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European Journal of Pharmaceutics and Biopharmaceutics 66 (2007) 95–105
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Characterization of hot-melt extruded drug delivery systems for onychomycosis

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Received 10 April 2006; accepted in revised form 21 August 2006
Available online 1 September 2006

Abstract

The objectives of this investigation were to study the physico-chemical properties of hot-melt extruded (HME) films for onychomycosis and to determine the stability of the model antifungal drug incorporated within these films. The influence of etching and instrument variables on the bioadhesion of these drug delivery systems for the human nail was also studied. Six 250 g batches (F1–F6) of hydroxypropyl cellulose (HPC) and/or poly(ethylene oxide) films containing ketoconazole (20%) were extruded using a Killion extruder (Model KLB-100). The thermal properties of HME films were investigated using differential scanning calorimetry (DSC). Scanning electron microscopy (SEM) was used to examine the surface morphology of the films and X-ray diffraction (XRD) was used to investigate the crystalline properties of the drugs, physical mixtures as well as the HME films. Stability studies were performed on the films stored at 25 °C/60%RH. The bioadhesive properties of these films were investigated on the human nail (ex vivo) using a Texture Analyzer®. The nail samples tested were either non-treated (control) or treated with an etching gel. The parameters measured were peak adhesion force (PAF) and area under the curve (AUC). The Hansen solubility parameter was calculated using a combination of Hoy and Hoftyzer/Van Krevelen methods to estimate the likelihood of drug–polymer miscibility. SEM provided direct physical evidence of the physical state of the drug within the films. The theoretical post-extrusion content of ketoconazole remaining in the six film batches ranged from 90.3% (±2.2) to 102.4% (±9.0) for up to 6 months and from 83.9% (±3.6) to 91.6% (±3.0) for up to 12 months. Bioadhesion studies of HPC film tested on 'etched' nails recorded significantly higher PAF and AUC than that of the non-treated 'control' nails. Ketoconazole was found to be relatively stable during the extrusion process. Melting points corresponding to the crystalline drugs were not observed in the processed films. The Hansen solubility parameters predicted miscibility between the polymers and the drug. The predictions of the solubility parameters were in agreement with DSC, XRD and SEM results. Bioadhesion measurements of the film on the human nail substrate were generally higher for the etched nails than that of the control nails.

Keywords: Nail; Hot-melt extrusion; Stability; Bioadhesion; Texture analyzer

1. Introduction

The transdermal and transmucosal route of drug administration offers many advantages to other methods of drug delivery, including elimination of first pass metabolism and when local therapy is desired [1]. Transdermal and transmucosal films for drug delivery are generally produced by casting techniques using organic or aqueous solvent systems. Aitken-Nichol et al., discussed the numerous disadvantages accompanying these techniques including long processing times, organic solvent disposal, and excessive costs [2].

Onychomycosis has received much attention recently due to the high incidence of nail infections and problems associated with its treatment [3]. Negative aspects

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doi:10.1016/j.ejpb.2006.08.013

associated with oral systemic antifungal therapy for onychomycosis include its limited success rate, toxicity, high cost of medication and increased microbe resistance [4]. In contrast, topical therapy does not lead to systemic side effects or drug interactions. Currently, however, there is no topical treatment modality that is effective, which is most likely due to poor penetration of antimycotics through the nail plate. The nail plate is a relatively thick and dense structure that inherently inhibits adequate penetration of the drug being applied.

Hot-melt extrusion (HME) has been and presently is one of the most widely applied processing techniques in the plastic industry. For pharmaceutical systems, several research groups have recently demonstrated that the HME technique is a viable method to prepare numerous drug delivery systems. These systems include granules, sustained release tablets, transdermal and transmucosal drug delivery systems [5–7]. For pharmaceutical applications, HME offers many advantages over traditional processing techniques which are as follows: (1) solvents are not used in this process; (2) fewer processing steps are needed; (3) there are no requirements for the compressibility of the active ingredients; (4) intense mixing and agitation during processing cause suspended drug particles to de-aggregate in the molten polymer, resulting in a more uniform dispersion of fine particles; and (5) bioavailability of the drug substance may be improved when it is solubilized or dispersed at the molecular level in HME dosage forms [5].

HME technology has recently been demonstrated to be applicable for topical treatment modalities including the recalcitrant disease process, onychomycosis (fungal nail) [8]. Morphology studies of the human nail via scanning electron and atomic force microscopy have revealed a significant change in surface topography (both qualitative and semi-quantitative) when the dorsal nail plate was subjected to ''etchants'' or surface modifiers [9].

