with 10% crystallization inhibitor, based on the amount of drug.

Soon after extrusion.

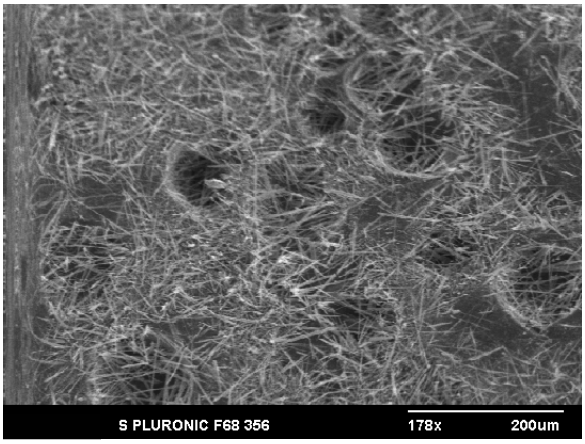
(a) PVP K25
(b) PEG 3350
(c) Poloxamer 188
(d) polycarbophil
(e) poly(ethylene oxide)



(a) PVP K25



(b) PEG 3350



(c) Poloxamer 188

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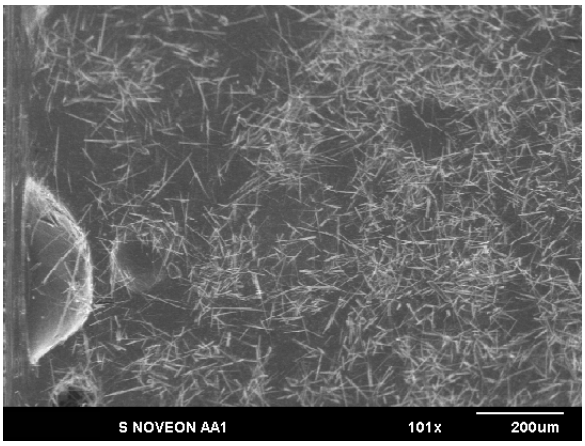
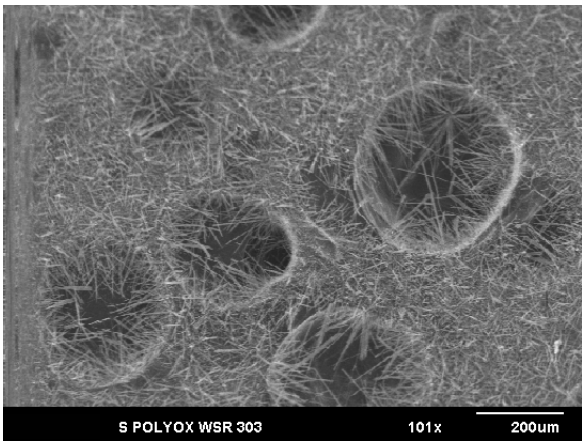


(d) Polycarbophil



(e) Poly(ethylene oxide)

Figure 4.11 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
(e) Poly(ethylene oxide)

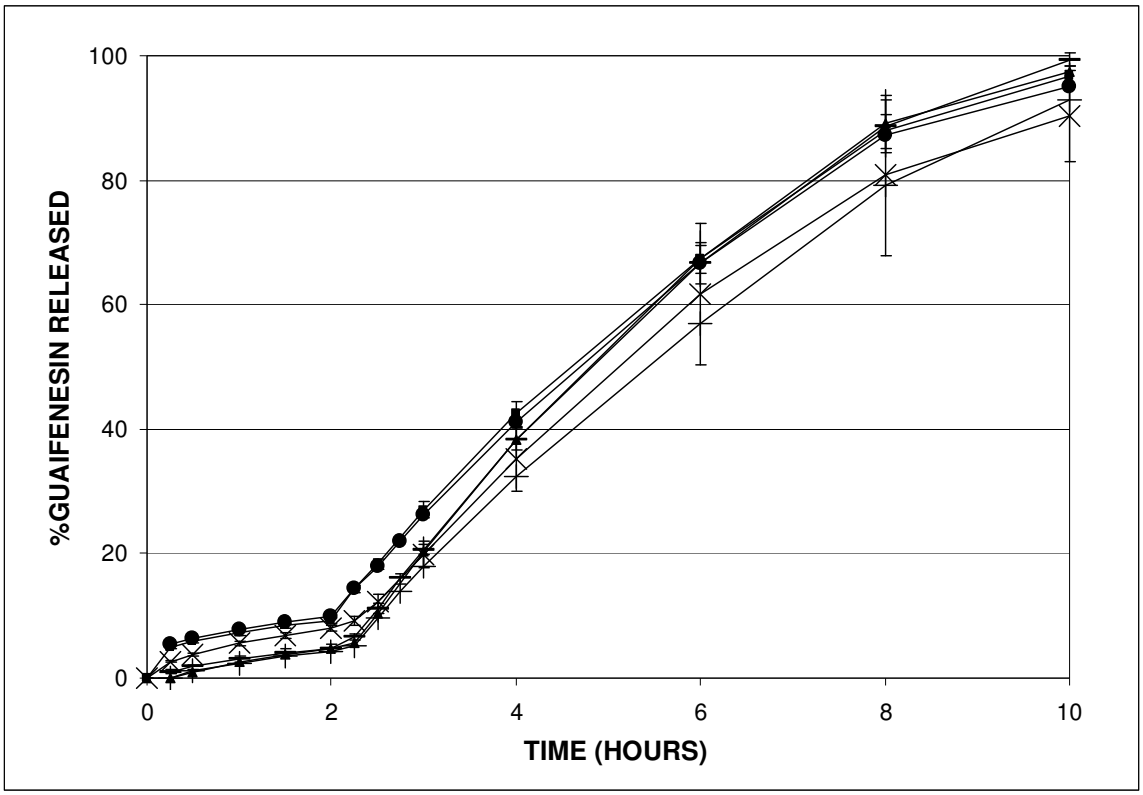


Figure 4.12 Influence of 10% crystallization inhibitor (based on drug content) on the dissolution of guaifenesin from tablets containing 25% guaifenesin and Eudragit L100-55®.

Soon after extrusion.

Basket, 900 mL, 37±0.5°C, 50 rpm, 2 hours 0.1N HCl, 8 hours pH 6.8 phosphate buffer, n=6.

▲ Polycarbophil
X PEG 3350
O Poloxamer 188
■ PVP K25
- No additive,
+ Poly(ethylene oxide)

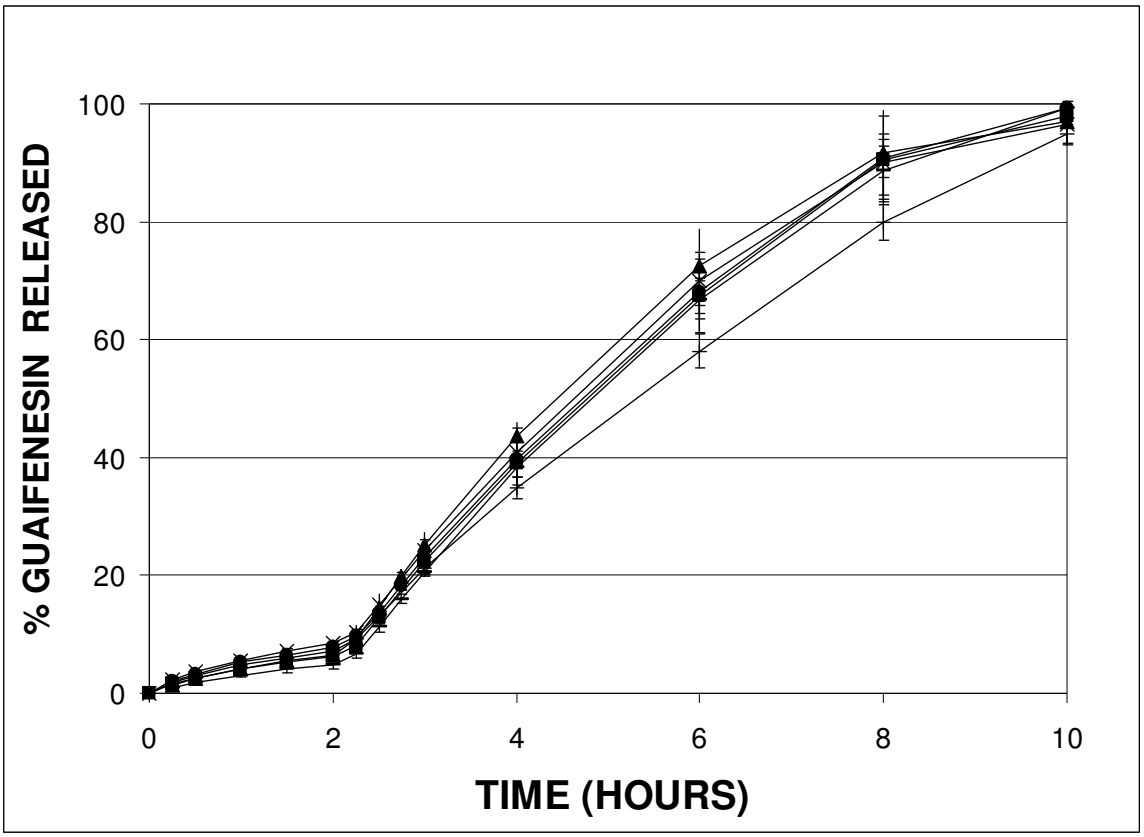


Figure 4.13 Influence of 10% crystallization inhibitor (based on drug content) on the dissolution of guaifenesin from tablets containing 25% guaifenesin and Eudragit L100-55®.

After 3 weeks of storage at 25°C/60% relative humidity.

Basket, 900 mL, 37±0.5°C, 50 RPM, 2 hours 0.1N HCl, 8 hours pH 6.8 phosphate buffer, n=6.

▲ Polycarbophil
X PEG 3350
O Poloxamer 188
■ PVP K25
- No additive,
+ Poly(ethylene oxide)

Chapter 5: The Influence of Heterogeneous Nucleation on the Surface Crystallization of Guaifenesin from Melt Extrudates Containing Eudragit® L100-55 or Acryl-EZE®.

Abstract

This study investigated the influence of heterogeneous crystallization due to humidity conditions in storage and talc as a formulation component on the amount of guaifenesin recrystallizing on the surface of melt-extruded matrix tablets. Tablets consisted of the model drug guaifenesin in a matrix of either Acryl-EZE® or Eudragit® L100-55 and either no talc, 25% or 50% talc. The guaifenesin-to-polymer ratio was held constant in all formulations. After processing, the hot-melt extruded matrix tablets were supersaturated with amorphous guaifenesin. The drug supersaturation in the polymer resulted in the development of guaifenesin drug crystals on exposed surfaces of the tablet upon storage. A quantitative test was developed to assay for surface guaifenesin, which was based on a 5-second immersion and intense movement of a tablet in a medium able to dissolve guaifenesin, but not the matrix. In tablets with a drug-to-polymer ratio of 19:81, only talc-containing tablets showed crystal growth after 4 days. The presence of talc increased the amount of surface crystallization. In tablets without talc (drug-to-polymer ratio of 37.5: 62.5), 0.15±0.02% of the total guaifenesin dose recrystallized within 15 days of storage at 17% RH. In tablets containing 25% or 50% talc, 0.37±0.05% or 0.37±0.02%, respectively, of the total guaifenesin dose recrystallized under identical storage conditions. The effect of talc was not concentration-depended, 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, as demonstrated on Acryl-EZE® tablets with an identical drug to polymer ratio, in which 0.26±0.037% of the total guaifenesin dose recrystallized after 15 days storage at 17% RH. High humidity during storage increased guaifenesin crystallization, but moisture uptake of tablets did not correlate with increased drug recrystallization. Storage at 78% relative humidity increased guaifenesin surface crystallization to 0.43±0.14% of total drug dose, up from 0.15±0.02% in tablets stored for the same duration at 17% RH (Eudragit® L100-55 matrix tablets without talc). Other tablets were stored at 17% relative humidity, and then moved to 78% relative humidity for 3 days before being returned to their previous low RH storage conditions. Recrystallization levels quickly increased during the high RH interval, and did not return to previous levels. When storage at 78% RH was interrupted by 3 days of low RH (17%), surface crystallization levels remained constant. Once nucleation was induced by atmospheric moisture, crystals remained on the tablet surface regardless of relative humidity conditions thereafter. Storage of melt-extruded dosage forms supersaturated with amorphous drug at high humidity and the addition of talc to the formulation was shown to induce and increase surface crystallization.

5.1 INTRODUCTION

Hot-melt extrusion (1, 2) has been employed to incorporate drugs into polymeric matrices (3-5). This process was shown 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 they move 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 (11) due to intense mixing during processing.

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, and 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 will be negatively affected by recrystallization. Furthermore, pure drug crystals located on the tablet surface can shear off, and thus diminish the 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). Figure 5.1 illustrates the problem and depicts the changes in the state of guaifenesin during melt extrusion. Guaifenesin melts during processing, since its melting point lies below the

extrusion temperature. The solubility of guaifenesin 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, if the matrix contains more then 20% drug (15). Recrystallization occurred quickly. Within 15 minutes, guaifenesin crystals developed on tablets with a guaifenesin-to-polymer ratio of 37.5 to 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® L100-55 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.

5.2 MATERIALS AND METHODS

5.2.1 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® L100-55 was provided by Evonik Degussa (Piscataway, NJ, particle size 95% below 250 micron). Triethyl citrate (TEC) was kindly donated by Vertellus (Greensboro, NC). The talc employed in the study (Imperial 500 USP, particle size 4.5 micron) was a gift from Luzenac (Centennial, CO). Drierite (Hammond, Xenia, OH) and sodium chloride, ACS reagent (Sigma-Aldrich, St. Louis, MO) were purchased.

5.2.2 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 5.1, and component functions are listed in Table 5.2. 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 40 minutes 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).

5.2.3 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 "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).

5.2.4 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.

5.2.5 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 to 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. Figure 5.2 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 (25x150 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 seconds, as timed by a stop watch. Immediately after vortex mixing, the medium was decanted and filtered through a 0.45 micron nylon filter. The filtered

medium containing the dissolved guaifenesin from the tablet surface was diluted in a 1-to-1 ratio with fresh medium. 200 microliter of the diluted sample was analyzed at 275 nm on a UV spectrometer (μQuant UV Spectrometer equipped with KC 4 software for data analysis, BioTek 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.

5.2.6 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 minutes 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.

5.2.7 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).

5.3 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).

5.3.1 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, formulations 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® L100-55 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® L100-55 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, air-borne 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.

5.3.2 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 Figure 5.3, Figure 5.6 and Figure 5.7, 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.

Figure 5.3 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 of 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 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.

5.3.3 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

Figure 5.4 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.

The correlation between polymer content and moisture uptake was further investigated by storing powder samples of Eudragit® L100-55 as well as the talc used in this study at 17% as well as 78% relative humidity. Figure 5.5 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.

5.3.4 Influence of relative humidity on guaifenesin recrystallization – continuous storage

To investigate the influence of relative humidity during storage, tablets containing Eudragit® L100-55, 37.5% guaifenesin and no talc were stored in open containers for 15 days. Figure 5.6 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 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.

5.3.5 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 Figure 5.7 and Figure 5.8. 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 4-fold 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.

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.

5.3.6 Identity of surface crystals

Mass spectrometry was employed to determine if 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.

5.4 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® L100-55 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 for 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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5.6 TABLES

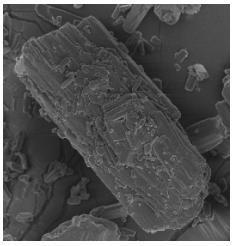
Table 5.1 Composition of hot-melt extruded tablets.

Formulation	Acryl-EZE® (%)	Guaifenesin (%)	Eudragit® L100-55 (%)	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

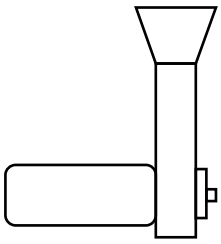
Table 5.2 Component Functions

Component	Function
Guaifenesin	Model Drug
Eudragit® L100-55	Polymeric matrix former
Triethylcitrate (TEC)	Plasticizer for Eudragit® L100-55
Talc	Glidant
Acryl-EZE®	Complete matrix blend

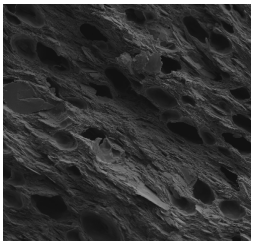
5.7 FIGURES



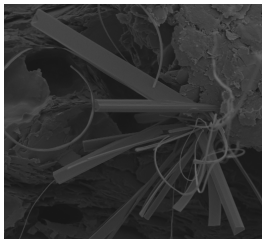
1. Crystalline Bulk Guaifenesin



2. Hot-melt Extrusion



3. Amorphous Guaifenesin in Matrix



4. Recrystallized Guaifenesin on Tablet Surface

Figure 5.1 The development of physical instability in hot-melt extruded tablets containing guaifenesin.

