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Crystal growth formation in melt extrudates

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Abstract

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

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

1. Introduction

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

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

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Table 1
Composition of tablets prepared by hot-melt extrusion

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

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

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

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

Table 2
Processing conditions for extrudates containing Acryl-EZE®

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