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RESEARCH PAPER

Production and Characterization of Hot-Melt Extruded Films Containing Clotrimazole

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ABSTRACT

Hot-melt extrusion technology (HME) was used to prepare muco-adhesive matrix films containing 10% w/w clotrimazole (CT) intended for local drug delivery applications for the oral cavity. This study was aimed at the production and characterization of these drug delivery systems for the prophylaxis and treatment of oral candidiasis. The film system's formulation contained hydroxypropyl cellulose and poly(ethylene oxide) as polymeric carriers, the bioadhesive polycarbophil, and other excipients. The CT formulation was processed at a temperature range of 125–130°C utilizing a Killion extruder (Model KLB-100) equipped with a 6-inch flex-lip die. The films were evaluated for postextrusion drug content, physical and chemical content uniformity, drug release, thermal and crystalline behavior, and bioadhesive strength. The extruded films demonstrated excellent content uniformity and a postprocessing drug content of 93.3% (± 1.0). The degradation product, (*o*-chlorophenyl)diphenyl methanol, was also identified and quantitated using high performance liquid chromatography. The films were determined to exhibit desirable and consistent release properties and bioadhesive strength ($p < 0.05$). The results of this study indicate that HME is a viable technique for the preparation of muco-adhesive films containing clotrimazole for oral candidiasis.

Key Words: Clotrimazole; Hot-melt extrusion; Buccal films; Muco-adhesion; Oral candidiasis; Texture analyzer.

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INTRODUCTION

Hot-melt extrusion technology (HME) is primarily used in the plastics industry for the production of polymeric consumer goods such as plastic bags, sheets, and pipes.[1] Only within the last decade has HME been utilized for the preparation of pharmaceutical dosage forms including pellets,[2] tablets,[3] and films.[4] In 1994, Follonier Doelker and Cole evaluated hot-melt extruded pellets containing high loadings of freely soluble drugs.[2] Repka, McGinity, and coworkers have proposed HME as a promising technique for various drug delivery systems, including films.[5–11] Indeed, the traditional method for preparing films has been the solvent cast method in which water or organic solvents are used; however, recent studies have outlined numerous disadvantages involving these techniques.[4,12] Hot-melt extrusion technology may eliminate or minimize many of these conventional processing limitations,[5–7] resulting in shorter and more efficient processing times to a final product, environmental advantages due to elimination of solvents in processing, and increased efficiency of drug delivery to the patient.

A recent U.S. Patent describes the method of preparation of a hot-melt extruded film for drug delivery.[13] The novel film system described in this patent can be sized and shaped to provide controlled delivery of a therapeutic agent to the buccal, rectal, vaginal, uterine, and other body orifices, in addition to its use for wound care applications. This delivery system could well be utilized in the prophylaxis or treatment of candidiasis in the oral cavity.

Oral candidiasis is an opportunistic, infectious condition caused by a ubiquitous, saprophytic fungus of the genus *Candida*, the most common of which is *Candida albicans*. Prescription drug data have indicated a remarkable increase in the frequency of the disease during the last two decades.[14] Fungal opportunistic infections (OI), including oral candidiasis, are a major cause of morbidity and mortality in cancer patients.[15] Many factors can predispose a patient to oral candidiasis, the most significant of which is the infection associated with AIDS immunosuppression.[16,17] General debilitation, poor oral or dental hygiene, and ill-fitted dentures are some of the other predisposing factors responsible for the cause of candidiasis in the oral cavity. Also, those individuals afflicted with xerostomia, diabetes mellitus, and patients receiving chemotherapy are high risk for opportunistic, fungal infections.[16–19]

Clotrimazole (CT), an imidazole, is used as a first-line topical treatment agent for oral candidiasis. The drug is stable in the solid state under normal storage conditions, but in solution, its stability is pH dependent. It is stable in alkaline medium, however, and hydrolyzes in acidic medium to (*o*-chlorophenyl)diphenyl methanol plus imidazole (CPDM).[20] It has been reported that only a minimal amount of CT is absorbed systemically following topical application to the skin[21] and that only a small percentage of the drug applied to the mucosa can be detected in the serum or urine.[22]