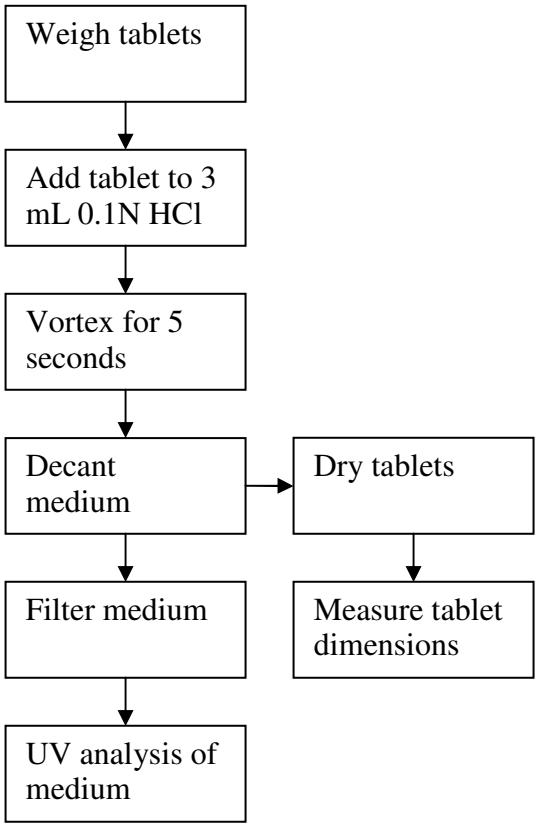


Figure 5.2 Flow diagram of the quantitative analysis of surface guaifenesin levels

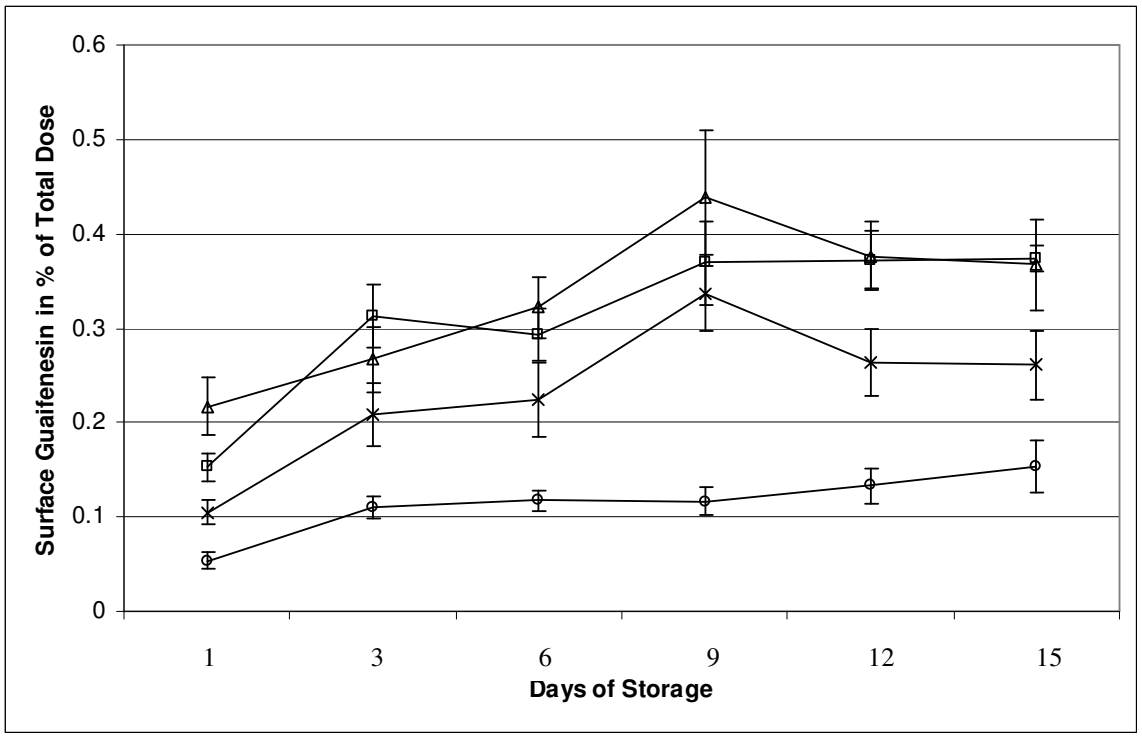


Figure 5.3 The influence of talc content on the recrystallization of guaifenesin.

All melt-extruded tablets contained the same guaifenesin-Eudragit® L100-55 ratio, and were stored at 24°C and 17% relative humidity, n=6.

○ No talc
Δ 25% talc
□ 50% talc
x Acryl-EZE® .

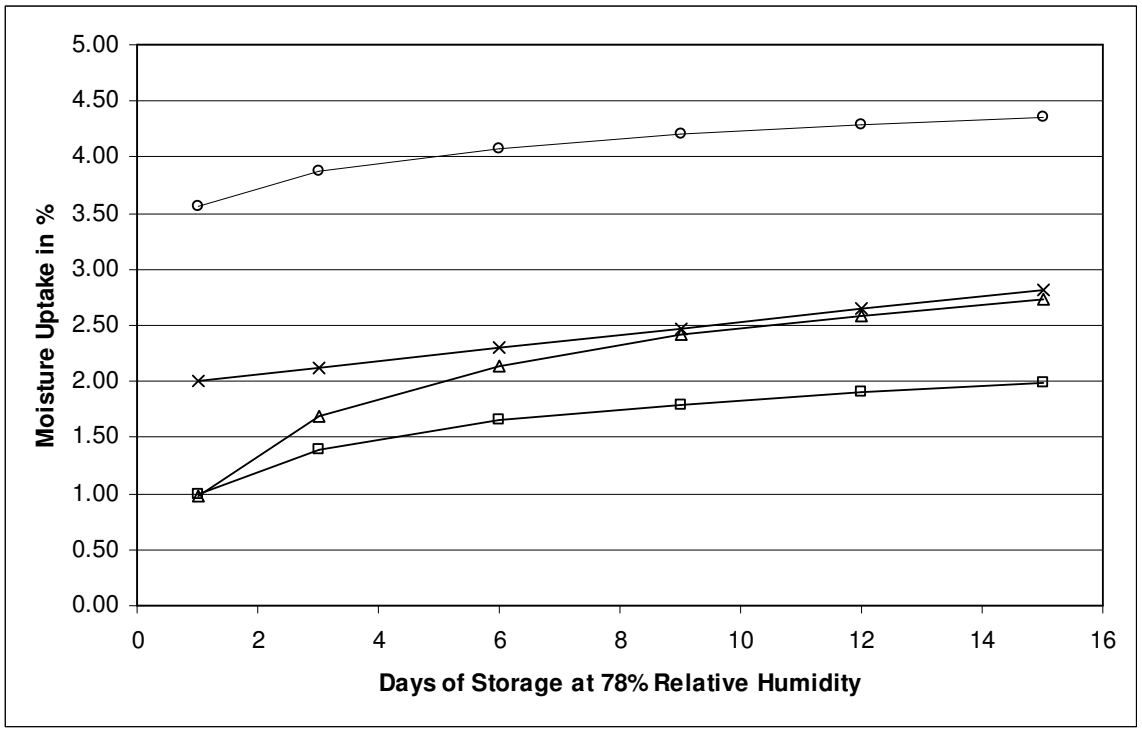


Figure 5.4. The influence of talc content on the water uptake of melt-extruded tablets.

All melt-extruded tablets contained the same ratio of guaifenesin to Eudragit® L100-55, storage at 24°C, n=3.

○ No talc
Δ 25% talc
□ 50% talc
x Acryl-EZE® tablets.

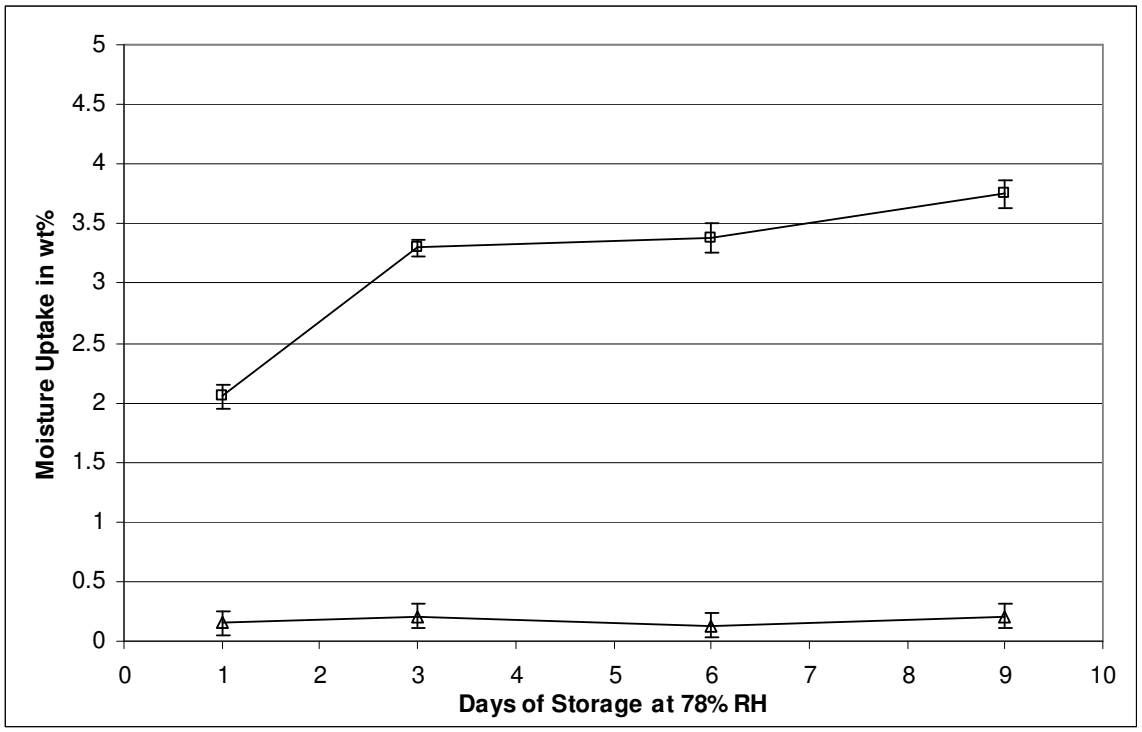


Figure 5.5. The influence of storage at 24°C and 78% relative humidity on the moisture content of excipient powders, n=3.

□ Eudragit® L100-55
Δ Talc.

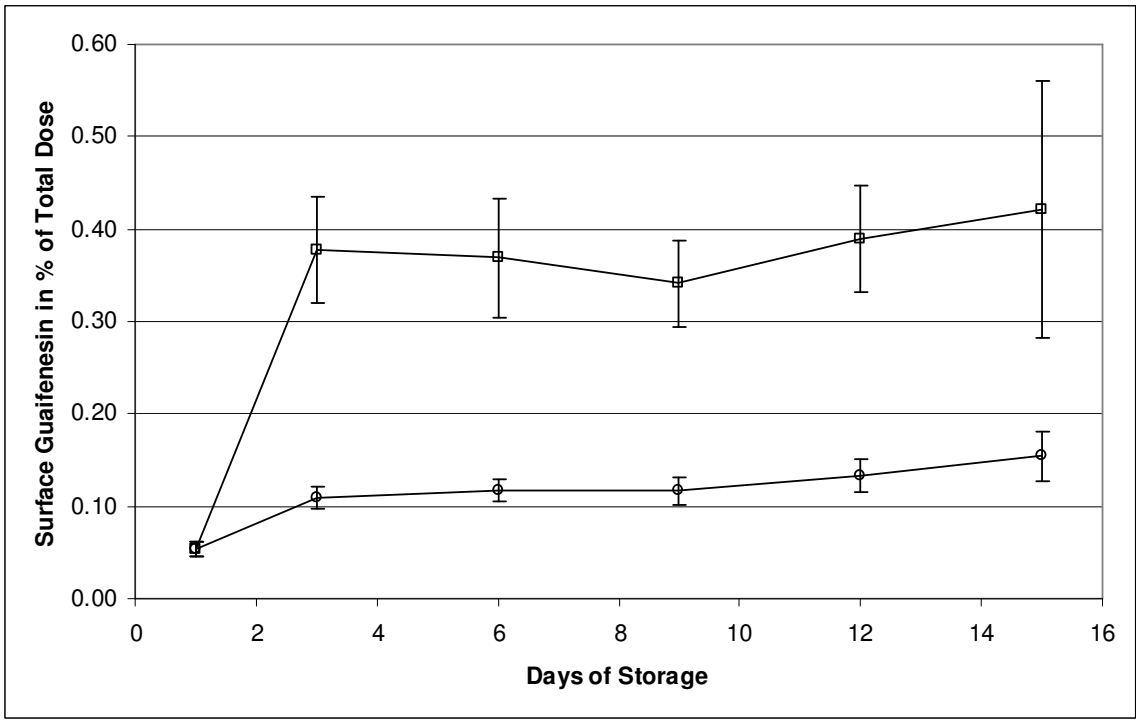


Figure 5.6. The influence of relative humidity conditions during storage on the recrystallization of guaifenesin on the surfaces of tablets containing 36.4% guaifenesin, 2.9% TEC and 60.7% Eudragit® L100-55

Storage temperature 24°C, n=6.

○ Storage at 17% relative humidity
□ Storage at 78% relative humidity.

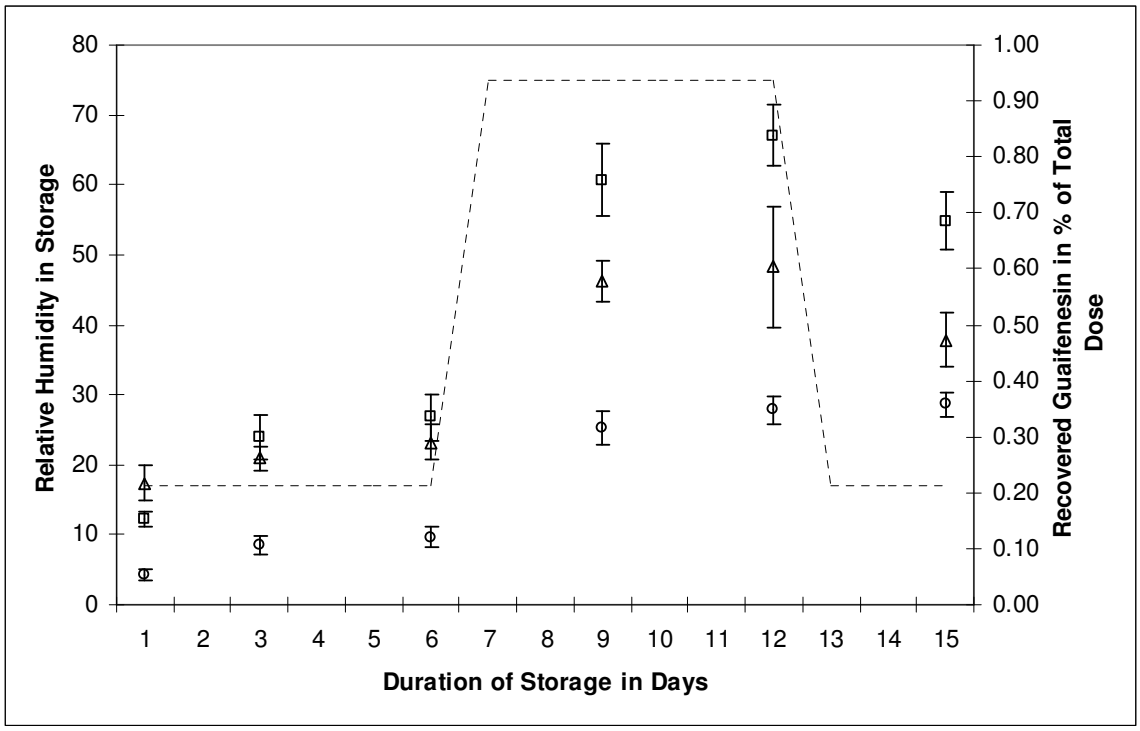


Figure 5.7 The effect of a temporary increase in relative humidity conditions on the surface crystallization of guaifenesin.

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® L100-55, storage temperature 24°C, n=6.

○ No talc
Δ 25% talc
□ 50% talc.