HME is one of the most useful techniques for the manufacture of numerous drug delivery systems via polymeric extrudates. Depending on the solubility of the drug in the polymer, the drug can exist in different physical states, such as in the dissolved state or in the crystalline state. The physical state of the drug in the formulation can greatly affect its *in vitro* and *in vivo* release characteristics [10]. Knowledge of the different states of the drug is also important to model appropriately the release kinetics of the drug from these formulations. Stability testing provides evidence on how the quality of an active varies with time under the influence of a variety of environmental factors, such as temperature and humidity, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

Bioadhesion is generally defined as the ability of a biological or synthetic material to stick to a substrate (e.g. nail) [11]. This results in the adhesion of the material to the tissue for an extended period of time. Numerous mechanisms of adhesion or mucoadhesion have been proposed. However, one factor in common to achieve increased bioadhesion in any system is an increase in surface area. It was proposed that surface modification of the dorsal nail plate (etching) may selectively increase microporosity or roughness and thus increase surface area and wettability for a drug delivery system's bioadhesion and retention. Optimal bioadhesion is essential for the successful application of a bioadhesive drug delivery system for ''trans'' delivery to the human nail such that controlled release is attainable to elicit the desired therapeutic response.

Ketoconazole was utilized as a model drug in the current study. It is an imidazole antifungal agent with a five-membered ring structure containing two nitrogen atoms, often used to treat fungal infections of the fingernails, toenails, mouth (thrush), lungs, vagina and blood. Ketoconazole works principally by inhibition of cytochrome P450 14-alpha-demethylase (P45014DM) [12].

No reports of *ex vivo* testing on the human nail have appeared in the literature. Physico-chemical, stability and bioadhesive characteristics are important parameters in the product development of films for transnail applications. Indeed, a polymeric film that possesses inherent bioadhesive properties has the added benefit of simplifying the dosage form design and reducing the preparation cost, due to the elimination of an additional adhesive layer in the system. It is also beneficial for the film to have adequate adhesion strength so that desirable retention at the application site can be achieved. The objective of this study was to investigate, *ex vivo*, the influence of etching and instrument variables on the bioadhesion of HME drug delivery systems for the human nail. In addition, the physico-chemical properties and the stability of the incorporated model antifungal agent within these films were also investigated.

2. Materials and methods

2.1. Materials

Tip nail pieces were obtained from the fingers of healthy volunteers (University of Mississippi, IRB # 03-045), using nail clippers. The samples were collected and immediately sealed in four mil polyethylene bags. Hydroxypropyl cellulose (HPC) (Klucel® EF; molecular weight (MW), 80,000 and Klucel® LF; MW, 95,000) was kindly gifted by the Aqualon Company (Wilmington, DE). Poly(ethylene oxide) (PEO) (MW, 100,000) was obtained from Aldrich Chemical Company (Milwaukee, WI). Noveon® AA-1 was obtained from Specialty Chemicals (Cleveland, OH).

2.2. Methods

2.2.1. Preparation of HME films containing ketoconazole

Six 250 g batches (F1–F6) of HPC and/or PEO films containing ketoconazole (20%) were prepared by HME using a Killion extruder (Model KLB-100). The extruder was preheated to melt temperature. For purging purposes, polyethylene pellets were added to the hopper and passed through the extruder for 5 min (this procedure was

repeated for each individual batch). All additives were blended and thoroughly dried at 50 °C for 24 h before extrusion. The dry blend of the drug and polymer was fed into the hopper and transferred into the heated barrel by a rotating extruder screw. The extruder temperature ranged from 150 to 160 °C. Homogeneous films were obtained with a thickness range of 9–13 mil or 0.23–0.33 mm (1 mil = 25.4 μm or 0.001 in.). The extrudate was collected in rolls, labeled and stored unpackaged at 25 °C/60%RH. Initial testing was commenced after 7 days of storage.

2.2.2. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of the drug, physical mixtures and HME films. The DSC thermograms were recorded using a differential scanning calorimeter (Perkin-Elmer Pyris 1 DSC). Data analysis was performed using Pyris Manager™ software. Samples were hermetically sealed in a flat-bottomed aluminum pan and heated from 25 to 200 °C at a linear heating rate of 10 °C/min. Ultra-high pure nitrogen was used as the pure gas at a flow rate of 30 ml/min.

2.2.3. Scanning electron microscopy

Scanning electron microscopy (SEM) was used to study the surface morphology of the HME films. The samples were mounted on an aluminum stage using adhesive carbon tape and placed in a low humidity chamber for 12 h prior to analysis. Samples were coated with gold for 90s using a Hummer® 6.2 Sputtering System (Anatech LTD, Springfield, VA) in a high vacuum evaporator. SEM was performed using a JEOL JSM-5600 scanning electron microscope operating at an accelerating voltage of 5 kV and a 15 μA emission current.

2.2.4. X-ray diffraction analysis

X-ray diffraction (XRD) studies were done to confirm the crystalline properties of the film samples. The studies were performed on a D-8 Advance X-ray Diffractometer (Bruker AXS) equipped with a Sol-X detector and a Diffrac Plus® software. The generator voltage and current were 40 kV and 40 mA, respectively. The 2θ scanning range was from 5° to 50°. The step size at each step was 0.02° and the dwell time at each step was 1 s.