Generally, systemic administration of antimycotics by mouth or intravenously has been used to treat existing mycotic infections. However, long-term systemic antimycotic therapy in high doses is undesirable for treatment of oral infections due to potential side effects. Therefore, to minimize these adverse effects and the ominous risk of drug resistance, topical therapy should be considered the first-line candidate for the treatment of initial or recurrent cases of uncomplicated oral and pharyngeal candidiasis, in addition to AIDS-related oral cavity-manifested fungal diseases.[16]

Unfortunately, topical treatment of candidiasis in the oral cavity is limited to a small number of therapeutic agents coupled with inadequate delivery systems. Nystatin is available as an oral suspension that is designed to be swished in the oral cavity and then expectorated.[23] This delivery system is inconvenient, lacks portability, is subject to a large degree of intersubject variability, and does not address esophageal infections. Nystatin and clotrimazole are available in lozenges that are designed to be dissolved in the oral cavity. The lozenges are sugar-based, and therefore cariogenic (introducing another set of complicating factors) and do not contain excipients with bioadhesive properties to ensure prolonged contact of the drug with the oral mucosa. In addition, this delivery system is not well tolerated by many patients,[24] including the elderly, children, and HIV immunocompromised individuals, due to factors such as decreased control of the oral musculature, xerostomia, and oral pain. Indeed, literature for the two lozenges containing Nystatin and clotrimazole contain cautions about their use in children and the elderly due to the inadvertent swallowing or choking by these two patient populations.[25] Another limitation of these topical delivery systems is the fact that the patient has to be awake or conscious. Several antifungal agents have also been used in the form of mouth rinses, dentifrices, solutions, and gels but have not proven to be completely

successful in eradicating *Candida*-related infections. This may be due to their inefficiency in maintaining the salivary concentrations of the drug above the effective therapeutic concentration for a prolonged period of time,[26] which may in turn be due to the diluent effect of saliva coupled with the cleansing action of the oral musculature.[27]

Inadequate drug delivery systems for oral and pharyngeal candidiasis still limit the efficacy of therapeutics for these and other infectious diseases. Hence an objective of the present study was to develop and produce polymeric matrix films containing clotrimazole utilizing hot-melt extrusion techniques to optimize drug delivery. Furthermore, the study objectives included characterizing and evaluating this antifungal treatment modality using analytical, bioadhesion, dissolution, and thermal studies. Outcomes of this work may provide more efficacious treatment alternatives for candidiasis and other disease processes for significant patient populations.

EXPERIMENTAL

Materials

Hydroxypropyl cellulose (HPC; Klucel® JF) was kindly gifted by Aqualon Div., Hercules, Inc., Wilmington, DE. Polycarbophil (Noveon® AA-1) was supplied by BF Goodrich Specialty Chemicals, Cleveland, OH. Poly(ethylene oxide) (M.W. 100,000) and polyethylene glycol 3350 were purchased from Aldrich Chemical Company, Milwaukee, WI. Butylated hydroxytoluene (BHT), propyl gallate, potassium dibasic phosphate, and clotrimazole were obtained from Spectrum Chemical, Inc., Gardena, CA. Other reagents (HPLC grade) were purchased from Fisher Chemicals, NJ. Schering-Plough HealthCare Products, Memphis, TN kindly gifted (*o*-chlorophenyl)diphenyl methanol.

Methods

Formulation and Hot-Melt Extrusion

Based on previous studies,[3,6,9] hydroxypropyl cellulose (HPC) and poly(ethylene oxide) (PEO) were chosen as polymeric carriers for the matrix film formulations. Polycarbophil (Noveon AA-1) was incorporated as a bioadhesive[7] and polyethylene glycol (PEG 3350) as a plasticizer. Butylated hydroxytoluene (BHT) and propyl gallate were utilized as antioxidants. Propyl gallate has also been reported to exhibit antifungal properties in addition to its potential synergistic effect with BHT.[28]

Table 1. Formulation ingredients of the films produced by hot-melt extrusion.