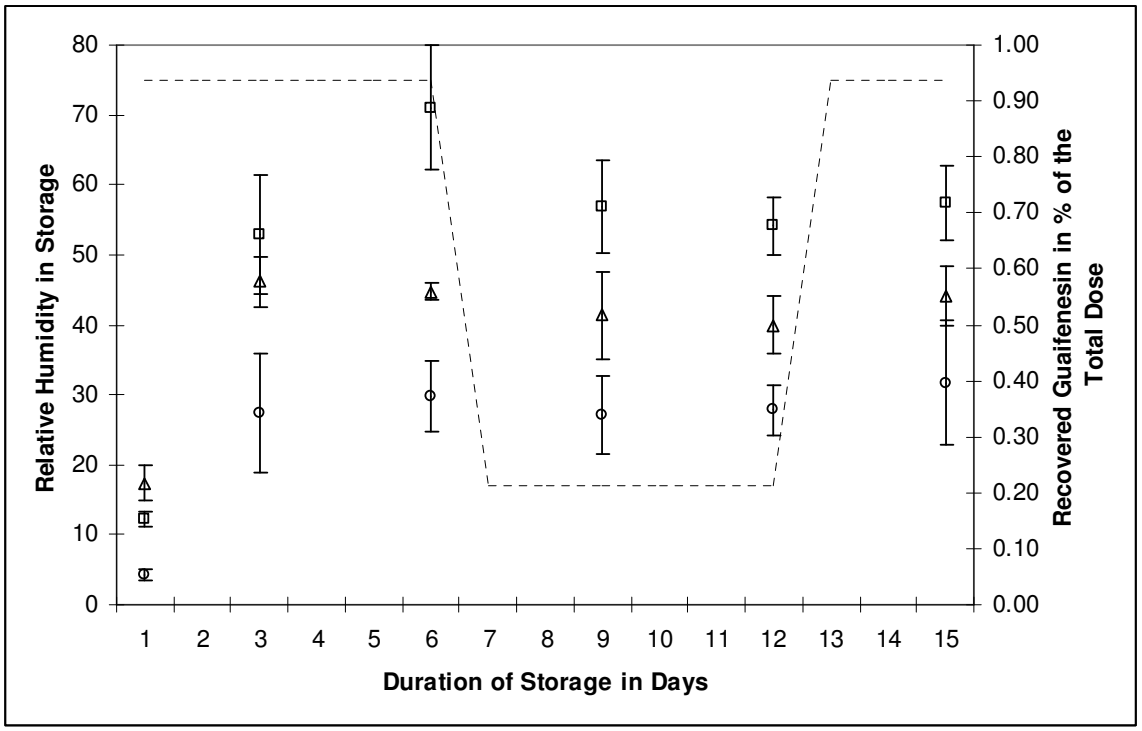


Figure 5.8. The effect of a temporary decrease in relative humidity conditions on the surface crystallization of guaifenesin.

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® L100-55, storage temperature 24°C, n=6.

○ No talc
Δ 25% talc
□ 50% talc.

Chapter 6: The influence of aqueous film-coating on the recrystallization of guaifenesin from hot-melt extruded acrylic matrix tablets

Abstract

This study investigated the effect of aqueous film-coating on the recrystallization of guaifenesin from acrylic, hot-melt extruded matrix tablets. After hot melt-extrusion, matrix tablets were film-coated with either hypromellose or ethylcellulose. The effects of polymer weight gain, curing conditions, storage temperature, and core guaifenesin concentration were investigated. The coating polymer was the most important factor determining the delay in the onset of crystallization, and crystal morphology was affected by the film coating. Ethylcellulose displayed a low solubility for guaifenesin, and at weight gains of either 7 or 15%, crystal growth occurred within 3 weeks (uncoated tablets: 30 minutes). Hypromellose was shown to have a high solubility for the drug, and at either 2 or 10% weight gain, films prolonged the onset of crystallization to 3-6 months. For a single polymer, greater film thickness resulted in a longer onset time of crystallization. Factors promoting drug and polymer diffusion, such as long curing times and elevated temperatures during both curing and storage, incomplete film coalescence and high core drug concentrations all contributed to an earlier onset of crystal growth. In conclusion, aqueous film coating of melt-extruded acrylic matrix tablets was demonstrated to retard the onset of recrystallization of amorphous guaifenesin, and the coating polymer influenced the delay in the onset of crystallization.

6.1 INTRODUCTION

The physical stability of amorphous drugs in dosage forms 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 in hot-melt extrusion, the change in solubilities at the elevated processing temperatures, compared to storage temperatures, also contributes to supersaturation (2).

The solubilization of drugs in polymeric matrices to form solid solutions has been investigated intensively. Earlier studies characterized the recrystallization of guaifenesin from the amorphous state on hot-melt extruded matrix tablets, and showed that extending the solubility of the drug in the matrix by adding hydrophilic polymers, in which the drug had a higher solubility, could reduce the amount of crystal growth (2). Subsequent studies demonstrated that formulation components, such as talc, and storage conditions, including humidity levels, can increase nucleation and crystal growth (3). In addition, the extrusion process used to manufacture the tablets (single-screw extrusion versus twin-screw extrusion) affected the properties of melt-extruded tablets, including their physical stability, due to differences in drug dispersion achieved by the equipment (4). Since crystal growth occurred on tablet surfaces, we investigated how the modification of surfaces through the application of an aqueous polymeric film-coating affected the guaifenesin recrystallization.

Polymeric materials have been used as barriers to diffusion in several applications, such as food products (5), packaging (6), membrane separations (7, 8) and sensors (9). Commercial film-coating systems have been developed to function as a moisture barrier (10). Relationships between water and gas permeabilities and membrane structure (11, 12) have been described, and transport mechanisms and behavior of block copolymers have been reviewed by Jonquières et al (13). Polymer morphology impacts diffusion through the matrix: crystallinity have been reported to be a major factor in permeation (11, 12), and amorphous regions throughout the sample may differ in structure, resulting in heterogeneous molecular mobilities (14). Barrier properties can be enhanced by the addition of compounds to the membrane that react with the molecules diffusing into the film (15).

Two polymers were selected based on their presumed interaction with guaifenesin, as derived from their respective chemical structures. Ethylcellulose as a hydrophobic polymer was expected to provide a barrier to the diffusion of hydrophilic guaifenesin due to their structural differences. A hypromellose film was anticipated to slow guaifenesin diffusion through the film as it was able to interact with guaifenesin via hydrogen bonding. The objectives of this study were to investigate the effect of aqueous film-coatings of hot-melt extruded matrix tablets on the physical stability of guaifenesin. The effects of polymer type, weight gain, curing time and temperature, storage conditions and core drug-to polymer ratio on the onset and extent of guaifenesin recrystallization were determined.

6.2 MATERIALS AND METHODS

6.2.1 Materials

Guaifenesin was used as the model drug, and was purchased from Spectrum (Gardena, CA). Acryl-EZE®, which was donated by Colorcon (West Point, PA), and Eudragit® L100-55, which was a generous gift from Evonik-Degussa (Piscataway, NJ, particle size 95% below 250 micron) were employed as matrix formers. The melt-extruded tablets were film-coated using Opadry® Clear YS-1-7006 (Polymer: hypromellose) and Surelease® (Polymer: ethylcellulose), which were donated by Colorcon (West Point, PA). FMC (Philadelphia, PA) provided Aquacoat® ECD 30 (Polymer: ethylcellulose). Dibutylsebacate (DBS) was used to plasticize ethyl cellulose, and triethylcitrate (TEC) was used to plasticize Eudragit® L100-55, both were gifts from Vertellus (Greensboro, NC). Films to investigate the solubility in polymers were cast using Ethocel standard 7 Premium (NF grade) by Dow Chemical (Midland, MI). 200 proof alcohol (USP grade) was purchased from AAPER Alcohol and Chemical Co (Shelbyville, KY).

6.2.2 Tablet Preparation

Tablets were prepared by hot-melt extrusion of the powder blends, followed by manual cutting of the extrudate strand. The formulations and the hot-melt extrusion parameters are presented in Table 6.1. 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 processing temperatures chosen for extrudates containing either Eudragit® L100-55 or Acryl-EZE® and guaifenesin were 65°C, 75°C, 85°C (zones 1, 2, 3, respectively) and 85°C (die). The extruder was equilibrated at the processing temperatures for a minimum of 40 minutes before extrusion. The extrudates were allowed to cool in a desiccator at room temperature for 1 day before manually cutting tablets. 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 desiccant Drierite® (Hammond, Xenia, OH) was obtained from Fisher Scientific.

6.2.3 Film-coating

Hot-melt extruded tablets were mixed with compressed placebo tablets up to a 1:1 weight ratio, and 300 gram batches (placebo plus melt-extruded tablets) were placed into a perforated pan-coater (HCT Mini HiCoater, Vector Corp, Cedar Rapids, IA), equipped with a peristaltic pump (505S Watson-Marlow, Wilmington, MA). The coating parameters are presented in Table 6.2. The coating dispersions were kept under constant low shear stir during preparation and the film-coating process. The tablets were coated to completion, and were dried for 10 minutes at the processing temperature in the rotating

pan. Some tablets were cured by placing them on open containers into ovens for the prescribed time. All tablets were stored in desiccators at 17% relative humidity until they were packaged.

6.2.4 Film Preparation

To investigate the solubility of guaifenesin in the coating polymers, drug-containing films of hypromellose, ethylcellulose and Eudragit® L100-55 were cast, stored at 17% relative humidity, and observed for signs of crystallization. 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. 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) 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).

6.2.5 Powder X-Ray Diffraction

Powder x-ray diffraction was used to study the morphology of guaifenesin and of the film-coating after SEM observations indicated crystal-like structures on the film. A coated tablet was arranged on a glass slide. The samples were scanned using a Philips Vertical Scanning Diffractometer, Type 42273 (Philips Electronic Instrument, Mount

Vernon, NY), employing CuKα radiation, operating at 40 kV and 30mA. The scan radius ranged from 10° to 60° degrees, and the step size was 0.05° every 4 seconds.

6.2.6 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 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 (Watford, UK) equipped with a thickness controller MTM 20 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 (Minneapolis, MN) equipped with a Gemini Column and SmartSEM software. The surface of the tablets was surveyed, and a representative area was chosen for the micrograph.

6.2.7 Assay for Surface Guaifenesin

An assay was developed to quantify the amount of guaifenesin on the tablet surface. Briefly, individual tablets were accurately weighed and a single tablet was placed into a large test tube (25x150 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) at a fixed

agitation force for 5 seconds. Immediately after vortex mixing, the medium was decanted and filtered through a 0.22 micron nylon filter (Puradics 25NYL syringe filter, Whatman, Maidstone, UK). The filtered medium containing the dissolved guaifenesin from the tablet surface 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).

6.2.8 UV Analysis of Guaifenesin

The guaifenesin content of samples from the surface guaifenesin assay was quantified at 273 nm in 400 microliter samples by UV spectroscopy (μQuant UV Spectrometer equipped with KC 4 software for data analysis, BioTek Instruments, Inc, Winooski, VT). 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.

6.3 RESULTS AND DISCUSSION

6.3.1 Choosing the coating polymers

At a drug concentration above the solubility limit, guaifenesin recrystallized from the amorphous state. Earlier studies characterizing hot-melt extruded matrix tablets which contained Eudragit® L100-55 and guaifenesin found that the drug concentration in the

matrix, the presence of nucleating agents and the processing conditions influenced the physical stability of guaifenesin (2-4).

The solubility of guaifenesin in both polymers and in Eudragit® L100-55 was measured by casting films containing one of the polymers and dissolved drug in increasing concentrations, and observing the physical stability during storage for 5 months at 17% relative humidity (Table 6.3). Recrystallization occurred in ethylcellulose films with 1% guaifenesin content, while hypromellose films solubilized 40% drug under the same conditions. Earlier studies found that the matrix-forming acrylic polymer, Eudragit® L100-55, could dissolve 20% guaifenesin (16).

Guaifenesin (Figure 6.1 a) is a hydrophilic molecule, with alcoholic and ether functional groups which enable it to hydrogen-bond to corresponding groups in the hydrophilic polymer hypromellose (Figure 6.1 b), while ethyl cellulose (Figure 6.1 c) is a hydrophobic material, whose lack of hydrophilic groups offers little hydrogen bonding interaction potential. Studies on barrier membranes indicated transfer by diffusion of small molecules depended on the intensity of interactions between the diffusing species and the polymer (14) Earlier studies from our group demonstrated that polymers with a higher solubility for guaifenesin than Eudragit® L100-55, such as hypromellose, were able to enhance the drug's solubility in a hot-melt extruded matrix when they were co-extruded with the acrylic polymer (2). By solubilizing guaifenesin, coating polymers function as a reservoir for the drug, and reduce guaifenesin supersaturation levels. In

addition, a polymeric film around a tablet minimizes the exposure of the amorphous drug to the environment containing impurities and moisture droplets, which can function as nucleating agents.

6.3.2 Film-coating of hot-melt extruded tablets

All coating operations were conducted in a perforated pan-coater (HCT HiCoater Mini). Coating parameters (Table 6.2) were chosen to promote complete film-formation and to minimize sticking and twin-formation. The tablets derived form hot-melt extrudates were initially flat-faced and cylindrical, a shape that can pose sticking problems during film-coating, regardless of the method used to prepare tablets (17). The elevated coating temperatures (35-45°C) softened the matrix, and Eudragit® L100-55 matrix tablets experienced sticking and twin-formation to a higher degree than Acryl-EZE® matrix tablets, since the talc in Acryl-EZE® functioned as a glidant and reduced stickiness of tablets. To counteract the sticking and twinning, the coating batch was made up of hot-melt extruded matrix tablets mixed with smaller, deep concave placebo tablets. These compressed tablets did not soften, and acted as spacers and buffers to reduce impacts between two hot-melt extruded tablets, reducing the number of twins.

A second phenomenon observed in the coating of hot-melt extruded tablets was the spheronization of the initially flat-faced tablets during film-coating. Tumbling the tablets in the coater at the processing temperature and RPM without spraying the coating

dispersion, or spraying deionized water at the same rate as the coating dispersion did not reproduce this effect. Spheronization was attributed to the presence of plasticizers in the coating dispersions, which diffused into the tablets and plasticized the matrix and, combined with the tumbling action of the pan, resulted in the change of tablet shape. In addition to the coating conditions, the age of the tablets (time after melt-extrusion) was of importance. Spheronization only occurred if the film-coating occurred within a few days of hot-melt-extrusion due to the development of surface crystallization on the tablets. Initially, small amounts of crystals are dispersed over the surface area of the tablet. As the recrystallization increased, a harder "crust" of crystals enveloped the tablet, which subsequently resisted deformation.

6.3.3 The influence of the film-coating layer on guaifenesin recrystallization

The recrystallization of guaifenesin from the amorphous state, which occurred within 30 minutes in uncoated tablets containing the same drug concentration as the coated tablets, was delayed when tablets were coated with either polymer. The polymeric film around the tablets separated the supersaturated matrix from exposure to the atmosphere containing impurities and moisture droplets. Bruce et al demonstrated that moisture can exert a nucleating effect on guaifenesin, which increased guaifenesin crystal growth (3).

When crystal growth appeared on film-coated tablets, the crystal morphology was altered compared to the crystals on uncoated tablets (Figure 6.2). While needle-shaped crystals grew outward in uncoated tablets, they developed within the film-coatings, and in hypromellose films, their habit changed. The identification by powder x-ray diffraction failed, as the amount of crystalline guaifenesin in the samples was below the detection limit of the matrix (about 5% (18) to 10% (19), Figure 6.3). The change in crystal habit in the presence of polymers (20) as well as polymer and surfactant combinations (21) has been reported, and was explained by viscosity effects and the preferential adsorption of polymers to some crystal faces due to hydrogen bonding, which retards the growth of those sites. The faster relative development of other crystal faces then changes the appearance of the crystal. Katzhendler et al describe a detailed mechanism for the hydrogen bonding interaction of carbamazepine and hypromellose to explain the polymer's effect on the drug (22). The change in the crystal habit of miconazole increased drug release from mucoadhesive patches (23), although no effect of recrystallization on drug release was found with the present system (2).

6.3.4 The influence of polymer type on guaifenesin recrystallization

Hypromellose prolonged the onset of drug release for 3-6 months (Table 6.5), while recrystallization in ethyl cellulose-coated tablets occurred within 3 weeks (Table 6.6). An assay detecting the guaifenesin present on the tablet surface was employed to

follow the increase in surface guaifenesin during storage (Figure 6.4). Determining the coating thickness before and after the test (Figure 6.5) showed that only the upper coating layer was dissolved in the assay due to the short immersion time, thus the assay captured guaifenesin present in the coating layer, and not from the matrix tablet. Hypromellose, was more efficient in delaying recrystallization. Polar interactions of drug and polymer facilitated guaifenesin solubilization, and delayed the onset of crystallization. Peppas et al found that drug-polymer binding impeded drug diffusion in hydrogels (24). Interactions between diffusants and polymers contribute to mass transport phenomena, and the diffusion through solid polymeric networks is complex (5).

Ethylcellulose was less effective than hypromellose in delaying the onset of guaifenesin, which was probably due to the amphiphilic nature of guaifenesin (it possesses a benzene ring, and short aliphatic chains), which enabled the transport through the hydrophobic ethylcellulose membrane. The low solubility of ethylcellulose for guaifenesin would quickly result in supersaturation of the film, followed by crystal growth on the surface.

6.3.5 The effect of weight gain and polymer film thickness

In both polymers, a higher polymeric weight gain prolonged the onset of crystallization (Table 6.5, Table 6.6). Increasing the hypromellose weight gain from 2% to 10% resulted in an increase in film thickness from 191 micron to 358 micron and a

delay in the onset of crystal growth form 3 to 5 months under identical storage conditions. A thicker film involves longer diffusion paths, and has a higher polymeric volume, which can solubilize higher amounts of drug. Such a film takes longer to reach supersaturation levels that trigger nucleation and crystal growth. However, polymer weight gain was not a predictor of the onset time of crystallization when comparing two different coating polymers. The data in Table 6.4 show that the higher film thickness of ethylcellulose coatings did not delay crystallization compared to hypromellose films (Table 6.5). The polymer type had a much larger influence on crystal growth than the film dimensions.