2.2.5. Stability testing of active substance

Stability studies were performed on the films stored at 25 °C/60%RH in an unpackaged condition. Random samples ($n = 4$) were taken from all of the batches immediately post-extrusion and at pre-determined intervals. These samples were analyzed for drug content by a stability indicating high performance liquid chromatography (HPLC) method.

2.2.6. Instrumentation and chromatographic conditions

The chromatographic system consisted of a Waters 600 pump and a dual wavelength Waters 2487 UV detector. A 3.9 × 300 mm, μBondapak column, 10 mm particle size (Waters, Milford, MA, USA) was used for the analysis of the drug. The mobile phase used was 75% methanol and 25% 0.02 M, pH 7.5 phosphate buffer. The flow rate was 2 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 225 nm for the active drug. The HPLC method used has proved capable of detecting the degradation product of ketoconazole. The peak of the degradation product was formed upon the exposure of drug solutions for stress testing (forced-degradation studies). Conditions for stress testing of drug substance in solution are shown in Table 1. The HPLC method used was validated with respect to limit of detection, limit of quantitation, range of detection, linearity, variation within replicates, intra- and inter-day

Table 1
Conditions for stress testing of drug substance (ketoconazole) in solution [26]

Storage conditions	Testing period[a]
pH ±2, room temperature	2 weeks
pH ±7, room temperature	2 weeks
pH 10–12, room temperature	2 weeks
H_2O_2, 0.1–2% at neutral pH, room temperature	24 h

[a] Storage times given or 5–15% degradation, whichever appeared first.

Fig. 1. Photo of texture analyzer (TA.XT*plus*) (from Texture Technologies Corp.).