Ingredient	Category
Hydroxypropyl cellulose (JF)	Thermoplastic polymer
Poly(ethylene oxide) (M.W.: 100 k)	Hydrogel
Noveon AA-1 (polycarbophil)	Bioadhesive polymer
Polyethylene glycol 3350	Plasticizer
Butylated hydroxytoluene	Antioxidant
Propyl gallate	Antioxidant
Clotrimazole (10% w/w)	Antifungal

Prior to the extrusion process, all of the ingredients in the formulation were subjected to particle-size reduction, sieving, and initial blending. Final blending was achieved using a V-blender for 20 min. The blended powders were then dried in an oven at 50°C for 24 h to minimize moisture content.[5] The extrusion temperatures ranged from 125–130°C with a screw speed of 70 rpm.

Based on prior knowledge of extrusion technology and preliminary formulations, a 500 g batch of a lead formulation (Table 1) was extruded into a thin film utilizing a Killion extruder (Model KLB-100, Davis-Standard Corp., Pawcatuck, CT, USA) (Fig. 1). This formulation containing the active, thermoplastic polymers, drug release retardants, and other additives was fed into the hopper and transferred inside the heated barrel by a rotating extruder screw. During HME, polymeric materials soften and become flexible primarily due to the shearing effect of the rotating screw; however, heat from the thermal devices attached to the barrel also aid in the softening of the polymers.[5] The molten polymeric mass is continuously pressurized as it moves forward in the barrel due to the rotation of the screw. The mass is then transformed into different shapes based on the shape of the die attached at the end of the barrel. In the present study, a 6-inch flex-lip die was utilized, and the extruded film had a thickness range of 0.34–0.36 mm. The film was then collected in a roll, labeled, and sealed in foil-lined 5-mil polyethylene bags (1 mil = 25.4 μm or 0.001 inch).

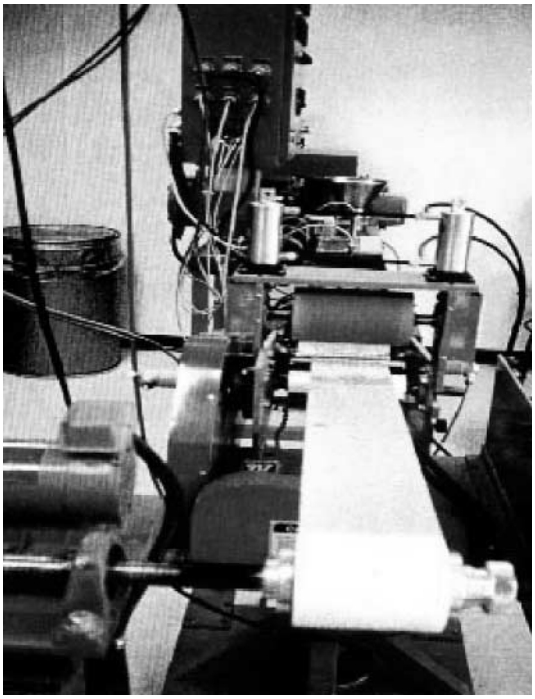

Figure 1. Hot-melt extruder with film die assembly (Killion KLB-100).

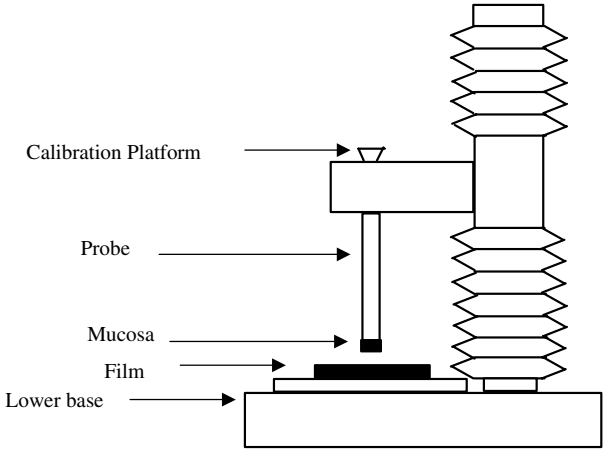

Figure 2. Schematic of texture analyzer.