6.3.6 The effect of temperature during curing and in storage

Tablets stored at higher temperatures developed recrystallization earlier (Table 6.5). Drug diffusion in polymers has been investigated by Zhao et al by molecular modeling of aspirin in polymer blends (25). The “wiggling” of polymer chains was found to be more important for the drug diffusion than its free volume. 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” (26-28). Zhao et al proposed that due to the bigger size of drug molecules compared to the gases, aspirin could not skip-jump between different cavities of free volume in the polymer, but rather moved forward with the wiggling of the polymer chains. This concept

is useful in explaining the observations made in this study. The change in crystallization rates with temperature in amorphous drugs were studied by Aso et al (29), who ascribed faster crystallization in part to higher molecular mobility. In general, the kinetic energy of molecules increases with temperature, resulting in higher molecular mobility and a faster diffusion of drug molecules through the polymer strands.

Curing is performed to complete film coalescence after film-coating. Hypromellose-coated tablets were cured for 24 hours at 40°C, and complete coalescence was observed in all cases, which was another factor influencing their effectiveness to prevent recrystallization.

In ethylcellulose-coated tablets, film coalescence and the prevention of recrystallization posed conflicting goals. Since film coalescence in uncured tablets was incomplete after coating (cracks in the film were visible under SEM directly after the process), a curing step was necessary to conclude film formation. Curing for 24 hours at 60°C was effective in attaining film coalescence, as observed under the SEM. However, in tablets cured at 60˚C for 24 hours, crystal formation was observed after one week regardless of matrix composition. Crystallization in uncured tablets differed despite equal storage conditions. Some tablets showed crystal growth, while others were crystal free. This was ascribed to different degrees of film formation in these tablets. Cracks in the film due to incomplete film formation resulted in easier access to the surface, while

curing at elevated temperatures promoted drug migration into the film. Both mechanisms hastened drug recrystallization.

6.3.7 The effect of drug-to-polymer ratio in the core tablet composition

Table 6.6 shows the impact of drug concentration in the core on the onset of guaifenesin crystal growth. For both matrix formers, a higher guaifenesin levels in the core tablets resulted in a higher drug-to-polymer ratio and an earlier onset of crystal growth, since the supersaturation of guaifenesin in the matrix was the driver for the recrystallization from the amorphous state.

6.4 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 of the amorphous drug from ubiquitous nucleating agents by covering the tablet surface. The drug morphology of guaifenesin crystals was altered due to the presence of polymers. Most formulation and processing factors investigated (polymer type; weight gain; curing time and temperature; storage conditions; and core drug-to polymer ratio) all affect diffusion, and promoting diffusion of either guaifenesin or the polymer resulted in an earlier onset of recrystallization. The choice of coating polymer was the largest single factor affecting the onset time of crystallization. In conclusion, the film-coating of hot-

melt extruded, acrylic matrix tablets successfully delayed the onset of guaifenesin recrystallization for up to 6 months.

6.5 ACKNOWLEDGEMENT.

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6.7 TABLES

Table 6.1 Formulation and extrusion parameters of hot-melt extruded tablets

Matrix Tablet Composition		Temperature Zones 1-2-3-die (°C)	Screw Speed (RPM)	Motor current (amps)
20% Drug	80% Acryl-EZE®	90 – 95 – 110 - 115	20	140±10
25 % Drug	75% Acryl-EZE®	80 -85 -90 - 90	20	165±5
20% Drug	80% Eudragit® L100-55*	70 – 85 – 90 - 95	20	322±9
37% Drug	63% Eudragit® L100-55*	80 – 85 – 85 - 90	15	157±8

*An additional 4.8% TEC (based on polymer weight) were added to the polymer.

Table 6.2 Coating parameter

Coating Polymer	Aquacoat®ECD	Opadry®
Apparatus	HiCoater HCT Mini	HiCoater HCT Mini
Batch Size	300 g	300 g
Spray Air	0.25 kg/cm2	0.25 kg/cm2
Spray Rate	1.5 g/min	2.0 g/min
Inlet Air	55-60 °C	75 °C
Outlet Air	41°C	42°C
Pan Speed	40 RPM	20 RPM
Drying	10 min	10 min
Curing	60°C/2 hrs or none	40°C/2 hrs
Solids Content	20	10
Weight Gains	7 and 15%	2 and 10%

Table 6.3 The solubility of guaifenesin in the coating polymers

Storage for 5 Months at 25°C/17% RH.

Coating Polymer	Drug concentration at which crystallization was first visible % w/w
Ethylcellulose	1%
Eudragit® L100-55®	21%
Hypromellose	40%

Table 6.4 Film thickness of coated tablets.

Based on measurements from SEM micrographs, reported value is the average of three determinations.

Coating Polymer	Film Thickness (lower tablet weight gain) (μm)	Film Thickness (higher tablet weight gain) (μm)
Opadry®	191.4	358.2
Aquacoat® ECD	150.7	503.1

Table 6.5 The effect of hypromellose weight gain and storage conditions on the onset time of crystallization for melt-extruded matrix tablets coated with hypromellose.

Tablets were cured for 24 hours at 40˚C.

Core Tablet Matrix former	Eudragit® L100-55 (Guaifenesin Concentration 37.5%)		Acryl-EZE® (Guaifenesin Concentration 25%)	
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

Table 6.6 The effects of guaifenesin concentration in matrix tablets containing either Eudragit® L100-55 or Acryl-EZE® on the recrystallization of guaifenesin from the amorphous state.

Tablets were cured for 2 hours at 60˚C and were stored in induction-sealed containers at 40˚C/75% relative humidity.

Matrix former	Eudragit® L100-55		Acryl-EZE®	
Guaifenesin Concentration	20%	25%	20%	37.5%
24 Hours after Coating	no	no	no	no
2 Weeks	no	yes	no	yes
3 Weeks	yes	yes	yes	yes

No – tablet surface was free of crystal growth
Yes – crystals were visible on the surface

6.8 FIGURES

Figure 6.1 (a) Guaifenesin (taken from Ref (30))

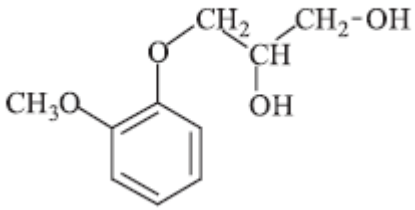
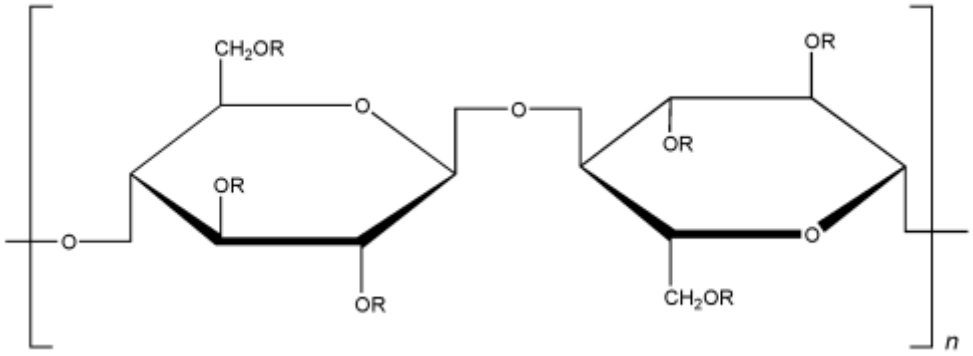
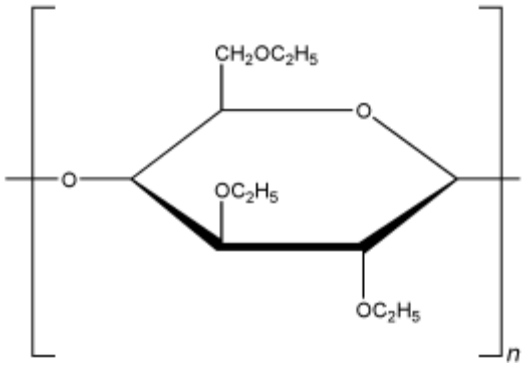


Figure 5.1 (b). Hypromellose (taken from Ref (31))



where R is H, CH3, or CH3CH(OH)CH2

Figure 5.1 (c). Ethylcellulose (taken from Ref (31))



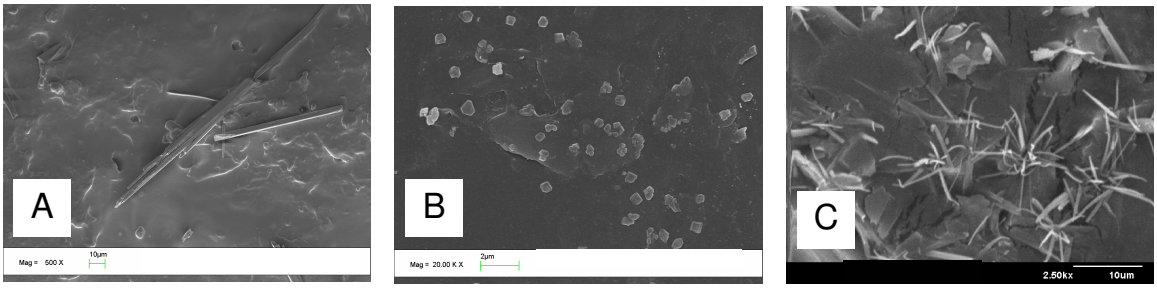


Figure 6.2 The influence of coating polymers on the growth of guaifenesin crystals.

A-ethyl cellulose-coated tablets
B-hypromellose-coated tablets
C-uncoated tablets

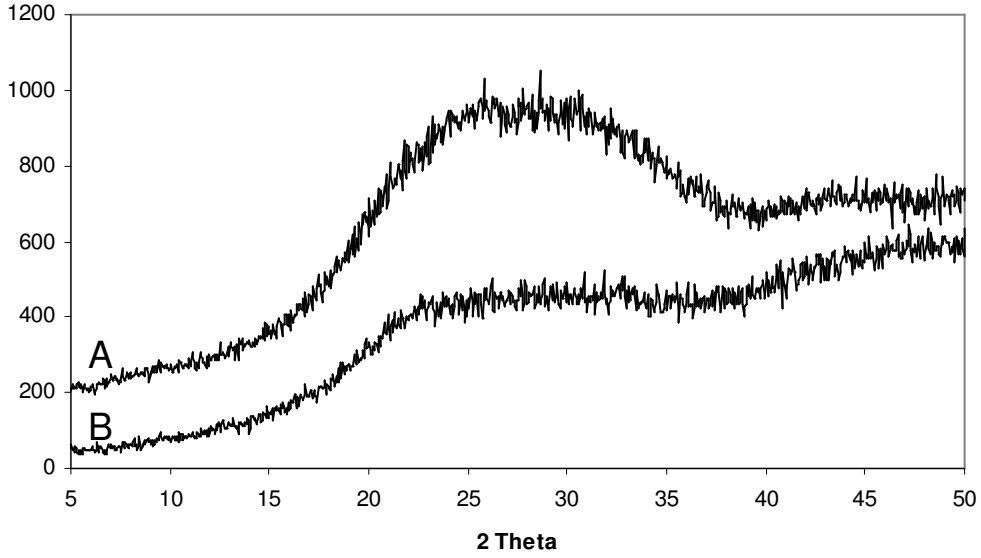


Figure 6.3 The influence of 4 months of storage at 25˚C/60% relative humidity on the surface morphology of film-coated matrix tablets.

PXRD scan at 40 kV and 30mA. The scan radius ranged from 10° to 60° degrees, and the step size was 0.05° every 4 seconds.

A-Acryl-EZE® tablets coated with Opadry 4 months
B-Eudragit® L100-55 tablets coated with Opadry 4 month

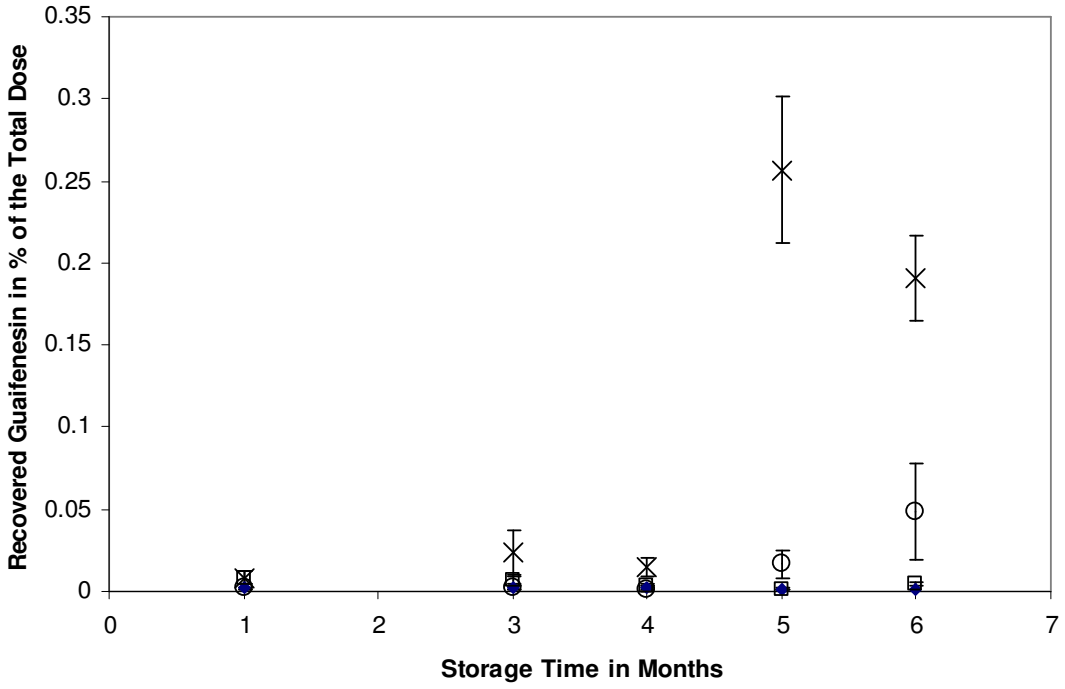


Figure 6.4 The influence of storage time on the recrystallization of guaifenesin hot-melt extruded matrix tablets film-coated with Opadry

10% polymer weight gain, n=6.

◊ - 25 C/60%RH Eudragit® L100-55 **□ - 25 C/60%RH Acryl-EZE®**
○ - 40 C/75%RH Eudragit® L100-55 **X - 40 C/75%RH Acryl-EZE®**

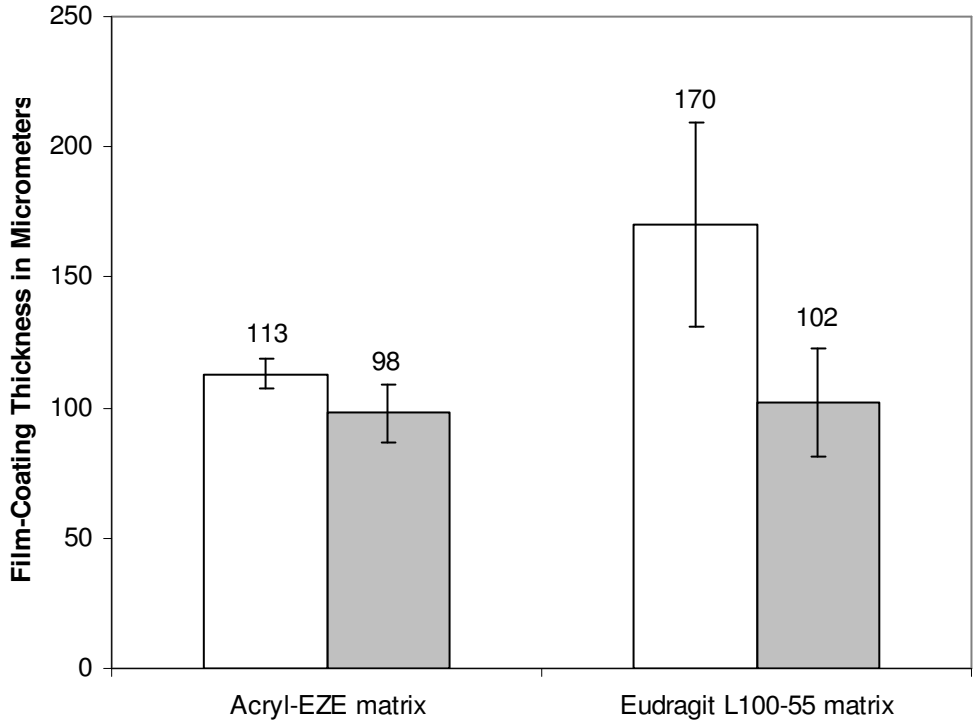


Figure 6.5 Influence of the quantitative analysis process on the film thickness of Opadry-coated tablets

n= minimum of 6 individual measurements.

