Hot Melt Extrusion of Acrylic Films

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INTRODUCTION

Currently, the most prevalent means for producing thin films for topical drug delivery devices is via organic or aqueous solution casting. Problems with this method include environmental concerns with solvent emissions and health concerns with residual solvent. In addition, solvent based processes require extensive processing times and drying times, that are expensive, time consuming and can negatively affect drug stability. Furthermore, solvent choice and residual solvents can affect film properties (1–3). Gutierrez-Rocca and McGinity showed for acrylic films cast from isopropyl alcohol, that there was a decrease in plasticity during storage due to a densification of the films which corresponded to a loss of free volume, as residual solvent evaporated from the films during drying and aging (1). They also found that the equilibration time required to obtain stable mechanical properties, i.e., no change in tensile strength and elongation at break, may be as long as 60 days, depending on storage conditions and plasticizer content.

The water permeability coefficients and dissolution rates for solvent cast cellulosic films also have been shown to decrease with aging time (3, 4). Problems have been associated with films cast from aqueous dispersion due to the latex nature of these films and the conditions required to obtain continuous, defect free films (5). Latex films must undergo a curing or equilibration phase, during which the water evaporates from the films and the polymer particles coalesce and fuse into uniform membranes. It has been shown that the level of plasticizer, type of plasticizer, curing time and temperature strongly affect the dissolution rate of drugs through films formed from aqueous dispersions (5–7).

The goal of the present study was to investigate the viability of melt technology for producing thin, flexible acrylic films for topical drug delivery. This manufacturing process is not restricted by solvent concerns and has the potential for operating in a continuous processing mode. Recently, Follonier, et al., showed that thermally stable drugs, such as diltiazem HCl, can be melt extruded into pellets without significant drug degradation (8). They also found that the stability of Eudragit® RSPM was adequate for extrusion at 130°C. In addition, there have been several studies on the feasibility of cast films from Eudragit® polymers for topical drug delivery (9, 10).

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MATERIALS AND METHODS

Materials

Eudragit® E100 was supplied by Rohm Tech, Inc., Malden MA. Plasticizers used include triethyl citrate (TEC) (Morflex, Inc., Greensboro, NC), triacetin (Aldrich Chemical Co., Milwaukee, WI), and polyethylene glycol 6000 (PEG 6000) (J. T. Baker Chemical Co., Phillipsburg, NJ). The high density polyethylene (HDPE) was from Dow Chemical Co., Midland, MI. The active ingredients in the films were lidocaine HCl and diphenhydramine HCl, both from Sigma Chemical Company, St. Louis, Mo.

Processing Methods

The pellets were dried for at least 24 hours at 35°C to remove moisture that could lead to degradation in the extruder. To incorporate the high levels of plasticizers required to make flexible films of Eudragit® E100 into the polymer, a Brabender roll mill was used (Figure 1). The compounder was first heated to 120°C, then approximately 100g of polymer pellets were added and melted for approximately 2 minutes. The plasticizer was then slowly added to the molten plastic and mixed for another minute. The mixing occurred in the nip between the two rollers. To enhance mixing, a knife was used to scrape off any excess material that was on the rollers and it was added to the nip area. The drug was added to the plasticized polymer and mixed for another 2 minutes. Three batches of plasticized polymer were then combined and ground together through a large Ball and Jewell mill.

A small single screw Brabender extruder with a two stage screw with a tape die, as shown in Figure 1, was used to form the films. The L/D ratio of the extruder was 24 and the operating speed was 35 RPM. To remove any residual polymer and to equilibrate the system, the extruder was heated to 200°C and flushed with HDPE. The temperature was then lowered to 150°C and unplasticized Eudragit® E100 was flushed through the system for approximately 20 minutes. It was critical to have the temperature below 175°C prior to adding Eudragit® E100 to the extruder, to avoid polymer degradation. When the plasticized pellets were added to the system, the temperature was further lowered to 80°C.

The cast films were prepared by dissolving the polymer and drug in ethanol and drying in a casting ring at room temperature for 1 week.

Analytical Methods

The mechanical properties of the films were characterized using an Instron 4201 testing apparatus with a head speed of 20 mm/min. For comparison, the strain rate was chosen to be the same as used by Lin et al. (11). The films, which were approximately 0.3 mm × 3.5 mm × 4 mm, were equilibrated at 50% RH, 25°C and tested as per ASTM Standard D 882-91 for Thin Plastic Sheeting (12).