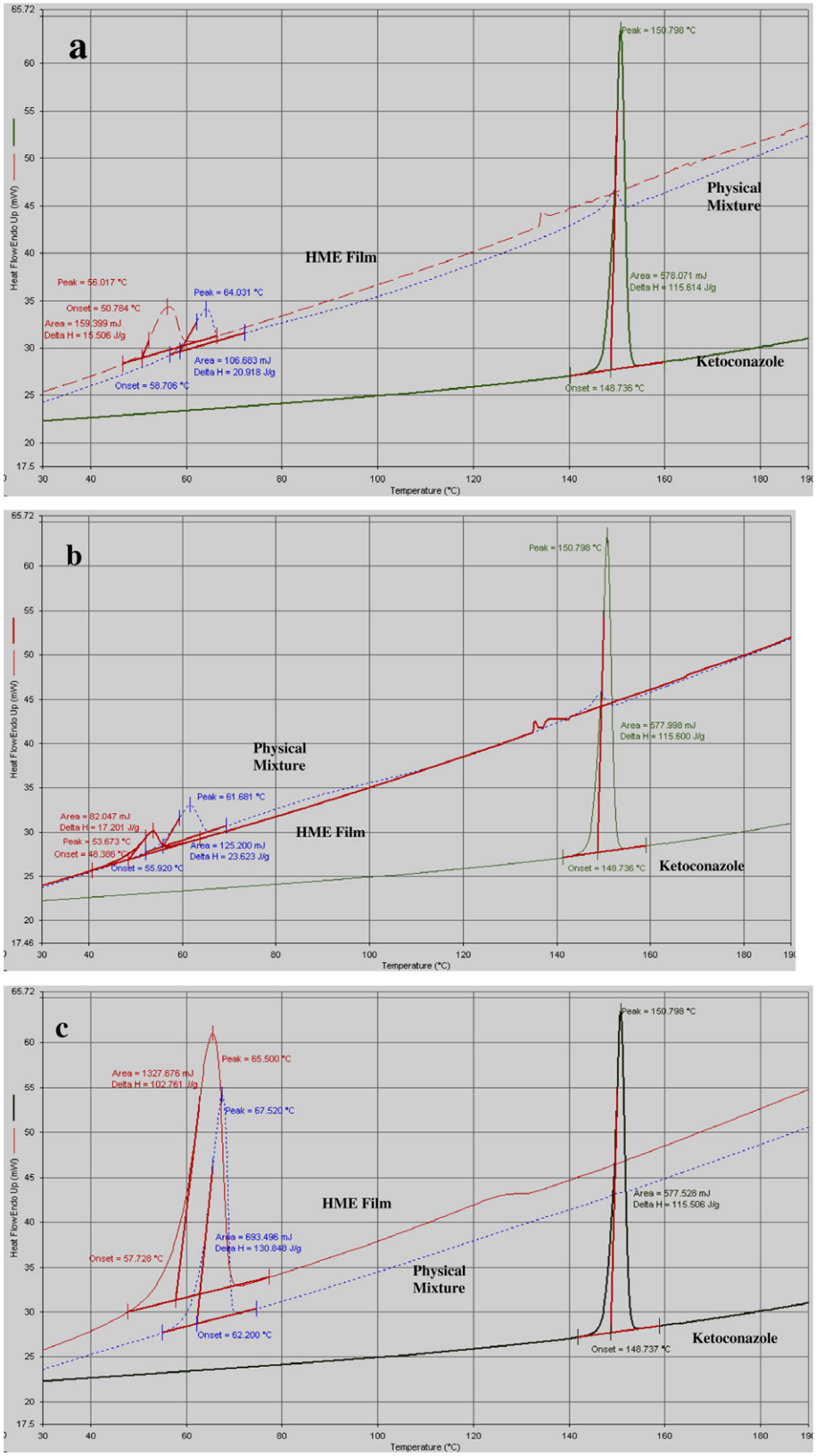

Fig. 2. Differential scanning calorimetry (DSC) thermograms of physical mixtures and hot-melt extruded films stored at 25 °C/60%RH (a) Klucel® EF film (b) Klucel® LF film and (c) PEO N-10 film.

accuracy and precision and robustness. The linear dynamic range for the detection of ketoconazole for the method was calculated to be 0.1–1000 μg/mL. Concentrations above 1500 μg/mL resulted in a saturated detector response. The percent coefficient variation within replicates varied from 0.024% to 1.427%.

2.2.7. Bioadhesive studies

Tip nail pieces were obtained from the fingers of healthy volunteers using nail clippers. Bioadhesion tests were performed with these HME films using a Texture Analyzer® (TA.XT2*i*, Texture Technologies Corp., Scarsdale, NY/ Stable Micro Systems, Godalming, Surrey, UK) (Fig. 1) equipped with Texture Expert™ software. The extruded films used in this work were wetted with 300 μl of nanopure water for approximately 10 s to allow the polymer chains to hydrate prior to testing. The films were then applied to human nail samples, *ex vivo*. The nail samples were either non-treated (control) or treated with PA gel (etched) for a time period of 60 s. Each nail sample was placed and secured on a slotted die-cut fixture (a modified TA Indexable Adhesive Test Ring) on the base of the Texture Analyzer®. The instrument variables such as contact force, contact time and speed of withdrawal of the probe were studied using these films. The parameters measured were peak adhesion force (PAF) and the area under the curve (AUC).

2.2.8. Solubility parameter calculation

The Hansen solubility parameters of the compounds were calculated from the chemical structures using a combination of Hoftyzer/Van Krevelen, and Hoy to estimate drug/polymer miscibility [13]. Solubility parameters were calculated for HPC, PEO and ketoconazole and the average value obtained from both the methods was used to predict polymer–drug miscibilities.

2.2.9. Statistical analysis

Statistical differences were determined utilizing either a Student's *t*-test or a one-way analysis of variance (ANOVA). A statistically significant difference was considered when $P < 0.05$.

3. Results and discussion

3.1. DSC studies

Fig. 2 depicts overlays of DSC thermograms of pure ketoconazole, physical mixtures and HME films containing ketoconazole. The DSC curve of pure ketoconazole showed only one endothermic peak at 148 °C. In case of ketoconazole/Klucel® EF and ketoconazole/Klucel® LF (Figs. 2a and b), the DSC thermograms of the physical mixture show melting endotherm corresponding to ketoconazole in the