Chapter 7: Properties of extruded tablets produced by either single-screw or twin-screw melt extrusion

Abstract

This study investigated the effect of single-screw extrusion (SSE) and twin-screw extrusion (TSE) on the properties of melt-extruded tablets containing guaifenesin and diltiazem hydrochloride (DIL) in an acrylic matrix. Tablets containing both drugs in a matrix of Eudragit® L100-55 were produced by extruding powder blends on either a single-screw (Randcastle Microtruder) or on a twin-screw extruder (Haake MinilabII Microcompounder) at three different temperatures, 75, 95 and 125°C. Tablets containing guaifenesin and the same acrylic polymer were extruded at five separate temperatures between 65 and 125 °C. Thermal analysis demonstrated that guaifenesin solubilized DIL, and plasticized Eudragit® L100-55, while DIL did not affect properties of guaifenesin or the polymer. Powder x-ray diffraction (PXRD) of guaifenesin-containing tablets extruded on the single-screw extruder at lower processing temperatures (65°C) demonstrated partial crystallinity of the drug, which was absent in tablets produced by twin-screw extrusion at the same temperature. Extrusion at 125°C resulted in amorphous extrudates in both units. Energy dispersive spectroscopy (EDS) of DIL-containing tablets revealed drug clusters in tablets produced at low temperatures on both extruders, while the drug distribution improved with processing temperature. Regardless of extrusion temperature, the twin-screw extruder yielded extrudates in which the DIL was more homogeneously dispersed. To study the effect of drug dispersion on tablet properties, drug content in

tablets, drug release profiles and physical stability of guaifenesin were investigated. Heterogeneous drug dispersion at the microscopic level did not translate into differences in drug content for an entire tablet. Drug release in phosphate buffer pH 6.8 was dominated by matrix erosion, and was not influenced by processing temperature and extruder type. In simulated gastric fluid without pepsin, tablets extruded at 125°C on the twin-screw extruder showed a significantly lower drug release rate than other formulations. This can be attributed to higher matrix integrity after surface drug dissolution due to a high degree of drug dispersion. Guaifenesin was physically unstable, as it was rendered amorphous by the extrusion process, and recrystallized on storage due to supersaturation in the matrix. An assay for quantifying guaifenesin surface crystallization demonstrated that formulations extruded on the twin-screw extruder developed less surface crystal growth than single-screw extrudates over 16 days. The more homogenous drug distribution achieved by twin-screw extrusion resulted in lower local guaifenesin supersaturation levels, which reduced the driving force of crystallization. This study demonstrated that properties of melt-extruded tablets depended on the degree of drug dispersion, which was influenced by extruder type and process parameters.

7.1 INTRODUCTION

Hot-melt extrusion is a versatile processing technique (Crowley et al., 2007, Repka et al., 2007, Repka et al., 2002) which enables the production of solid solutions of poorly

water soluble drugs (Breitenbach, 2002, Forster et al., 2001, Leuner and Dressman, 2000). Blends are fed into the heated barrel, and the mass is conveyed towards the die by one (single-screw extruder) or two (twin-screw extruder) rotating screw(s). While the residence time in the extruder barrel at elevated temperatures is in the order of minutes, a number of unit operations can be performed in an extruder (Riaz, 2000), including pumping and conveying, mixing and compounding as well as venting of gases.

Typical pharmaceutical compositions contain an active ingredient blended with a matrix former, glidant, release modifier and other excipients. Extrusion can occur above or below the melting point of the active ingredient. Solid solutions (Leuner and Dressman, 2000) form when the drug melts under the processing conditions, and is molecularly dispersed in the polymer (or the polymer blend). When the melting point of the drug lies above the extrusion temperature, the drug can dissolve in the molten polymer, or another matrix component such as citric acid (Schilling et al.), resulting in a solid solution. In a solid dispersion, the drug particles are finely dispersed throughout the matrix, but do not dissolve in the matrix. The physical state and degree of mixing in the melt are “frozen” in place as the extrudate cools after exiting the die.

The physical stability of such solid solutions depends on the concentration of the active and its solubility in the matrix. Earlier studies demonstrated a 20% w/w solubility of guaifenesin in Eudragit® L100-55 (Dietzsch et al., 2005), and extrudates with a drug concentration below the solubility limit were physically stable over the 6 month study.

When the solubility limit was exceeded, the amorphous compound recrystallized within 30 minutes at a guaifenesin concentration of 37.5%. (Bruce et al., 2007a).

Mixing increases the tendency towards uniformity in a formulation. The mixing of polymers in melt extrusions has been discussed by Rauwendaal (Rauwendaal, 1991) and White (White et al., 2001). If the active does not melt during the process, the particles can be reduced in size or deagglomerated (dispersive mixing) or are just homogeneously blended with the melt (distributive mixing), depending on the processing conditions and extruder specifications. Thermal homogenization refers to distributive mixing in liquids. In melt extrusion, the screw design determines whether distributive or dispersive mixing will dominate the mixing action of a particular screw or screw element. This is determined by the shape of the screw, and how it interacts with the melt. Distributive mixing occurs as the melt flow is divided and recombined, while stretching and folding promote dispersive processes. In twin-screw extruders, the mixing effect of the screw can be customized by assembling the screw using several smaller units which can have different designs and thus differ in their mixing action.

Mixing in single-screw extruders is influenced by a number of factors, and different screw designs exist to enhance mixing. The channel depth in flighted screws decreases along the length of the screw, compressing the material as it moves toward the die, which does not promote homogeneous distribution (Luker, 2003). Material properties influence the transport in the barrel, since it depends on frictional interactions between

the material, the screw and the barrel (Wildi and Maier, 1998). The feeding rate influences the mean transit time and filling of the barrel, which affects the mixing efficiency and extrudate properties in products extruded on a single-screw extruder (Ding et al., 2005, Luker, 2003, Yeh et al., 1992). Extruder screws are divided into sections to perform different unit operations; a typical set-up successively includes a feeding, melting and a metering section, and then the die. Mixing often occurs close to the die, when the material in the barrel is fully melted, and viscosity is near its minimum to take advantage of the pressure generated upstream (Luker, 2003). This arrangement is well suited for melt homogenization (distributive mixing), but reduces the ability of the extruder to perform dispersive mixing, which requires a higher stress rate to overcome the yield points of the morphological units that are to be reduced in size. In recent years, improved single-screw extruder screw designs (Markarian, 2004) have been developed which increase distributive and dispersive mixing and enable venting.

Material transport in co-rotating twin-screw extruders works by the same fundamental mechanism, but the presence of the second screw decreases the dependence on material properties (Dreiblatt, 2003). In twin-screw extrusion, the two screws can be configured with elements that perform different processes, including forwarding, distributive or dispersive mixing, and zoning (White et al., 2001). Such a set up can be customized for a specific application by combining screw elements of different designs. These extruders can also accommodate additional feeds further down the barrel, enabling

the introduction of temperature-sensitive substances into the molten, compounded matrix to minimize the exposure to higher temperatures necessary to prepare the matrix.

The effect of extruder type on product properties has been investigated for the dispersion of fillers in polymers (Cho and Paul, 2001, Dennis et al., 2001). In these studies, twin-screw extrusion yielded more uniform products, and was able to exfoliate the filler clays due to better dispersive mixing in these extruders. Lower levels of filler were necessary to achieve similar improvements in mechanical properties in composites produced by twin-screw extrusion (Wu et al., 2002). However, complete homogeneity is not always necessary to improve the properties of extruded products. Six et al demonstrated that the melt-extruded dispersions of itraconazole with hypromellose had a heterogeneous composition (Six et al., 2003), yet the dissolution rate of an extruded itraconazole matrix was comparable to the commercial Sporonox® formulation (Six et al., 2005).

The current study was undertaken to investigate the behavior of blends containing guaifenesin and diltiazem hydrochloride (DIL), drugs with a low and a high melting point, respectively, in melt extrudates and to compare the mixing efficiencies of a single-screw extruder and a twin-screw extruders on a molecular level, followed by as assessment of how the degree of mixing translated into differences in tablets properties produced by these two techniques. The objectives of this study were, first, to characterize the thermal properties of guaifenesin-DIL blends, and to measure their effect on the

matrix former, Eudragit® L100-55. Secondly, the goals of this study were to examine drug morphology (in guaifenesin-containing tablets) and the drug distribution (in DIL-containing extrudates) of melt-extruded tablets produced by either single-screw or a twin-screw extrusion and to investigate the effect of extruder type on the drug content of the extrudates, their dissolution rate, and the recrystallization of guaifenesin from the amorphous state on storage.

7.2 MATERIALS AND METHODS

7.2.1 Materials

Guaifenesin and diltiazem hydrochloride (DIL) were purchased from Spectrum (Gardena, CA). DIL was sieved, and only the particle fraction smaller than 75 micron (200 mesh) was used for this study. Eudragit® L100-55 was provided by Evonik Degussa (Piscataway, NJ, particle size 95% below 250 micron). Colloidal silicon dioxide (Cab-O-Sil M-5P, Cabot Corporation, Alpharetta, GA, average particle size 0.2-0.3 micron) was kindly donated by Cabot. The desiccant Drierite® (Hammond, Xenia, OH) was obtained from Fisher Scientific.

7.2.2 Tablet Preparation

Tablets were prepared by hot-melt extrusion of powder blends on either a single-screw (SSE) or a twin-screw extruder (TSE), followed by manual cutting of the extrudate

strand. The formulations are presented in Table 7.1. To prepare tablets by single-screw extrusion, premixed powder blends were fed into a Randcastle extruder (Randcastle Microtruder® Model RCP-0750, Cedar Grove, NY) equipped with a Nitralloy 135M flighted screw (L/D ratio 42, 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 a minimum of 40 minutes before extrusion. Extrusions were carried out at constant temperatures, only the feeding zone (in the single-screw extruder) and the force feeder (in the twin-screw extrusion) were set to lower temperatures to facilitate material flow into the extruder. In the single-screw extruder, the first temperature zone (feeding section) was set to 65°C for all extrusions, and the remaining two temperature zones (melting and metering sections) and the die were set to the same temperature for any given extrusion. To extrude guaifenesin-containing tablets (formulation I), separate extrusions were carried out at 65, 75, 85, 95 and 125°C. Tablets containing guaifenesin and DIL (formulation II) were extruded at 75, 95 and 125°C. Identical powder blends were processed at the same temperatures on a twin-screw extruder, (Haake Minilab II Microcompounder, ThermoScientific, Waltham, MA) equipped with a single heating zone, a conical flighted screw (L/D ration 7.82-21.9), a water-cooled force-feeder and a round die (diameter 2 mm). The melt was not circulated through the back-flow channel. Processing parameters are listed in Table 7.2. All extrudates were allowed to cool at room temperature for 24 hours in a desiccator before being manually cut into tablets.

7.2.3 Thermal analysis

Differential scanning calorimetry (DSC) was used to determine the melting points of guaifenesin and diltiazem hydrochloride in binary powder blends and in the extrusion blend. Modulated DCS (MDSC) was used to determine the glass transition temperature of Eudragit® L100-55 in mixtures with the drugs and the extrusion blend. All powder blends were prepared in a ceramic mortar and pestle. Three to seven milligram samples were analyzed in crimped aluminum pans (Kit 0219-0041 Perkin-Elmer Instruments, Norwalk, CT) on a calorimeter (Thermal Advantage Model 2920, 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. per minute. The DSC analysis was conducted from 50 to 230°C at a heating rate of 10°/minute. MDSC determinations proceeded from 50 to 170°C at a heating rate of 15°C/minute with a temperature amplitude of 0.5° every 40 seconds.

7.2.4 Powder X-Ray Diffraction

Powder x-ray diffraction was used to study the crystalline or amorphous state of drug and polymer in extrudates and the physical mixture containing guaifenesin. The powder samples were screened prior to analysis, and a thin powder layer was prepared. Cross-sections of extrudate rods were placed on sample holders. The samples were scanned using a Philips Vertical Scanning Diffractometer, Type 42273 (Philips Electronic Instrument, Mount Vernon, NY), employing CuKα radiation, operating at

40kV and 30mA. The scan radius ran from 10° to 40° degrees, and the step size was 0.02° every 2 seconds.

7.2.5 Scanning Electron Microscopy (SEM) and Energy-Dispersive Spectroscopy (EDS)

To study the effect of processing temperature as well as extruder type on the tablet morphology and the molecular dispersion of the drug within the extruded matrix, tablets containing DIL were prepared by either single-screw or twin-screw extrusion, and analyzed by SEM-EDS. 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 (Watford, UK) equipped with a thickness controller MTM 20 at 2.5 kV, 20 mA under Argon. SEM imaging and EDS mapping were carried out using a LEO 1530 electron microscope (LEO Electron Microscopy, Thornwood, NY) equipped with a Gemini field emission column and a Gresham Sirius 10 detector (e2v scientific instruments, Woburn, UK) for EDS. SEM micrographs were captured at 10 kV using LEO-32 software. EDS mapping of carbon, oxygen and chlorine present in the sample was carried out using EDS2006 software (IXRF systems, Houston, TX). Each sample was investigated in both cross-sections as well as longitudinal sections through the extrudate strand in at least 3 distinct locations to ensure that the scans were representative.

7.2.6 Drug Content Determination

The drug content was determined to study the drug distribution in the extrudates. Thin sections of the extruded rods were accurately weighed and placed in volumetric flasks containing 100.0 mL of phosphate buffer pH 6.8 (n=3). After the sections had dissolved, the medium was filtered through a 0.22 micron nylon filter (Puradics 25NYL syringe filter, Whatman, Maidstone, UK). The drug content of each sample was analyzed by UV testing as described in section 2.8.

7.2.7 In-Vitro Drug Release Testing

Dissolution testing was performed to study the drug release properties of tablets in a USP 30 Apparatus 1, basket method (Varian Industries, Inc. VK 7000, Palo Alto, CA) equipped with an auto sampler (Varian VK 8000, Palo Alto, CA). Dissolution studies of guaifenesin tablets were conducted in 900 mL 0.05 M phosphate buffer pH 6.8 (n=3) at 37°C and 50 rpm for 8 hours. Dissolution studies on melt-extruded tablets containing DIL and guaifenesin were conducted in 900 mL simulated gastric fluid without pepsin (n=3) at 37°C and 50 rpm for 8 hours. At the end of each dissolution test, complete drug release was obtained by mixing the vessel contents with a homogenizer for one minute to ensure total disintegration of the tablets. The dissolution samples were filtered through a 0.22 micron nylon filter (Puradics 25NYL syringe filter, Whatman, Maidstone, UK) to remove insoluble excipients before quantifying the drug by UV spectroscopy.

7.2.8 Assay for Crystalline Surface Guaifenesin

Melt-extruded tablets containing guaifenesin were assayed for surface crystallized drug substance using the procedure described in Figure 7.1. Briefly, individual tablets were accurately weighed and a single tablet was placed into a large test tube (25x150 mm) filled with 5.0 mL of 0.1 N HCl. The test tube was subjected to vortex mixing (SP vortex mixer, Baxter Diagnostic, Deerfield, IL) at a fixed agitation force for 5 seconds. Immediately after vortex mixing, the medium was decanted and filtered through a 0.22 micron nylon filter (Puradics 25NYL syringe filter, Whatman, Maidstone, UK). The filtered medium containing the dissolved guaifenesin from the tablet surface 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). Test conditions, including immersion time, vortex intensity, vessel size and dilution for the UV test, were chosen to ensure discrimination between samples.

7.2.9 Sample Analysis

The drug content in samples from dissolution testing, drug content analysis and recrystallization testing was determined by UV analysis. The guaifenesin content was quantified at 273 nm in 400 microliter samples by UV spectroscopy (μQuant UV Spectrometer equipped with KC 4 software for data analysis, BioTek Instruments, Inc, Winooski, VT). 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.

DIL was analyzed at 230 nm using the same instrument. For drug content analysis, 50 microliter samples were diluted with 350 microliters of 0.05M phosphate buffer pH 6.8. Dissolution test samples were diluted with simulated gastric fluid without pepsin in a 1 to 1 ratio. Linearity was established for drug concentrations between 10 and 200 mg/mL (R^2=0.9994).

7.3 RESULTS AND DISCUSSION

7.3.1 Thermal analysis

The two drugs were chosen based on their melting points in relation to the processing temperatures. Thermal analysis was employed to study the mutual influence of the two active ingredients. DSC analysis of guaifenesin-DIL blends was used to determine the melting points of guaifenesin (81.2°C) and DIL (215°C, Table 7.3). The melting peak of DIL was present in 1:9 blends (guaifenesin:DIL), but was absent from the thermogram in 1:1 and 9:1 (guaifenesin:DIL) mixtures. The disappearance of the DIL's melting peak was ascribed to the solubilization of DIL in the guaifenesin melt during the analysis. A similar event was reported by Schilling et al, who demonstrated that DIL was solubilized by citric acid during melt extrusion (Schilling et al.). The

similarity is plausible given that both citric acid and guaifenesin are small, hydrophilic molecules with hydroxy functional groups (-OH) in the alpha position.

The effect of the drugs on the carrier, Eudragit® L100-55, was measured by MDSC (Table 7.4). In the presence of 11.25% guaifenesin, the glass transition temperature (Tg) of Eudragit® L100-55 decreased from 125.2 ± 3.67 to 93.8 ± 0.56, both for the binary guaifenesin-polymer blend and for the extrusion blend, demonstrating that guaifenesin plasticized the polymer as reported earlier (Bruce et al., 2007b). Guaifenesin was demonstrated to plasticize other polymers, such as polyethylene oxide (Crowley et al., 2004a). The presence of DIL had no effect on the Tg of Eudragit® L100-55. These results demonstrate that when guaifenesin melted at elevated temperatures during extrusion, it exerted a plasticizing effect on the polymer, and solubilized the second model drug, DIL.