A Perkin-Elmer differential scanning calorimeter (DSC −2) at 20°/min was used to measure thermal transitions in the polymer films. Wide Angle X-Ray Diffraction (WXRD) was performed on a Phillips APD 3520 using copper with a wavelength of $\lambda = 1.54$ Å. The d-spacing was calculated from

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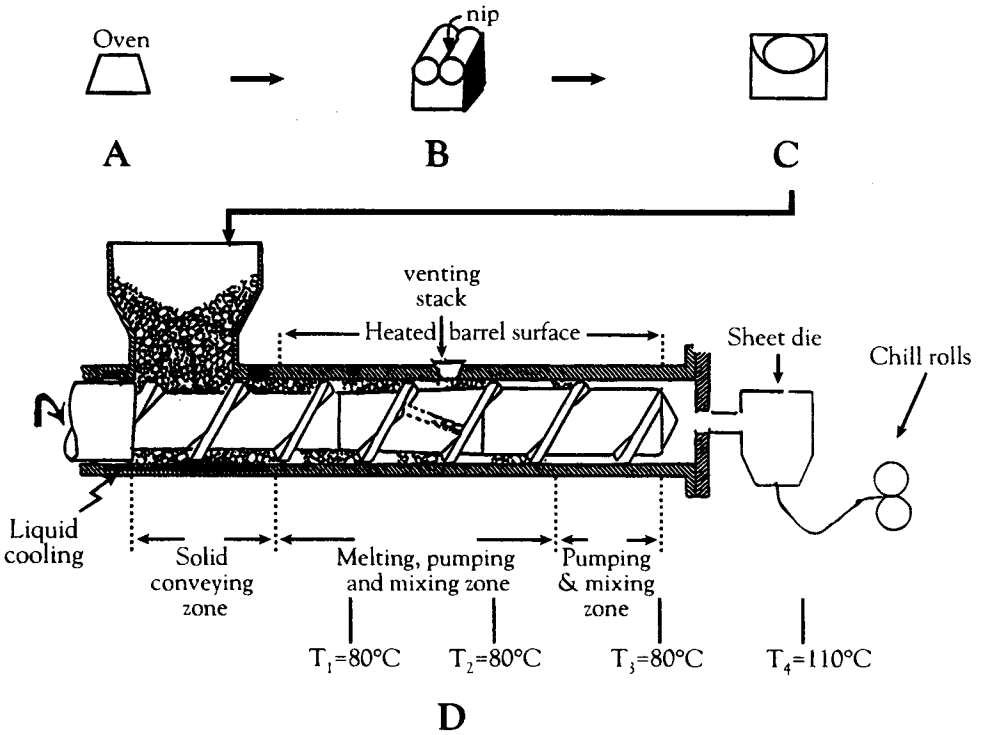

Fig. 1. Schematic of the processing method for forming extruded films. A) drying the polymer pellets at 40°C, B) Brabender roll mill for melt mixing the polymer, plasticizer and drug, C) Ball and Jewell Mill for grinding the premelt into powder after cooling, and D) Brabender single screw extruder for forming the polymer film.

Braggs Law, $n\lambda = 2d \sin\theta$, were 2θ was the angle at the midpoint of the maximum peak. The broad peaks observed for amorphous materials are indicative of the most probable distance between polymer chains. The d-spacing calculated is, therefore, an indication of the average distance between axes of neighboring chains in the polymer matrix.

Dissolution was performed via USP XXII, apparatus 3 with a stainless steel disk assembly for transdermal delivery systems at 32°C and 50 RPM. For lidocaine chemical analysis, a Waters® high pressure liquid chromatograph (HPLC) with a 486 ultraviolet (UV) detector at 238 nm and a Whatman Partisil® 10 ODS-3, 4.6mm I.D. × 25 cm column. The mobile phase was 95% acetonitrile/ 5% distilled, deionized water with 0.5g/L 1-octane sulfonic acid, sodium salt. The approximate retention time was 8 min with a flow rate of 2.0 ml/min. The HPLC column used for the diphenhydramine HCl assay was a Supelcosil® LC-8-DB 5 μm 15 cm × 4.6 cm equipped with a guard column or pre-column filter and the detector wavelength was 254 nm. The mobile phase was 17.5% acetonitrile, 30% methanol, and 52.5% water with 0.05M potassium phosphate

Table I. Mechanical Properties of Eudragit® E100 Films Containing Diphenhydramine HCL (DPH) and Lidocaine HCL (L-HCL)