Determination of Drug Content and Degradation by High-Performance Liquid Chromatography (HPLC)

Instrumentation and Chromatographic Conditions

The chromatographic system consisted of a Waters 600 pump and a dual wavelength Waters 2487 UV detector. The column used was a Novapak C18 (3.9×150 mm ID and 4 μ particle size). The mobile phase consisted of methanol and 0.025 M potassium dihydrogen phosphate in the ratio of 3:1, and the flow rate was 1 mL/min. The injection volume for the standard and the sample preparations was maintained at 20 μL, and the column effluent was monitored by UV absorption at 215 nm for both the active clotrimazole (CT) and its degradant, (*o*-chlorophenyl)diphenyl methanol (CPDM).

Stock solutions of CT and CPDM were prepared using methanol. Five calibration standards were prepared for both CT and CPDM by diluting their stock solutions with methanol in appropriate quantities and were then injected into the HPLC system. Regression analysis was performed on the data points generating the calibration curve. Random samples ($n = 7$) were taken from the extruded film. The samples were weighed and placed in a 50 mL volumetric flask. Thirty mL of methanol was added to the flask and sonicated for 10 min or until the entire film was dissolved. The flasks containing the samples were then made up to 50 mL using methanol and centrifuged for 10 min. The supernatant was removed and filtered using a 0.45 μL nylon filter and injected into the chromatographic system. The content of CT and CPDM was calculated from the equation obtained from the regression analysis.

Bioadhesion

Tests for bioadhesion were performed on the HME film containing clotrimazole using a Texture Analyzer (TA.XT2*i*, Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK) (Fig. 2) equipped with Texture Expert™ software. Random samples ($n = 7$) were collected from different areas of the film. Each sample was wetted with nanopure water for 60 s and placed on a slotted die-cut fixture (TA-303 Indexable Adhesive Test Rig) on the base of the Texture Analyzer. Rabbit intestinal mucosa was attached to a 7 mm diameter, circular steel probe using a cyanoacrylate adhesive. The Texture Expert software was programmed such that the probe approached the film at a predetermined rate of 1 mm/s, applied a force of 3.5 N for 60 s, and then withdrew at a speed of 0.5 mm/s. These parameters were chosen based on previous studies.[6–10] During the withdrawal phase of the probe, the Texture Expert software recorded the

force deflection profiles. The maximum force required to detach the film on the lower base die from the upper probe, known as the peak adhesive force (PAF), the elongation at adhesive failure (EAF) of the films, and the area under the curve (AUC), representing the work of adhesion, were determined by the generated profiles. The results were used to determine the adhesive uniformity within the extruded film.

Dissolution Studies

Dissolution studies were performed utilizing a Hanson SR8-Plus dissolution test system according to USP XXIII apparatus 5, paddle-over-disk method. Nine hundred milliliters of 1% w/v SLS at 37°C was used as the dissolution medium and the paddle rotation speed was 50 rpm. Samples were collected at predetermined time intervals and analyzed by HPLC. The studies were performed in triplicate.

Differential Scanning Calorimetry (DSC)

The DSC thermograms were recorded on a differential scanning calorimeter (Perkin-Elmer Pyris 1 DSC). Approximately 3–4 mg of each sample of pure drug, physical mixture, and extruded film were hermetically sealed in a flat-bottomed aluminum pan and heated over a temperature range of 20–200°C at a linear heating rate of 10°C/min. The samples were then immediately cooled from 200–20°C at a linear cooling rate of 10°C/min.

X-ray Diffractometry (XRD)

An APD 3520 Philips x-ray diffractometer with a PW 1720 x-ray generator and a PW 1710 diffractometer control was employed to study the crystallinity of the drug and excipients in the hot-melt extruded films and also in their respective physical mixtures. The generator operating voltage and current were 40 kV and 40 mA, respectively. The scanning speed was 2°/min, and the 2θ scanning range was from 5° to 50°.

Data Analysis

Statistical analysis was carried out using Microsoft Excel® and the results are reported as mean ± standard deviation (SD). A $p < 0.05$ was considered statistically significant for drug content and bioadhesive uniformity within the extruded film.