7.3.2 Drug morphology in the extrudates

The macroscopic appearance of the extrudates differed by extruder type: tablets produced on the single-screw extruder appeared white and opaque, while extrudates processed at 75°C or above on the twin-screw extruder were clear and transparent. Materials extruded at 65°C on the twin-screw extruder were more transparent than all

extrudates produced with the single-screw extruder, but not as clear as the twin-screw products extruded at higher temperatures.

PXRD was employed to study the drug morphology in more detail (Figure 7.2). Tablets for PXRD were formulated without DIL to avoid a possible interference of the drugs'crystalline peaks. Bulk guaifenesin powder displayed a characteristic crystalline spectrum, while the Eudragit® L100-55 powder was amorphous (Bruce et al., 2007a). In a physical mixture (the extrusion powder blend, formulation I), lower intensity peaks due to crystalline guaifenesin were observed (Figure 7.2 a). The PXRD profiles of all but one of the melt-extruded tablets (Figure 7.2 b) showed amorphous characteristics without any peaks, and the spectra were of much lower intensity.

The only tablet which displayed crystalline peaks overlaying the amorphous curve was extruded on the single-screw extruder at 65°C. This indicated that both amorphous and crystalline structures were present, and since all matrix components except for guaifenesin were inherently amorphous, the peaks were due to crystalline guaifenesin particles present in the matrix. For the crystalline content to be picked up by the method, it must have been above the limit of detection for PXRD, between 5 (Kitahara et al., 2004) and 10% (Schilling et al.). Since the samples were cut from the extrudate just before analysis, these peaks were not due to guaifenesin recrystallization. At 65°C, processing conditions on the single-screw extruder were evidently not sufficient to melt guaifenesin (melting point 79-81°C), and the appearance and PXRD spectra resulted

from the distributive and dispersive mixing of crystalline drug particles. At higher extrusion temperatures (125°C) on the single-screw extruder, the entire amount of guaifenesin, melted during processing, and remained amorphous in the cooled extrudate, which resulted in the amorphous spectrum when analyzed by PXRD. Extrusion at higher temperatures thus changed the morphology of guaifenesin in the extrudate, and the melted guaifenesin plasticized Eudragit® L100-55, which decreased melt viscosity and improved mixing. The effects of the melting guaifenesin on the processing conditions are presented in Table 7.2.

Crystalline peaks were absent in all formulations extruded on the twin-screw extruder, irrespective of temperature. These results demonstrated the higher dispersive mixing capabilities of the twin-screw extruder compared to the single-screw extruder. The transparency of the tablets produced on the twin-screw extruder indicated that more intense dispersive mixing reduced the guaifenesin particle size during extrusion.

7.3.3 Drug distribution in the extrudates

The quality of mixing after melt extrusion was judged by the degree of dispersion of the drug in the matrix. Energy-dispersive spectroscopy (EDS) can distinguish and locate the chemical elements present in a single point of a specimen, and surfaces can be scanned in many points to create a surface map. In addition, the electron beam

responsible for producing the signal penetrated a few micron into the sample, the images therefore depict the elemental distribution within the penetration depth. EDS has been used to study inorganic impurities in paracetamol (Hulse et al., 2008), the itraconazole distribution in amorphous compositions (Miller et al., 2008, DiNunzio et al.) and the elemental distributions of aluminum, nickel, oxygen and platinum in thin films (Hotovy et al., 2001). An active moiety can only be distinguished from its surroundings if it contains a chemical element not present in other sample components and if it gives a distinct signal in the EDS spectrum. The matrix contained hydrogen, carbon (C) and oxygen (O) (due to the Eudragit® L100-55) as well as a small amount of silicon (due to silicon dioxide). Guaifenesin lacks a unique atomic species for tracking, thus EDS profiling could not be performed on formulation I. Formulation II contained 25% w/w diltiazem hydrochloride, and the chlorine atom (Cl) of the salt gave a distinct signal which was used for elemental analysis to study the distribution of drug by the two extruder types. In general, one to two atomic percent of an element in a sample are necessary to detect it by EDS (EDS2006, 2006). The DIL powder was sieved to prevent a "false positive" signal of chlorine atoms due to large DIL particles in the matrix, and only the particle fraction smaller than 75 micron (200 mesh) was used to prepare the powder blends. Since the melting of guaifenesin was considered an important part of the mixing process, guaifenesin was incorporated into the tablets for EDS analysis, where it functioned as a thermal glidant and solid state plasticizer for Eudragit® L100-55. Guaifenesin also solubilized DIL, as was apparent by the disappearance of the melting

peak of DIL during DSC analysis (Table 7.3). DIL did not influence the glass transition temperature of the acrylic polymer (Table 7.4).

Figure 7.3 and Figure 7.4 show the distribution of carbon and chlorine atoms in the matrix, as detected by EDS. The distribution of carbon can be interpreted as depicting the matrix. Within the extruded formulation, the chlorine atoms are unique to DIL, and thus pinpoint the position of DIL in the matrix. (Trace amounts of Cl were considered to be statistically distributed.) Pores in the matrix, identified in the SEM images of the scanned area, result in signal interference manifesting in black regions on the EDS map.

Both extrusion temperature and the type of extruder influenced the distribution of DIL. The Cl distribution in the formulations extruded at 65°C showed clusters of Cl atoms and areas of lower chlorine concentrations (black in the chlorine spectrum, more intense yellow in the carbon spectrum), regardless of extruder type. The distribution was more homogeneous at 125°C in formulations extruded on the SSE, and the fewest chlorine clusters were found in TSE tablets extruded at 125°C. These distributions confirm that the degree of mixing improves with processing temperature, and that twin-screw extrudates were more homogeneous than in single-screw extruded tablets for the conditions studied.

The effect of processing temperature on drug distribution can be explained by the Tadmore melting model (Tadmor, 1966), which states that initially, melting is the result

of sliding friction of solids against the heated barrel, where heat is transferred from the barrel to the blend particles. Further downstream, most of the solid materials have melted, and unmolten solids are distributed in the melt pool "like ice cubes in water", and are thus isolated by the surrounding melt. At that point, melting becomes less efficient as the heat transfer to the remaining solids must be transmitted through the melt as an intermediary, which slows the heat transfer. In this context, an increase in the processing temperature will promote the melting of all remaining solids by heating the polymer melt pool to a higher temperature, which will speed the energy transfer to the suspended solids. Increasing the extrusion temperature also reduces the melt viscosity of the melt (Allcock et al., 2003), which improves distributive mixing.

7.3.4 Drug content and Dissolution testing

Neither extruder type nor processing temperature influenced the drug content in extrudates (data not shown). The differences in drug distribution on a microscale as seen in EDS did not translate into concentration differences in tablets, probably because the small-scale differences in drug distribution averaged out in a volume the size of a tablet, and the analysis only measured total drug content. The effect of tablet homogeneity on drug release was investigated in phosphate buffer pH 6.8. The samples (formulation I) contained guaifenesin in Eudragit® L100-55, and were extruded at either 65 or 125°C on either a twin-screw extruder or a single-screw extruder. The drug release profiles are shown in Figure 7.5, and depended on the tablet dimensions (surface area/volume ratio)

of the tablets, which was described for hypromellose matrix tables and water-soluble drugs (Reynolds et al., 2002). However, the processing temperatures and the extruder type did not influence the drug release. The matrix former Eudragit® L100-55 started to dissolve above pH 5.5, so at the pH of the dissolution test, the drug as well as the matrix dissolved, obscuring any differences in drug distribution due to the extrusion conditions.

Formulations containing guaifenesin and DIL (formulation II) were used to study the effect of processing conditions on the dissolution profile in simulated gastric fluid without pepsin, as shown in Figure 7.6. Under acidic conditions, the carboxylic groups on Eudragit L100-55 were un-ionized, and the matrix remained intact, which resulted in reduced dissolution rates at low pH. However, only the formulation extruded at 125°C on the twin-screw extruder released less than 10% drug after 2 hours in acid. The homogeneous drug distribution probably maintained the integrity of the tablets, which impeded the diffusion of drug located further inside the matrix. Clusters of drug, as seen in tablets extruded at 65°C, dissolve to leave behind pores in the matrix. During dissolution, the medium will quickly penetrate the entire tablet before drug release is observed, as demonstrated by Mäder et al. (Strübing et al., 2007). Dissolving clusters could reduce matrix tortuosity by opening up passages for drug molecules to leave the tablet and thus shortening diffusion paths. Higher tortuosity is correlated to lower drug release (Crowley et al., 2004b).

7.3.5 Recrystallization of guaifenesin from the amorphous state

Previous studies investigated the physical stability of guaifenesin in melt-extruded matrix tablets (Bruce et al., 2007a), which was compromised by the recrystallization of guaifenesin from the amorphous state on tablet surfaces. To quantify the development of guaifenesin crystals, an assay was developed as the use of x-ray diffraction and DSC to quantify surface crystallization were not well suited for the samples in this study. The limit of detection for crystalline-in-amorphous samples by powder x-ray diffraction is 5 (Kitahara et al., 2004) to 10% (Schilling et al.), and thus too high to capture early crystal growth. DCS analysis was undertaken without results, since the crystalline guaifenesin re-dissolved in the matrix on heating the sample, and the small amounts involved made it desirable to study the entire tablet surface area.

Tablets produced by either the single-screw extruder or the twin-screw extruder at temperatures between 65 and 125°C were investigated. All tablets were cut from extruded rods 24 hours after processing, and were stored in a desiccator (17% relative humidity) for the duration of the study, since previous studies demonstrated that moisture increased the recrystallization of guaifenesin.

The surface guaifenesin assay measured the amount of guaifenesin that was present on tablet surfaces over a 16 day period and was normalized to tablet surface area to account for geometric variations in tablet dimensions. It is also important to note that a certain amount of amorphous drug was expected to be present on the surfaces of the

matrix tablets. To establish a base line, the “day 1” time point was tested immediately after tablet preparation to ensure that no surface recrystallization had occurred (at the present drug concentration, recrystallization appears within 15-30 minutes). The amount of guaifenesin found in the “day 1” analysis was considered to be the amount of amorphous drug present on the surface.

Figure 7.7 depicts the amount of surface guaifenesin over 16 days on tablets stored at 24°C at 17% relative humidity. The higher the extrusion temperature in the single-screw extruder, the less guaifenesin was found in the initial test. Over the 16 day study, the amount of surface guaifenesin increased in all formulations, indicating that guaifenesin crystals developed on the tablet surfaces. These results are consistent with the EDS data showing improved drug distribution at higher processing temperatures, resulting in a more homogeneous matrix with lower local drug concentrations. On the twin-screw extruded tablets, extrusion temperature did not influence guaifenesin recrystallization. Both the initial amounts and the increases in surface crystallization over the 16 day study period were lower than in tablets produced on the single-screw extruder. The results match the better drug dispersion in twin-screw extruders seen by EDS. The exception was the formulation extruded at 65 °C. Though initial surface guaifenesin values were comparable to those of the other formulations extruded on the twin-screw extruder, it experienced an increase in surface crystal growth similar to the tablets extruded on the single-screw extruder at the same temperature. This was attributed to the presence of solid guaifenesin in the tablet, which could not be ruled out due to the low

extrusion temperature. Twin-screw extrusion may have reduced the particle size, and the crystalline content may have been below the detection limit of the PXRD, but very small remnants of the solid drug are sufficient to act as a nucleating agent, and cause the increase in crystalline guaifenesin.

The difference in surface guaifenesin levels between day 1 and day 16 is presented in Figure 7.8, showing the amount of surface crystallization developing over the study period. The differences are larger in formulations extruded on the single-screw extruder. Formulations which showed a homogenous morphology and drug distribution also had lower amounts of drug on the surface in the "day 1 test", and developed lower amounts of surface crystals over 16 days. Two factors influenced the high amounts of guaifenesin recrystallization, the presence of solid guaifenesin during processing and the degree of mixing. Even small remainders of solid guaifenesin particles in the melt could function as nucleants for crystallization in the supersaturated matrix. In the single-screw extruder, the extrusion blend was molten as it entered the mixing zone. A higher process temperature decreased melt viscosity, enhancing distributive mixing, which improved drug dispersion and particle deagglomeration. The resulting lower local supersaturation levels decreased the tendency of to system to recrystallize.

7.4 CONCLUSION

The reciprocal influence of two model drugs, guaifenesin and diltiazem hydrochloride, and their effect on melt extrusion, as well as the extrusion of pre-mixed powder blends on either a single-screw or a twin-screw extruder and the consequences of mixing efficiency for tablet performance were investigated. Thermal analysis revealed that guaifenesin affected the extrusion process by plasticizing the polymer, and by solubilizing the second model drug, diltiazem hydrochloride. Energy-dispersive spectroscopy (EDS) demonstrated that low extrusion temperatures (65°C) resulted in heterogeneously mixed tablets for both single-screw extruder and twin-screw extruder. In tablets extruded on the single-screw extruder, low extrusion temperature (65°C) was also correlated with a partially crystalline drug in the matrix, while all other extrudates were amorphous. These differences in drug morphology and level of mixing had consequences for the physical stability of the tablets. Surface recrystallization of guaifenesin was higher in tablets extruded on the single-screw extruder, and decreased with increasing processing temperature. Surface crystal growth in tablets extruded on the twin-screw extruder was independent of processing temperature, except for those extruded at 65°C. Better mixing resulted in homogeneous tablets without drug clusters, which reduced local supersaturation levels. Higher matrix homogeneity therefore reduced the driving force for crystallization. Higher processing temperature and more intense mixing promoted the complete melting of the extrusion blend. The absence of guaifenesin crystals in the matrix made them unavailable to act as nucleants, which can reduce the induction time of crystal growth. In conclusion, extruder type affected the properties of melt-extruded

tablets, and control of the processing conditions can be used as a strategy to increase the physical stability and modify the dissolution properties for melt-extruded dosage forms.

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7.6 TABLES

Table 7.1 Formulation compositions.

Formulation	Component	Function	%
I	Guaifenesin	Model drug	37.5
	Colloidal Si O2	Glidant	0.5
	Eudragit® L100-55	Matrix former	62
II	Diltiazem HCl	Model drug	25
	Guaifenesin	Model drug	11.25
	Colloidal SiO2	Glidant	0.5
	Eudragit® L100-55	Matrix former	63.25

Table 7.2 The influence of extrusion temperature on processing conditions

The extrusion blend consisted of formulation I.

Extrusion Temperature (°C)	Single-Screw Extruder		Twin-Screw Extruder	
	RPM	DriveAmps	RPM	DriveAmps
65	1.5	649	50	280
75	20	266	200	345
85	20	220	200	276
95	20	145	200	235
125	20	70	200	

Table 7.3 The melting points of guaifenesin and diltiazem hydrochloride, pure and in powder blends with each other.

DSC, heating rate 10°/min, 50-230°C, n=3, average reported.

Powder Blend	Peaks detected (°C)	
Guaifenesin	81.2±0.6	--
Diltiazem HCl	--	215.4±0.3
Guaifenesin: Diltiazem HCl 1 : 9	79.0±2.0	203.5±1.4
Guaifenesin: Diltiazem HCl 1 : 1	79.4±0.3	not detected
Guaifenesin: Diltiazem HCl 9 : 1	81.5±0.3	not detected

Table 7.4 The influence of guaifenesin and diltiazem hydrochloride on the glass transition temperature of Eudragit® L100-55.

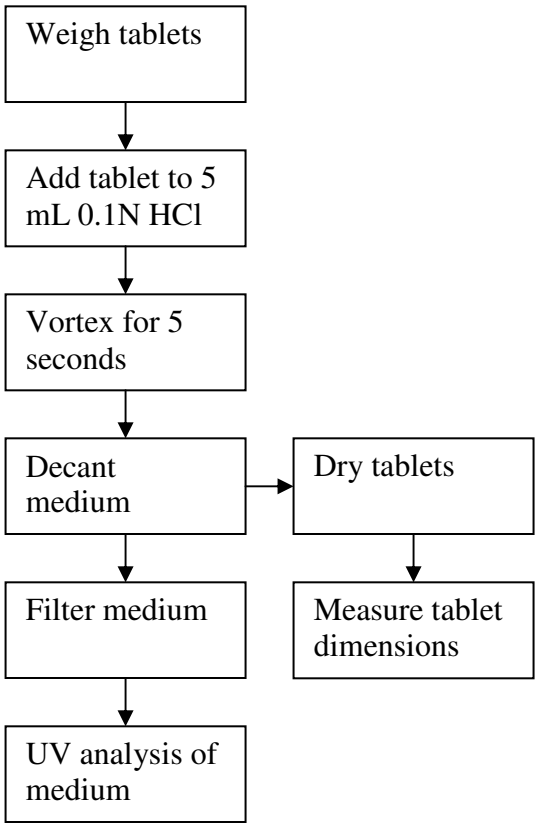
All samples were powders, MDSC, heating rate 15°C/min, temperature amplitude 0.5°C every 40 sec, 50-170°C, 2nd run, n=3.