Polymer	Plasticizer	Drug	T_g (°C)	d-spacing (Å)	Peak Stress(c) σ (kg/cm2)	Elongation at Break ϵ (%)
E100	none	none	40	4.76	N/A	N/A
E100-Ex	15% TEC	none	18	4.92	13.4	59.3
E100-Ex	12% triacetin	none	25	4.76	29	47.9
E100-Ex	15% TEC	5% DPH	20	N/A	12.9	53.5
E100-Cast	15% TEC	5% L-HCL	20	5.03	3.65	549
E100-Ex	15% TEC	5% L-HCL	21	4.79	9.88	218
E100-Ex	15% TEC	10% L-HCL	10.5	4.80	2.47	376.8
HDPE-E100	none	5% L-HCL	35[c]	4.76[d]	77.7[a]	110.0[a]
1:1—Ex					3.0[b]	3.0[b]
Ex—Extruded						

[a] Tested in the direction of orientation.
[b] Tested perpendicular to orientation.
[c] T_{melt} at 111°C.
[d] Crystalline peaks at 4.1, 3.60, and 2.49 Å.

monobasic and 2% triethylamine with the pH adjusted to 3.0 with phosphoric acid. At a flow rate of 1.5 ml/min, the approximate retention time was 5.2 minutes.

RESULTS AND DISCUSSION

Eudragit® E100 was extruded into clear, flexible films with mechanical properties as indicated in Table I. Without plasticizers, these films were extremely brittle, therefore, several different plasticizers including PEG 6000, triacetin, and triethylcitrate (TEC) were evaluated to increase the ductility of the films. Of the plasticizers investigated, TEC appeared to be the most suitable for this application because of its low volatility and its miscibility with the polymer. As shown in Table I, the films containing 15% TEC were more ductile materials than those with 12% triacetin. In addition, the incorporation of the plasticizers also lowered the glass transition temperatures to approximately room temperature. The T_g of the TEC plasticized film is slightly lower than that for the triacetin containing film. A maximum of 12% triacetin could be incorporated into the films without encountering significant processing problems due to the sticky nature of the blend and resulting pellets, whereas 15% TEC could be successfully added. The extruded films with 12% triacetin were more brittle than the solvent cast 15% triacetin films tested by Lin et al. (11). Triacetin is miscible with Eudragit® E100 and at very high plasticizer levels it will act as a solvent for this polymer. The solubility parameters of triacetin and this acrylic polymer were both calculated to be 9.7 $(cal/ml)^{1/2}$ by Lin et al. (11). The calculated solubility parameter of TEC was somewhat higher at 10.3 $(cal/ml)^{1/2}$. These differences in solubility parameters indicate that TEC was not as miscible as triacetin with the Eudragit® E100, however, this lower interaction resulted in better flow in the hopper of the extruder. PEG 6000 was found not to be a viable plasticizer for this system since the addition of only 1% PEG 6000 wax to the Eudragit® E100 pellets resulted in a loss of flow in the extruded. Thus, the polymer was exposed to high temperature for long time periods which resulted in polymer degradation.

Polymer blending is an alternative method to modify the properties of a material rather than using plasticizers which can be lost during processing or storage. A 50:50 blend of high density polyethylene (HDPE) and Eudragit® E100 with 5% lidocaine was mixed in a tumbler blender and extruded into films. As shown in Table I, these films were strong in the direction of crystalline orientation, i.e. the extrusion direction, but quite brittle when tested perpendicular to the flow.

Wide angle X-ray diffraction (WXRD) was used to gain further insight into the physical properties of the films. Unplasticized Eudragit® E100 has a maximum at an angle 2Θ of 18.2° which indicates, from Bragg's law, an average chain spacing of 4.76 Å. The addition of plasticizers shifts this peak to higher average d-spacing values as shown in Table I. The WXRD scans also show that a shoulder is formed at low angles whenever plasticizer is added to the system (Figure 2). This new peak or shoulder which occurs at low angles is not accounted for in the calculated average d-spacing measurements, which only consider the angle at maximum peak height. Therefore, the effect of the plasticizer on d-spacing is probably underestimated and may affect the free volume in the dense films more than the average calculations indicate.