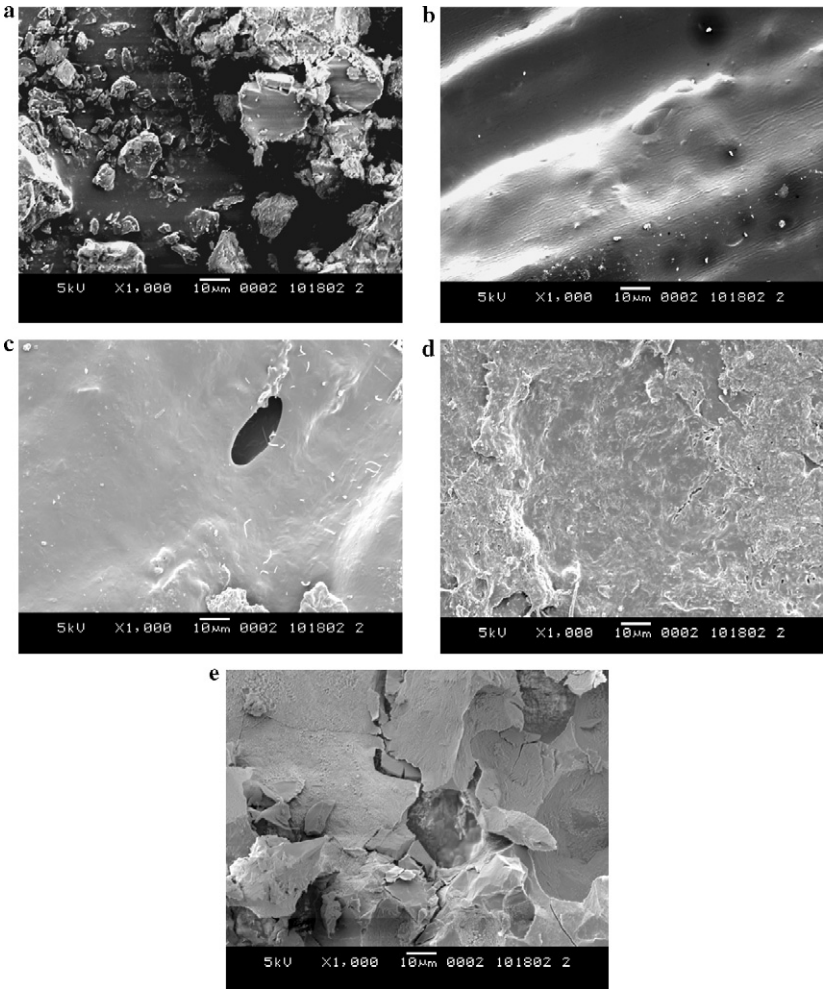

Fig. 3. Scanning electron micrographs of (a) ketoconazole, (b) Klucel® EF Film, (c) Klucel® LF Film, (d) PEO N-10 Film, (e) cross-section of HME film.

heating phase. However, the DSC thermograms of HME films indicate the absence of melting endotherm corresponding to ketoconazole. The absence of the endothermic peak of ketoconazole in the HME films clearly demonstrates the formation of solid solution within the polymer matrix [8]. The DSC thermograms of the formulation containing ketoconazole and PEO-N10 (pre- and post-extrusion) are represented in Fig. 2c. It was observed that there was no melting endotherm corresponding to ketoconazole in the thermograms of both the HME formulation as well as the physical mixture. Therefore, the absence of the ketoconazole melting peak in the thermogram of the HME film can be either due to the drug being in amorphous solid solution or merely due to the solubilizing of the crystalline drug in the melted PEO during the heating cycle of the DSC study. Hence, it was suggested that DSC studies should be augmented with XRD studies (discussed later in this section) to study the crystallinity of the drug incorporated into the PEO films.

The DSC thermograms of ketoconazole/PEO N-10 HME film also demonstrated a decrease in the melting point of the PEO (by approximately 6 °C) post-extrusion (Fig. 2c). Depression in melting points of extruded PEO was also observed in studies reported earlier which was, however, not further explored [7,14]. This may be due to the transition of the extended chain crystallites into folded-chain crystallites upon rapid cooling of the melt after HME [15,16]. The less stable folded-chain crystallites melt at a lower temperature than the melting point of extended crystals [15,17,18]. It was also reported earlier that the greater the number of folds, the lower the melting point [19]. This decrease in melting point can also possibly be due to drug–polymer interactions [1].

3.2. Scanning electron microscopy

SEM was used to examine the surface morphology of the drug and HME films. This technique provided direct visual evidence of the presence of dispersed drug within the matrix. SEM study of the pure drug indicated that the compound exists as plate-like crystals (Fig. 3a). The SEM studies of drug loaded HME films did not reveal crystallization of ketoconazole on the surface of all of the films extruded (Fig. 3b–e). This can be explained by the fact that if the compound is in its crystalline form, the surface of the film would not have been smooth when viewed with SEM. Theoretically, some of the compound will extend above the surface of the film and can be viewed with a SEM, if the crystal form of the compound is positively or neutrally buoyant relative to the melted polymer medium. If the compound is negatively buoyant relative to the medium, the compound should sink and can be observed if a cross-section of the film is observed with an SEM. Therefore, the SEM studies indicated that at 20% w/w drug load, the antimycotic was most likely molecularly dispersed within the polymer suggesting drug/polymer miscibility. These studies suggest that it is highly probable that ketoconazole is present in solid solution within the HME films. The solid-state dissolution of the drug may also attribute to the good content uniformity of the HME systems. Therefore, the SEM results are consistent with the results obtained from DSC study. These findings are in agreement with previous research on hot-melt extrudates containing clotrimazole [20]. Studies utilizing X-ray diffraction techniques are discussed below to confirm the crystalline properties of these and other hot-melt extruded dosage forms.

3.3. X-ray diffraction analysis

The XRD patterns of ketoconazole, physical mixtures and the HME films are presented in Fig. 4. Ketoconazole has distinct crystalline peaks at 2θ angles of 10° and 14°. These diffraction patterns of high intensity reveal crystallinity of the drug. However, there were no crystalline peaks corresponding to ketoconazole observed in the HME films stored at 25 °C/60%RH for 14 days post-extrusion. This suggests that the drug existed in an amorphous solid solution within the polymer matrices post-extrusion. This can be explained by the fact that ketoconazole was solubilized in polymer during the extrusion process and did not recrystallize upon quench cooling over the chill roll after the extrusion process. Prodduturi et al., found similar results with hot-melt extruded clotrimazole films for up to one month of storage at 25 °C/60%RH [18].