Sample	Glass Transition Temperature, °C
Eudragit® L100-55	125.2 ± 3.67
25% Diltiazem HCl in Eudragit® L100-55	125.9 ± 0.52
11.25% Guaifenesin in Eudragit® L100-55	93.8 ± 0.56
Extrusion Blend* (formulation II)	94.8 ± 2.12

*contained 11.25% guaifenesin and 25% DIL in Eudragit® L100-55

7.7 FIGURES

Figure 7.1 Flow diagram of the quantitative analysis of surface guaifenesin levels.



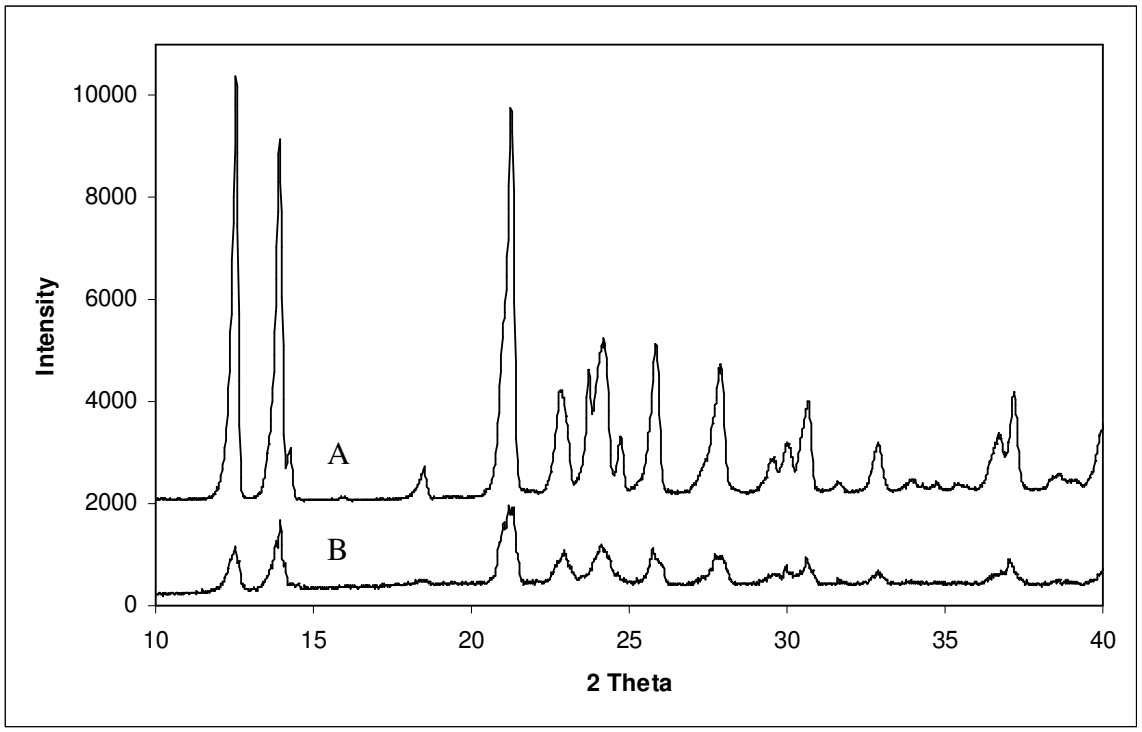


Figure 7.2 a. Powder x-ray diffraction profile of powdered guaifenesin and the physical mixture.

Step size 0.02°, dwell time 2.0 sec.

A – Guaifenesin powder (bulk drug); B – Physical mixture (formulation I)

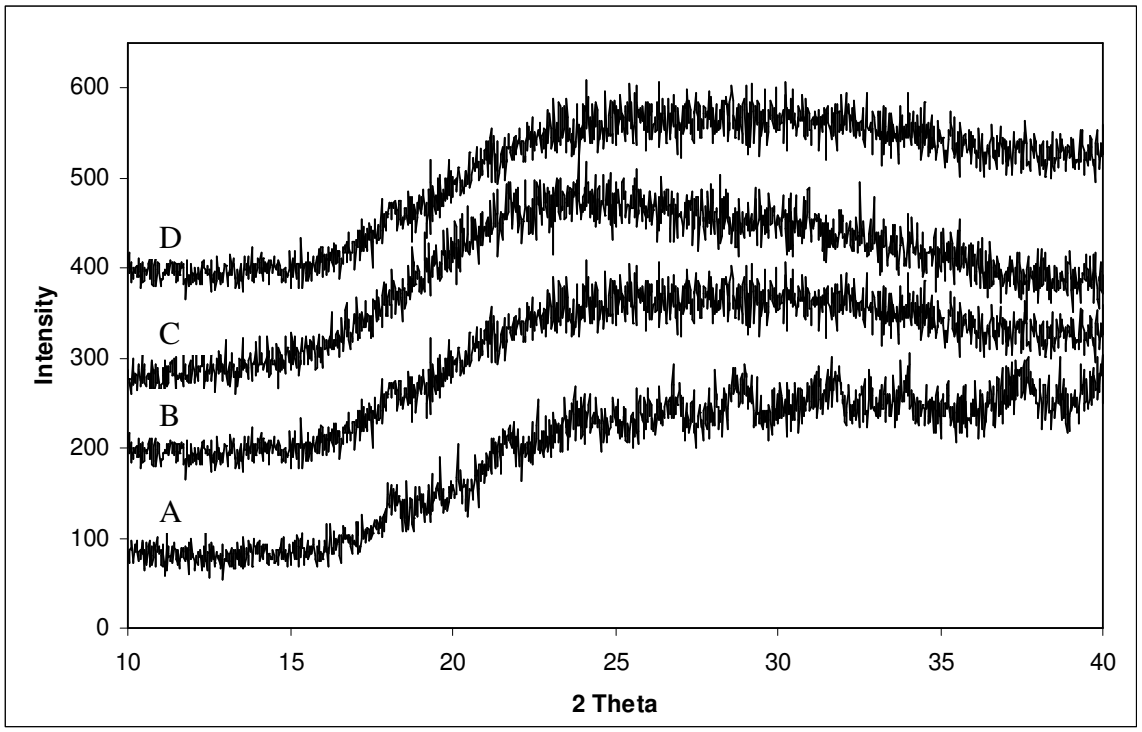


Figure 6.2 b. The influence of extruder type and temperature on the morphology of guaifenesin.

Formulation I, step size 0.02°, dwell time 2.0 sec.

A - Single-screw extrusion, 65°C
B - Single-screw extrusion, 125°C
C - Twin-screw extrusion, 65°C
D - Twin-screw extrusion, 125°C

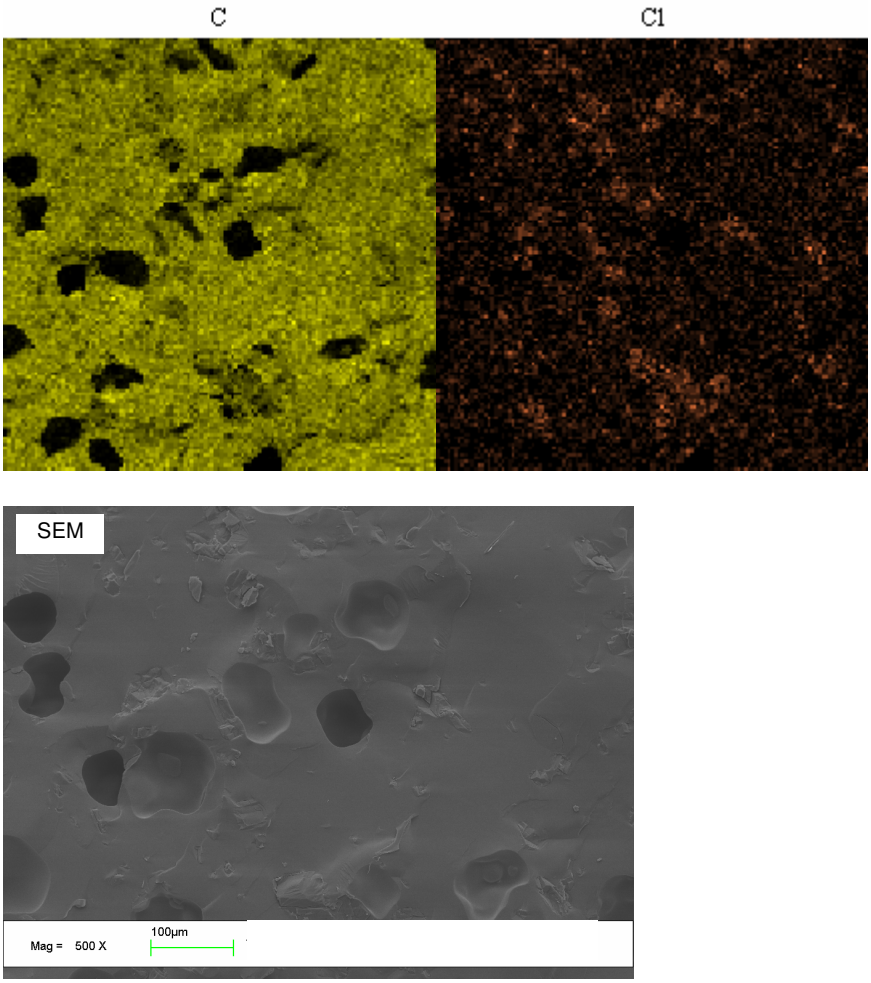


Figure 7.3 a. The effect of single-screw extrusion at 75°C on the diltiazem hydrochloride distribution in melt-extruded tablets (formulation II).

C – EDS mapping of the carbon present in the sample
Cl – EDS mapping of the chlorine present in the sample
SEM – SEM micrograph of the area mapped by EDS

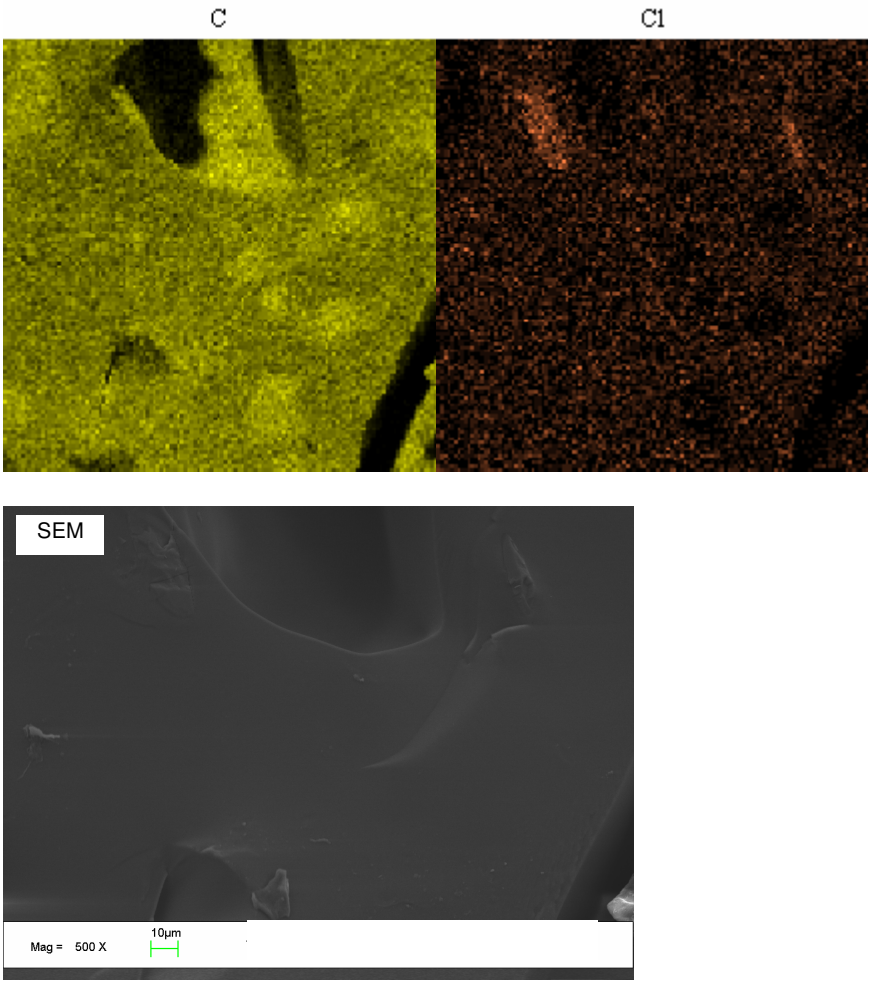


Figure 6.3 b. The effect of single-screw extrusion at 125°C on the diltiazem hydrochloride distribution in melt-extruded tablets (formulation II).

C – EDS mapping of the carbon present in the sample
Cl – EDS mapping of the chlorine present in the sample
SEM – SEM micrograph of the area mapped by EDS

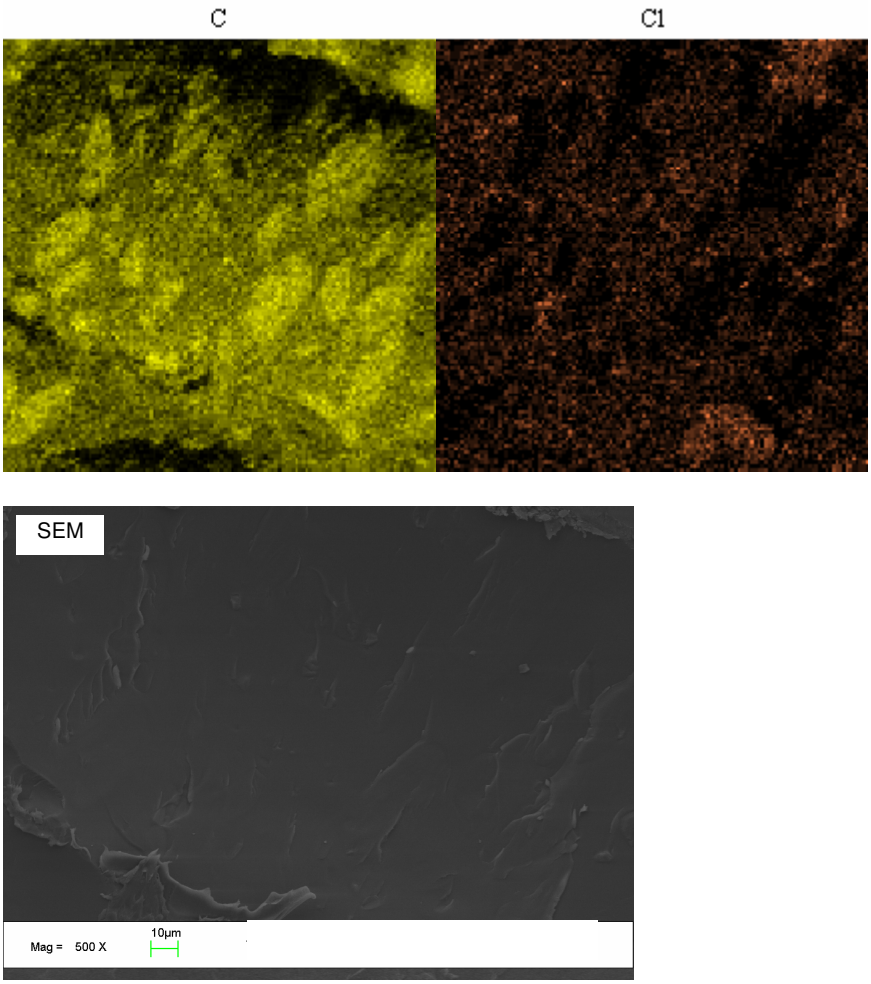


Figure 7.4 a. The effect of twin-screw extrusion at 75°C on the diltiazem hydrochloride distribution in melt-extruded tablets (formulation II).

C – EDS mapping of the carbon present in the sample
Cl – EDS mapping of the chlorine present in the sample
SEM – SEM micrograph of the area mapped by EDS

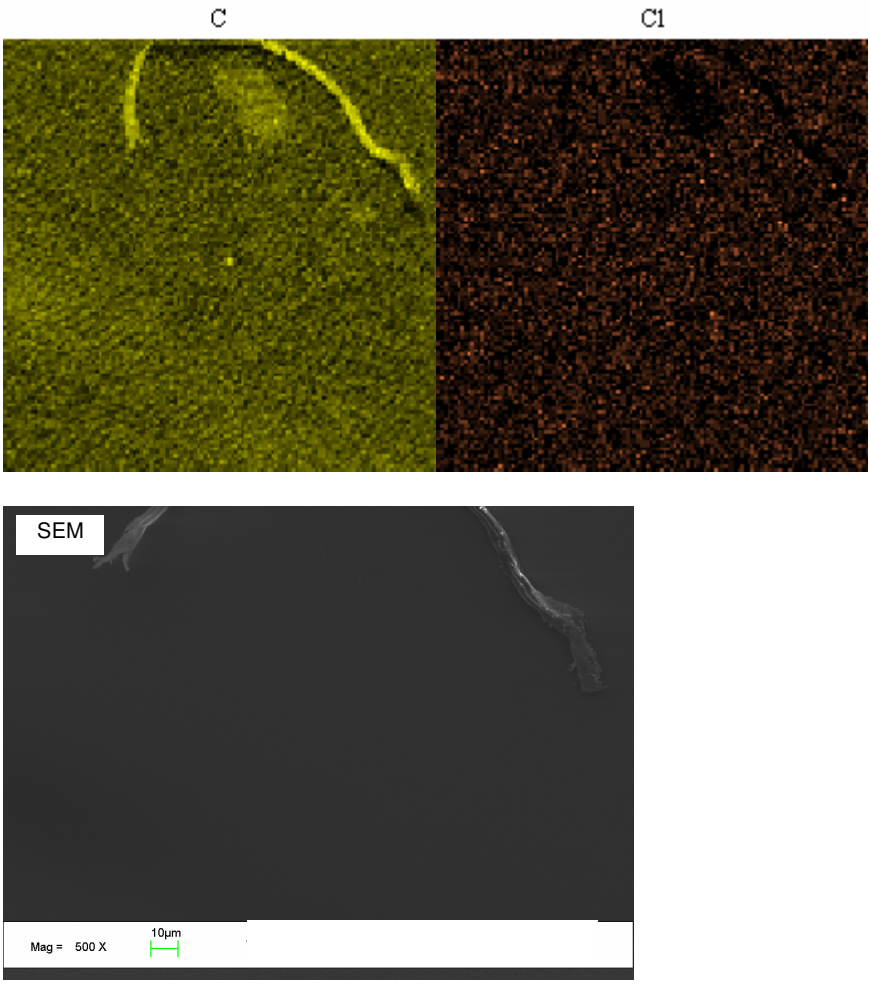


Figure 6.4 b. The effect of twin-screw extrusion at 125°C on the diltiazem hydrochloride distribution in melt-extruded tablets (formulation II).