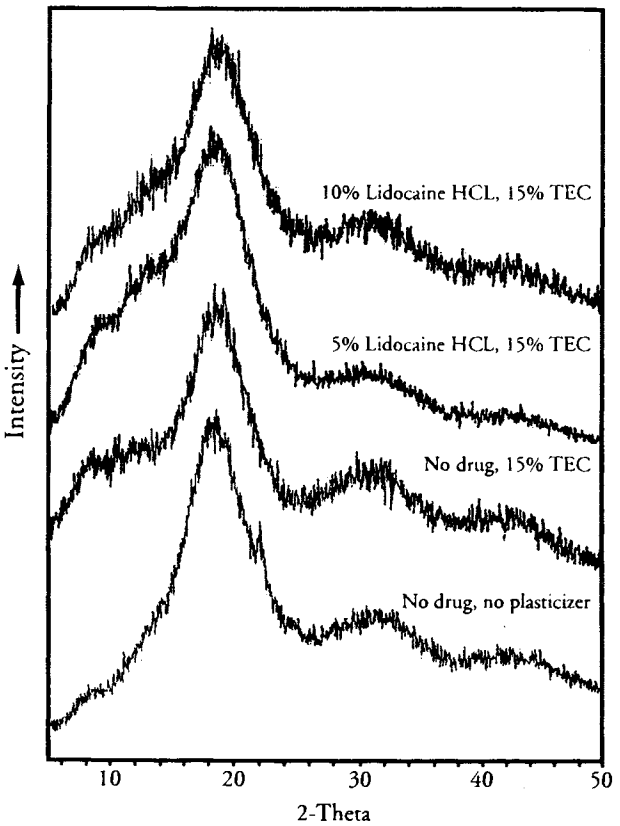

Fig. 2. Wide angle X-ray diffraction scans of extruded Eudragit® E100 films showing the effect of plasticizer and drug on the packing of the polymer film.

The wide angle X-ray diffraction pattern for the polyethylene-E100 blend suggests a semi-crystalline structure with sharp WXRD peaks at 21°, 23.8°, and 36°. These peaks agree with the literature values for polyethylene (13). There was not a shift in the average d-spacing or T_g for the acrylic film upon blending with polyethylene (Table I). Because of the lack of miscibility between the two polymers, the blended product was not particularly strong, especially in the direction normal to the extrudate flow.

Diphenhydramine HCl did not have adequate thermal stability for this process. A yellow discoloration appeared in the extruded film. Immediately after extrusion, 80% of the theoretical amount of diphenhydramine remained in the films. However, after one month at room temperature less than 50% of the theoretical drug content was present. The addition of 5% diphenhydramine did not affect the mechanical properties of the films as seen in Table I.

Interesting results were obtained with the addition of 5% lidocaine HCl to the films. Lidocaine HCl was more thermally stable than the diphenhydramine HCl and displayed no measurable degradation via HPLC analysis after one month at room temperature. In addition, our studies indicate that the lidocaine in these films was amorphous since there were no endotherms in the DSC scans and no peaks in the WXRD scans. Also, no crystallites were visible with optical microscopy under polarized light. To verify that the absence of any crystalline peaks in the X-ray scans was not an artifact of the low levels of drug present in the films, X-ray diffraction was performed on dry

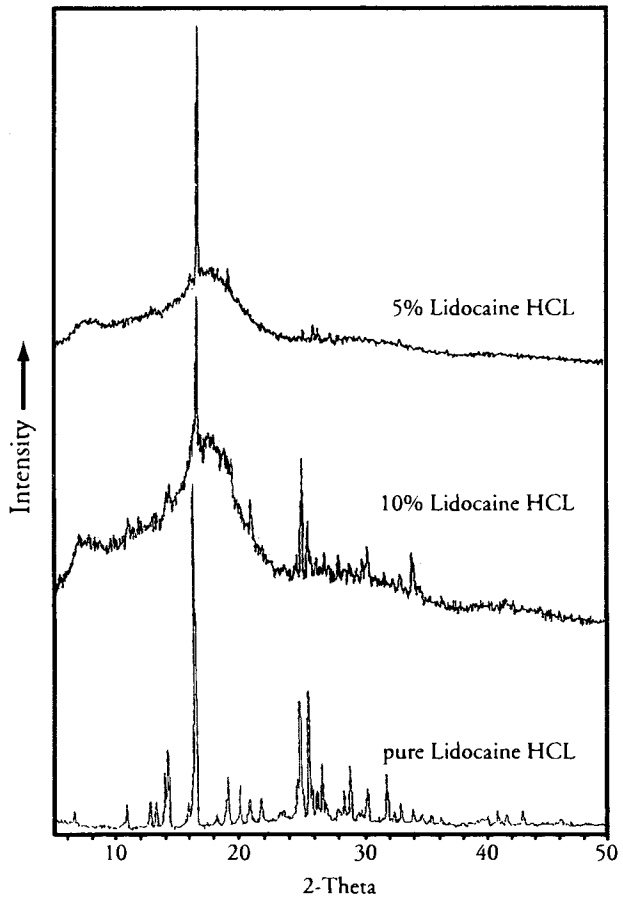

Fig. 3. Wide angle X-ray diffraction scans of a physical blend of Eudragit® E100 with 5% and 10% lidocaine HCL compared with lidocaine HCL crystals.

physical mixtures of 5% lidocaine HCl and 10% lidocaine HCl with Eudragit® E100 that had been powdered with a mortar and pestle. It is shown in Figure 3 that at these drug loadings, lidocaine HCl crystallites are readily identifiable in the unprocessed physical mixtures which is in contrast to the X-ray scans for the extruded films with the same percentages of drug. The absence of crystallinity in the extruded films may be a result of the processing temperatures used that were just above the melting point of lidocaine HCl (80°C).