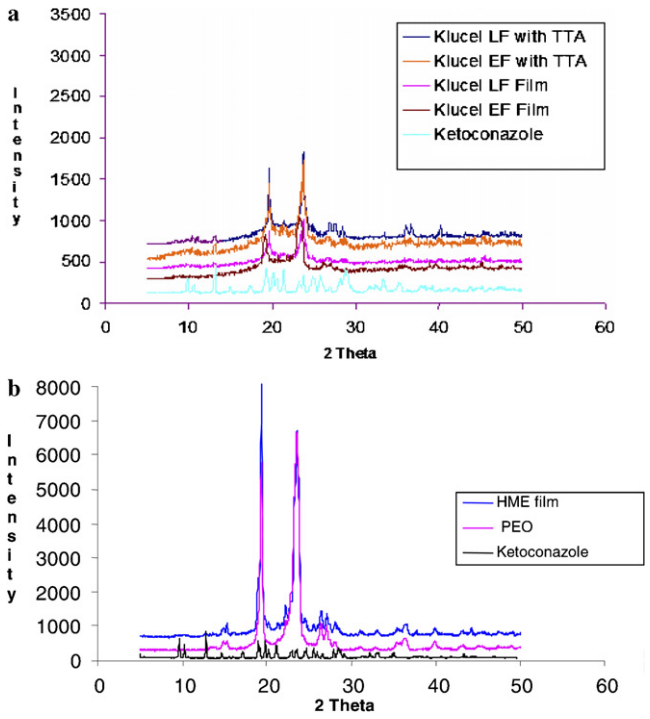

Fig. 4. (a) XRD patterns of ketoconazole and hot-melt extruded films of HPC and ketoconazole (b) XRD patterns of ketoconazole, PEO and hot-melt extruded film of PEO and ketoconazole (stored at 25 °C/60%RH, for 14 days post-extrusion).

3.4. Stability studies

Stability testing of the antimycotic in all of the formulations (F1–F6) was performed (unpackaged) at 25 °C/60% RH for 12 months. The HPLC analysis of the extruded film samples was performed using a stability indicating HPLC method. The drug content remaining in the films stored at the aforementioned conditions is illustrated in Fig. 5.

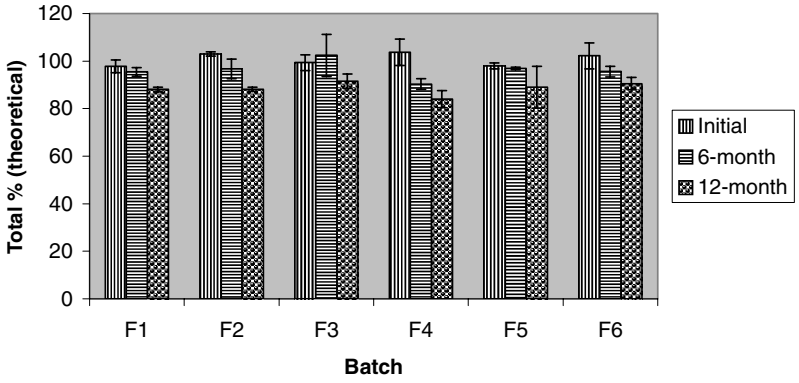

Fig. 5. Twelve-month stability testing of the antimycotic in HME films at 25 °C/60%RH for 12 months. Films contain HPC, PEO, Noveon® AA-1 and ketoconazole.