RESULTS AND DISCUSSION

Drug Content and Degradation

The hot-melt extruded films demonstrated excellent content uniformity both physically and chemically. The theoretical postextrusion content of CT remaining in the films was determined to be 93.3% (±1.0) via HPLC analysis. The degradation product within the extruded films can be visualized in Fig. 3(a). It has been proposed that this degradant of CT results

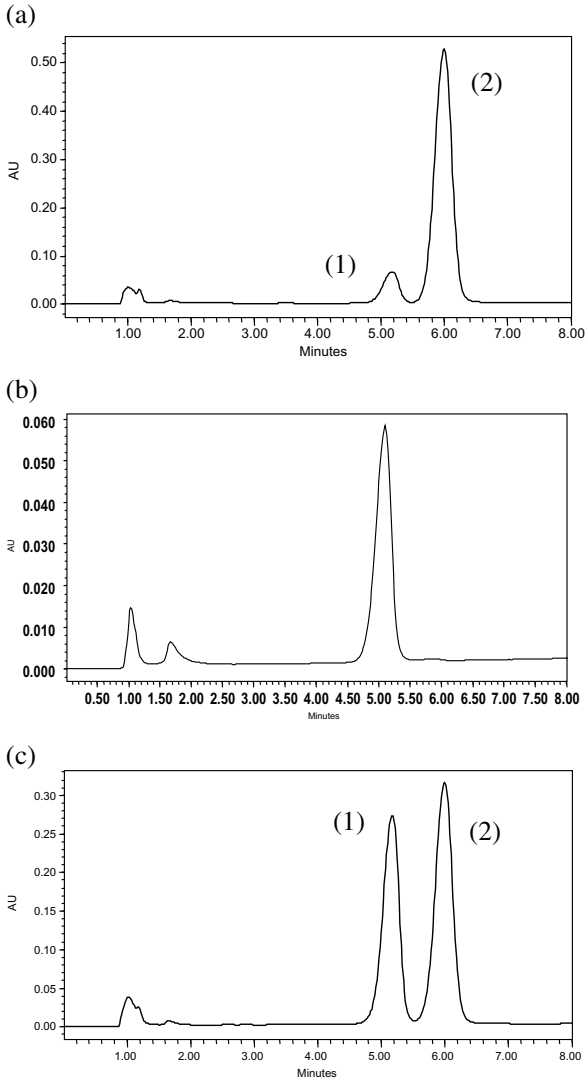

Figure 3. (a) Chromatogram of the HME film showing (1) (*o*-chlorophenyl)diphenyl methanol (CPDM) and (2) Clotrimazole (CT); (b) Chromatogram of pure CPDM; and (c) Chromatogram of HME film after spiking with CPDM showing (1) CPDM and (2) CT.

from hydrolysis of the imidazole group to form (*o*-chlorophenyl)diphenyl methanol (CPDM).[29] Indeed, the degradation product in the films was identified as CPDM by spiking the extracted sample of the film with a standard CPDM stock solution. The chromatogram of pure CPDM is shown in Fig. 3(b). Figure 3(c) illustrates the spiking of the extruded film sample with CPDM stock solution. It was consequently observed that there was an increase in the AUC of the degradant peak after addition of the standard CPDM sample. In addition, the retention times of the degradant peak and that of CPDM were identical. Hence, it was concluded that the degradation product in the film was (*o*-chlorophenyl) diphenyl methanol. The CPDM content in the films was calculated to be 6.8% (± 0.3).

Bioadhesion

A representative force deflection profile obtained for the HME films containing CT is shown in Fig. 4. Peak adhesive force (PAF), elongation at adhesive failure (EAF), and work of adhesion (AUC) calculated from this type of profile are expressed in SI units and listed in Table 2. These values are consistent with and appropriate for bioadhesion as reported by other researchers.[30] It should be noted that these data indicate that there is insignificant variation in the PAF, AUC, and EAF within the extruded film ($p < 0.05$). These results demonstrate that the films produced via hot-melt extrusion in this study are uniform and therefore are supportive of further optimization and evaluation in the clinical setting.