Lidocaine HCl was found to act as a plasticizer in these films as indicated by the T_g and stress-strain values in Table I. This plasticizing effect was more significant in the 5% lidocaine films cast from ethanol than in the 5% lidocaine extruded films with an average elongation at break of 549% versus 218% and a much lower peak stress of 3.65 kg/cm^2 versus 9.88 kg/cm^2, respectively. The relative error for these measurements ranged from 6 to 19%. When the drug load was increased to 10%, the extruded films were much softer and ductile with an average peak stress of 247 kg/cm^2 and elongation at break of 376%. In addition, increasing the amount of lidocaine from 5% to 10% resulted in a lowering of the glass transition temperature by 10°C. These data show that the lidocaine is a more effective plasticizer in the solution cast films than in the extruded films. This could be a result of the better intermolecular mixing obtained in a solution than in a high viscosity melt.

No plasticizing effect was observed when diphenhydramine HCl was added to Eudragit® E100 with the same plasticizer level. The mechanical properties and the T_g were not affected by the presence of diphenhydramine HCl as shown in Table I. The solubility parameter for lidocaine HCl as calculated by the methods of Hildebrand and Scott(14) is 9.4 $(cal/ml)^{1/2}$, while the solubility parameter of diphenhydramine HCl is 9.7$(cal/ml)^{1/2}$. The solubility parameter of Eudragit® E100 at 9.7$(cal/ml)^{1/2}$ (11) is quite close to that of both actives, indicating that both drugs might be miscible with this polymer. However, the melting point of lidocaine HCl (77–79°C) is much lower than that of diphenhydramine HCl (166–170°C) and, thus, it appears that because the processing temperature (80–130°C) is above the melting point of the active, solubilization can occur which leads to a plasticizing effect.

Complete miscibility between lidocaine HCl and Eudragit® E100, however, was not obtained via hot melt extrusion. The appearance of a two phase system was visually obvious upon adding the drug to the drug-polymer system and thus, the extruded films were somewhat brittle. As previously discussed, however, these regions were amorphous. In addition, there was no change in the X-ray diffraction or DSC scans after 6 months at room temperature. This suggests that lidocaine is partially in solution in the extruded polymer and this partial solubility inhibits the recrystallization of the drug.

The release rate of the drug from the extruded films with 5% lidocaine HCl was much slower than from the cast films with 16% released in 24 hours and 18% in 48 hours. In contrast, the release of drug from the extruded films with 10% lidocaine HCl closely followed that of the solution cast films with 60% released in 5 hours. However, only 78% of the drug from the 10% lidocaine HCl extruded film is released in 24 hours, as compared to 100% of the 5% lidocaine HCl solution cast film. The release rate was slowest from the HDPE-E100 blend in which the polymer was semi-crystalline and there were no water soluble plasticizers present in the films.

The release data of lidocaine from the extruded films are similar to those from other matrix systems (15); i.e., films with low drug content have slow initial release rates that decrease with time. While the dissolution data for the extruded film with 10% lidocaine is similar to the solution cast film, it appears that there is still some drug entrapped in the film. Percolation theories predict that there is a threshold level at which drug clusters in the matrix are no longer isolated, but rather, are connected and may diffuse to the surface (15). The threshold limit for the dispersed drug might be somewhat higher than 10% lidocaine, however, because lidocaine plasticizes Eudragit® E100 and makes it quite sticky at higher drug loadings, it was not possible to extrude these films.

CONCLUSIONS

Extrusion technology is a viable means for preparing free films of the acrylic resin based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters. Triethylcitrate was found to be an acceptable plasticizer for this polymer and processing method. In addition, lidocaine HCl was found to be amorphous, partially miscible with the polymer and able to plasticize the films. Wide angle X-ray diffraction studies showed that the plasticizing effect was correlated to a more open polymer packing. The dissolution rate of the lidocaine extruded films was substantially

affected by drug loading in contrast to the solvent cast films. Both the ductility and dissolution differences between the two film preparation methods were attributed to differences in the amount of drug dissolved in the polymer.

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