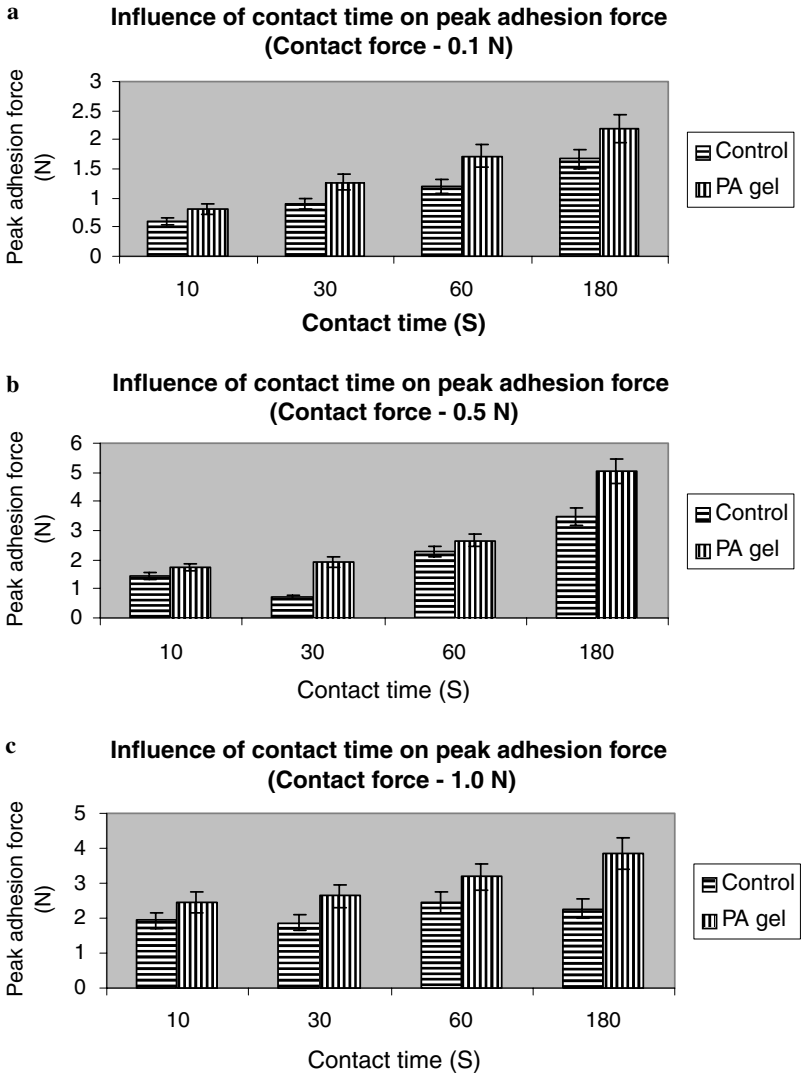

Fig. 6. Effect of contact time on peak adhesion force of HME film containing HPC and ketoconazole on human nail.

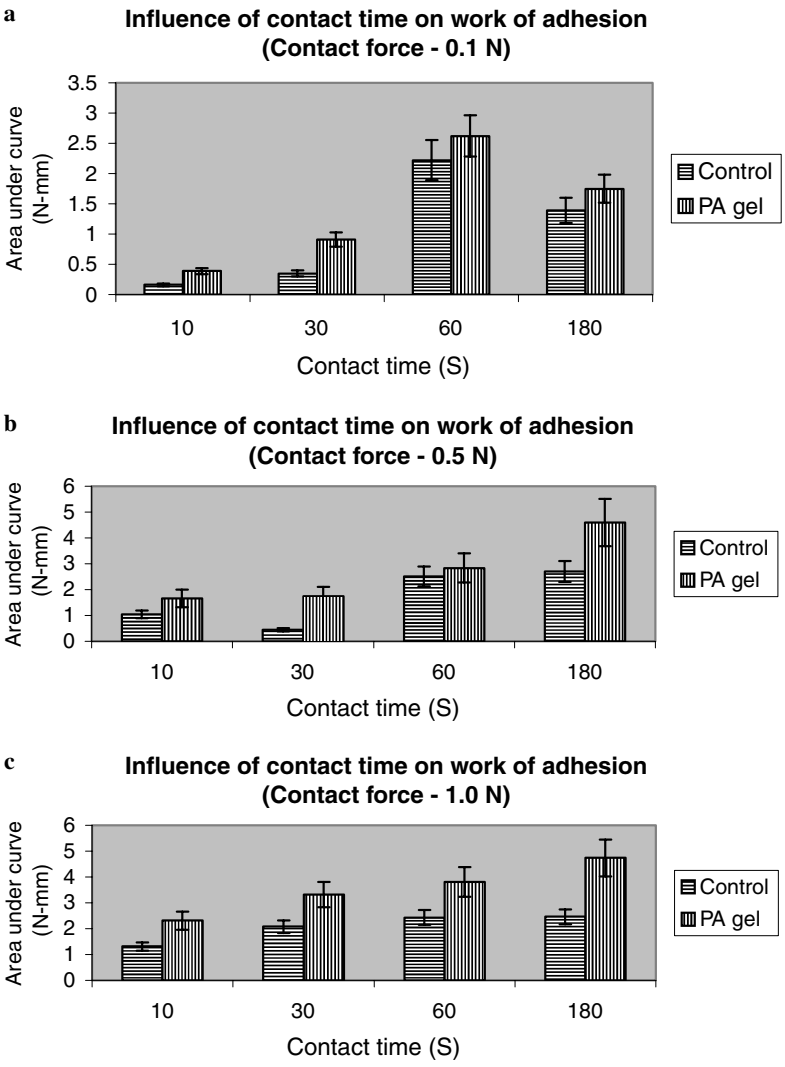

Fig. 7. Effect of contact time on work of adhesion of HME film containing HPC and ketoconazole on human nail.