Dissolution Profiles

The in vitro release profile (Fig. 5) indicated an apparent zero-order release over 6 h of testing (80% drug release) ($R^2 = 0.999$). Nevertheless, the entire curve indicates that there is a prolonged release of the drug extending up to 10 h. The dissolution data were fitted according to the following exponential equation,[31] which is often used to describe the drug release behavior from polymeric matrices:

$$M_t/M_\infty = kt^n \quad (1)$$

where M_t/M_∞ is the fraction of drug released, t is the release time, k is a kinetic constant characteristic of the drug polymer system, and n is a release exponent indicative of the release mechanism of the drug. When $n = 0.5$, the drug is released from the polymer with a Fickian diffusion mechanism. Furthermore, for $0.5 < n < 1$, a nonFickian solute diffusion is observed. The condition in which $n = 1$ provides a case II transport mechanism (erosion) with zero-order kinetics.[32]

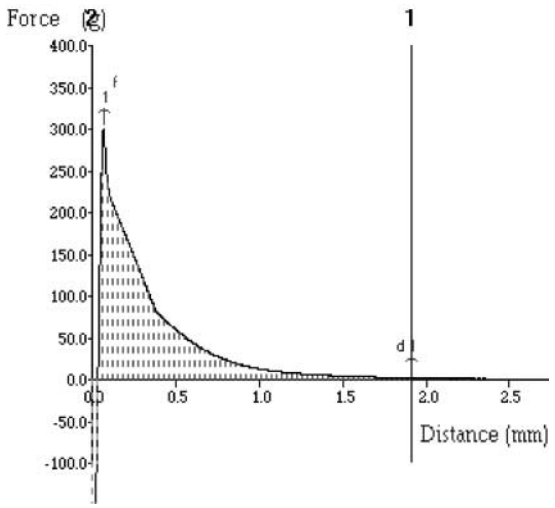

Figure 4. Force deflection profile of an HME film sample containing clotrimazole recorded by Texture Expert software.

Table 2. Results of in-vitro bioadhesion studies[a] performed on hot-melt extruded films containing clotrimazole utilizing a Texture Analyzer equipped with Texture Expert software.

Peak force (PAF) (N)	Work of adhesion (AUC) (N mm)	Elongation at adhesive failure (EAF) (mm)
3.63 (0.15)	0.61 (0.03)	1.22 (0.05)

[a]Rabbit intestinal mucosa used as substrate ($n = 6$). Standard deviation denoted in parenthesis.

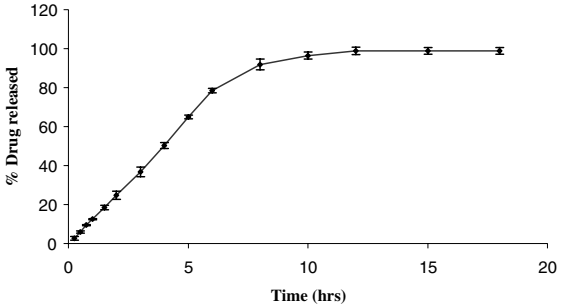

Figure 5. Dissolution profile of clotrimazole released from the hot-melt extruded films in artificial saliva at pH 6.8 (rpm = 50) ($n = 3$).

Via a power regression model (MS Excel) and Eq. (1), the value of n for the release of clotrimazole from the HME films was calculated to be 1.04, thus suggesting an erosion controlled release. These data are also suggestive of a polymer dissolution model (one of the three mechanisms of constant drug release), which is best described for a drug of low aqueous solubility and for a release that proceeds with zero-order kinetics.[33] These data, coupled with the drug content uniformity and bioadhesion testing results, indicate that the formulation and the delivery system prepared by HME may be a promising prototype for extended release of clotrimazole to the oral mucosa for the treatment of oral candidiasis. However, further optimization of the formulation and extrusion techniques is needed to reduce the clotrimazole degradation within the films. These objectives are the subject of ongoing studies.