C – EDS mapping of the carbon present in the sample
Cl – EDS mapping of the chlorine present in the sample
SEM – SEM micrograph of the area mapped by EDS

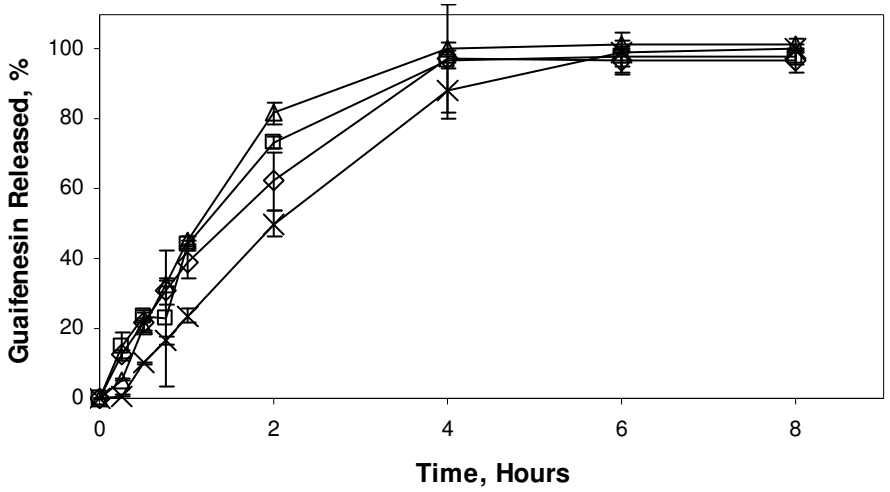


Figure 7.5 The influence of extruder type and processing temperature on the release of guaifenesin from melt-extruded tablets.

Formulation I, basket method, 50 RPM, 900 mL, phosphate buffer pH 6.8, 37°C, n=3.

◊ - Single-screw extrusion, 65°C extrusion temperature
□ - Single-screw extrusion, 125°C extrusion temperature
Δ - Twin-screw extrusion, 65°C extrusion temperature
× - Twin-screw extrusion, 125°C extrusion temperature

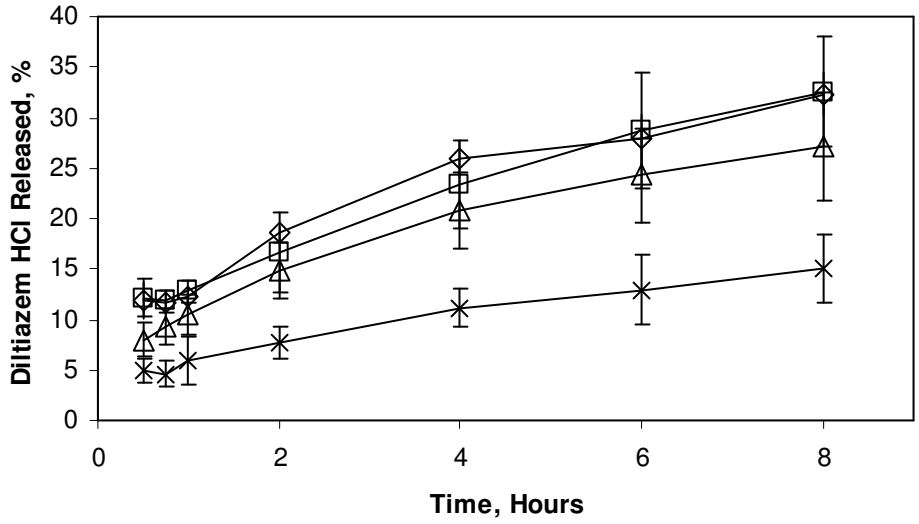


Figure 7.6 The influence of extruder type and processing temperature on the release of diltiazem hydrochloride from melt-extruded tablets.

Formulation II, basket method, 50 RPM, 900 mL, simulated gastric fluid without pepsin, 37°C, n=3.

◊ - Single-screw extrusion, 65°C extrusion temperature
□ - Single-screw extrusion, 125°C extrusion temperature
Δ - Twin-screw extrusion, 65°C extrusion temperature
× - Twin-screw extrusion, 125°C extrusion temperature

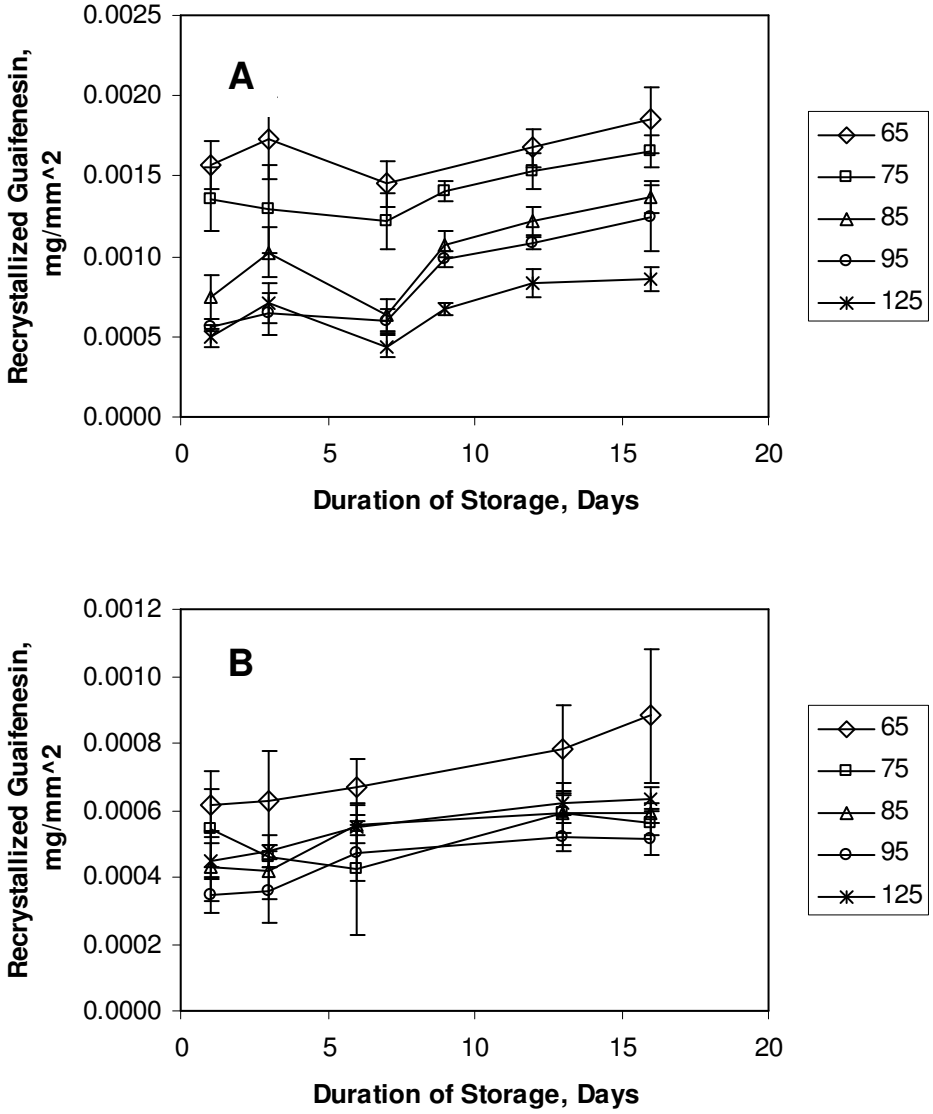


Figure 7.7 The influence of extruder type on the recrystallization of guaifenesin from melt-extruded tablets containing 37.5% guaifenesin in a matrix composed of Eudragit® L100-55.

Formulation I, storage in open containers, 21°C, 17% relative humidity, n=6.

A - Tablets extruded on single-screw extruder
B - Tablets extruded on twin-screw extruder

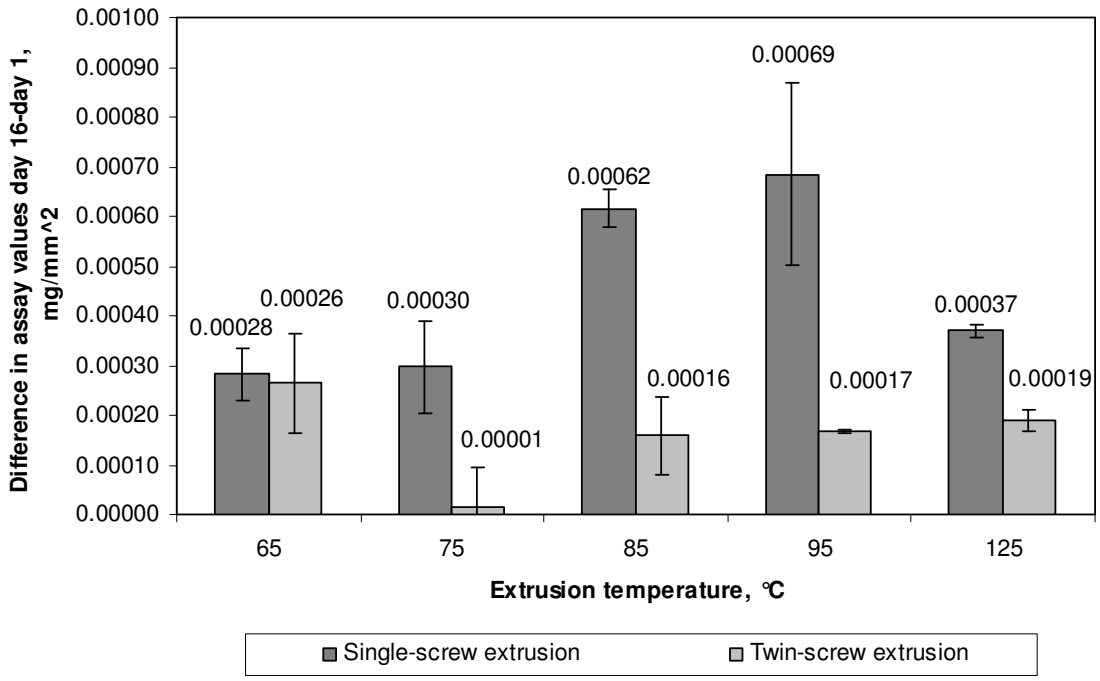


Figure 7.8 The amount of guaifenesin crystal growth developing between day 1 and day 16 in melt-extruded tablets containing Eudragit® L100-55 and guaifenesin

Tablets consisted of formulation I. The results from the surface guaifenesin assay from day 1 were subtracted from day 16 values, n=6.

Chapter 8: Summary and Conclusions

8.1 CONCLUSIONS OF SUPPORTING OBJECTIVES

Acryl-EZE® and Eudragit L100-55® were successfully extruded with guaifenesin as the model drug. Guaifenesin had a plasticizing effect on the acrylic polymer, and formed a solid solution in the acrylic polymer during processing. 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.

Supporting objective II 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® L100-55 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 for 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.

Supporting objective III investigated the effect of film-coating on the recrystallization of guaifenesin. 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, probably by protecting the amorphous drug from ubiquitous nucleating agents. The drug

morphology of guaifenesin crystals was altered due to the presence of polymers. Most formulation and processing factors investigated (polymer type; weight gain; curing time and temperature; storage conditions; and core drug-to polymer ratio) all effect a single variable: diffusion. A variable promoting either guaifenesin or the polymer diffusion resulted in an earlier onset of recrystallization. The choice of coating polymer was the largest single factor affecting the onset time of crystallization. In conclusion, the film-coating of hot-melt extruded, acrylic matrix tablets successfully delayed the onset of guaifenesin recrystallization for up to 6 months.

The extrusion of pre-mixed powder blends on either a single-screw or a twin-screw extruder, effects of guaifenesin and diltiazem hydrochloride on each other and the polymer during thermal treatment, and the consequences of mixing efficiency for tablet performance were investigated in supporting objective IV. Thermal analysis showed that guaifenesin solubilized the high-melting drug diltiazem hydrochloride, and that it plasticized the polymer. EDS demonstrated that low extrusion temperatures (65°C) resulted in heterogeneously mixed tablets for both single-screw extruder and twin-screw extruder. In tablets extruded on the single-screw extruder, low extrusion temperature (65°C) was also correlated with a partially crystalline drug in the matrix, while all other extrudates were amorphous. These differences in drug morphology and level of mixing had consequences for the physical stability of the tablets. Surface recrystallization of guaifenesin was higher in tablets extruded on the single-screw extruder, and decreased with increasing processing temperature. Surface crystal growth in tablets extruded on the

twin-screw extruder was independent of processing temperature, except for those extruded at 65°C. Better mixing resulted in homogeneous tablets without drug clusters, which reduced local supersaturation levels. Higher matrix homogeneity therefore reduced the driving force for crystallization. Higher processing temperature and more intense mixing promoted the complete melting of the extrusion blend. The absence of guaifenesin crystals in the matrix made them unavailable to act as nucleants, which can reduce the induction time of crystal growth. In conclusion, the extruder type affected the properties of melt extruded tablets, and control of the processing conditions can be used as a strategy to increase the physical stability and modify the dissolution properties for melt extruded dosage forms.

8.2 OVERALL CONCLUSION

This study demonstrated that the recrystallization of guaifenesin from the amorphous state in melt-extruded tablets depended on the solubility of the drug in the matrix. Polymer blends of Eudragit® L100-55 with hydrophilic polymers reduced recrystallization by extending the guaifenesin solubility in the matrix blend. Formulation factors, such as the presence of talc in the matrix, and storage conditions, such as the relative humidity during storage, promoted the recrystallization by a nucleating effect. Film-coating of tablets delayed the onset of crystallization by modifying the surface of matrix tablets, where recrystallization occurred. The selection of the coating polymer had the largest impact in determining the delay in the onset of guaifenesin recrystallization,

but all factors which influence diffusion can be used to prolong the physical stability. The degree of drug dispersion achieved by melt-extrusion differed between extruder types, and was demonstrated to be a factor in determining the quantity of recrystallization. In conclusion, to maximize the physical stability of amorphous drugs in melt-extruded dosage forms, the study identified several options, which function by different mechanisms, and which can be applied concurrently. The processing equipment, post-processing modifications of the dosage form, formulation components and their mutual solubilities, as well as storage conditions were all demonstrated to influence the physical stability of amorphous guaifenesin in matrix tablets containing Eudragit®L100-55.

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Vita

Caroline D. Bruce was born Caroline Dietzsch on September 6th, 1976 to Drs. Steffen and Birgit Dietzsch. She attended LaFayette High School in Lexington, KY, in 1991/92, and graduated from the Buehring-Gymnasium in Berlin, Germany, in May 1996. From 1996-2002, she attended the College of Pharmacy at Freie Universitaet in Berlin, Germany, during which time she completed two research internships. After her second German licensure examination in 2002, her rotations were spent in the labs of Dr. McGinity at the University of Texas at Austin, where she collaborated with Christopher R. Young on a project investigating the compression of hot-melt extruded controlled-release pellets, and in the Petersburger Apotheke in Berlin, Germany (2002 – 2003). She became a licensed German pharmacist in June 2003 and in August 2003, she started graduate school at the University of Texas at Austin in Dr McGinity's group. She has since worked on projects investigating the physical stability of guaifenesin in hot melt-extruded matrix tablets, has served as head TA in the compounding lab, TA in the intravenous admixtures lab, and has completed two industrial internships, at Andrx in Ft. Lauderdale, FL and at Colorcon in West Point, PA. She has been awarded the Max and Mary Anne Burlage Fellowship 2007-08 and the Graduate School Professional Development Award, 2006-07, and has presented at numerous national conferences. She was married to Mr. J. E. Bruce in May 2007. She has accepted a position at Pharmaform in Austin, Texas.

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