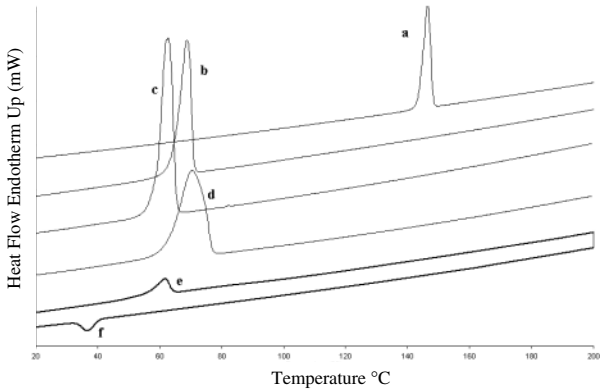

Figure 6. DSC thermograms of (a) clotrimazole; (b) polyethylene glycol (PEG 3350); (c) the physical mixture; (d) poly(ethylene oxide) (M.W. 100,000); (e) the extruded film (heating phase); and (f) the extruded film (cooling phase). (Note: Thermograms separated for clarity).

Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD)

Figure 6 shows an overlay of DSC thermograms of pure clotrimazole, PEO and PEG 3350, the physical mixture and the HME film containing clotrimazole. The endotherm exhibited by the extruded film [Fig. 6(e)] at 66°C indicates that PEO and PEG are in crystalline form (M.P of PEO is 69.1°C and PEG 3350 is 62.9°C). It was also observed that there was no clotrimazole peak present in either the film or the physical mixture. The observation from the thermogram of the film could be due to the clotrimazole existing in solid solution within the extrudate or due to its solubilization in PEO and PEG, which melt well below the melting point of clotrimazole. However, there was no recrystallization exotherm corresponding to clotrimazole observed upon cooling the film from 200–20°C at a linear cooling rate of 10°C/min [Fig. 6(f)]. Therefore, it is highly probable that clotrimazole is present in solid solution within the HME film.

Wide angled x-ray diffraction (WAXRD) studies were performed on the extruded film, the physical mixture, PEO, and the pure drug to further study the crystallinity of the drug at room temperature. Results of this study are shown in Fig. 7. A high degree of crystallinity was found in the pure CT with primary peaks observed at a 2θ value of 9.15 and 12.35 [Fig. 7(a)]. These primary peaks were also observed in the physical mixture [Fig. 7(c)] but no crystalline pattern corresponding to clotrimazole was observed within the extruded films [Fig. 7(b)].

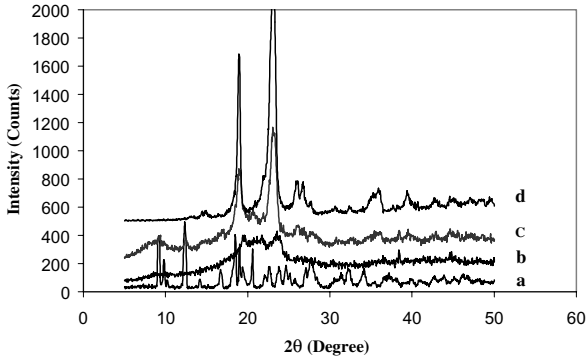

Figure 7. X-ray diffraction patterns of the (a) pure clotrimazole; (b) extruded film; (c) the physical mixture; and (d) poly(ethylene oxide) (M.W. 100,000).

These data indicate that clotrimazole is in a molecular dispersed state within the HME films. However, these studies also confirmed that PEO exhibits crystallinity within the extruded films in that the peaks at a 2θ value of 18.95 and 22.90 [Fig. 7(d)], which correspond to the pure PEO, are still present within the extruded film.

CONCLUSIONS

This study demonstrates that hot-melt extrusion is a viable technique for preparing sustained-release bioadhesive films for use in topical treatment of candidiasis in the oral cavity. The data presented suggest that a homogenous, mucoadhesive film can

be produced via HME, and that release of clotrimazole can be sustained for more than 8 hours, thus reducing the frequency and increasing the efficiency of the dose administered. The degradation observed, most likely due to hydrolysis of clotrimazole, may be minimized or eliminated by modifying formulation, processing, and/or production methods of the system. Hot-melt extrusion is the subject of further studies for production of bioadhesive dosage forms for oral candidiasis and other mucosal and topical applications.

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