The percentage of the drug found in the random samples collected from different areas of the extruded films immediately post-extrusion ranged from 97.8% (±2.7) to 103.7% (±5.5). In spite of extruding the films at temperatures well above the melting point of the drug, there was no significant degradation of the drug observed in the films. This could be attributed to the high thermal stability of ketoconazole and the short residence time of the drug inside the barrel of the extruder [21]. The drug content remaining in the six film batches ranged from 90.3% (±2.2) to 102.4% (±9.0) for up to 6 months and from 83.9% (±3.6) to 91.6% (±3.0) for up to 12 months. Significant degradation of the drug was found in the film formulations F2 ($P = 0.023$), F4 ($P = 0.004$) and F6 ($P = 0.006$), for the 6-month period. The absence of significant degradation in the films F1, F3 and F5 may be due to a relatively low moisture level in comparison to the 44–51% increase in moisture content in the films F2, F4 and F6. These findings are consistent with those of Prodduturi and co-workers, who found significant degradation of clotrimazole in the films stored at higher relative humidities [22]. Optimum packaging to increase stability is currently being investigated.

3.5. Bioadhesive studies

HPC is a polymer that contains a significant number of carboxylic groups. Its use as a dosage form can increase the surface charge density of the films. Moreover, the carboxylic groups can form hydrogen bonds with a biological substrate (e.g. nail). In addition, the HPC films had a faster hydration rate than those containing PEO and achieved maximum swelling at a shorter period of time, which could promote interpenetration of the polymer chain with the highly disulfide-bond-linked layer of the human nail tissue. All of these factors contributed to the bioadhesive strength of HPC films and therefore these films were used to study the influence of etching on bioadhesion to the human nail. Results of force-deflection profiles for HME films containing HPC on the human nail are shown in Figs. 6 and 7. The

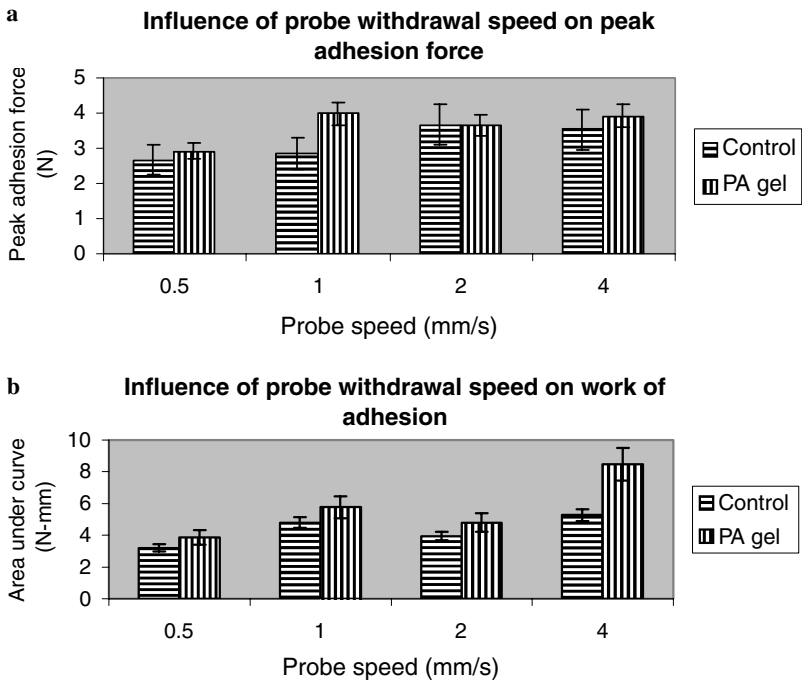

Fig. 8. Effect of probe withdrawal speed on (a) peak adhesion force and (b) work of adhesion (contact force – 0.5 N, contact time – 180 s).

nail samples were either non-treated (control) or treated with PA gel (etched). The differences in bioadhesive properties of the two nail samples are clearly demonstrated. The deflection measurements of the profiles are expressed in millimeters (mm) and the force is given in N. The PAF is the maximum force required to remove the extruded film from the human nail and the work of adhesion was determined from the area under the force-distance curve. Figs. 6 and 7 show the effect of contact time on peak adhesion force and work of adhesion, respectively. Although HPC is reported to have bioadhesive qualities, one can observe the marked differences between the 'control' and the 'etched' nail [23]. It can be determined from the two figures that both the PAF and AUC were higher for treated samples compared to that of the control. As can be seen in Fig. 6b, for a contact time of 30 s, the PAF was, approximately, 2.5-fold higher for the 'etched' nail compared to that of the 'control' nail. Indeed, PAF was statistically higher for the 'etched' nails at all contact forces and at all contact times tested. The area under the curve, for a contact time of 180 s (Fig. 7b), for the PA treated nail was 1.7-fold higher than that for the 'control'. This increase in adhesiveness of the treated sample is likely due to increased interpenetration and entanglement of the polymer with the increased surface area of the etched nail, which results in formation of a greater number of secondary covalent bonds between the entangled chains [11]. Another supporting explanation for the different bioadhesion profiles between the films is that the etching increases the surface area of the human nail and forms physical entanglements followed by increased number of hydrogen bonds resulting in the formation of a strengthened network, which allows the bioadhesive system to remain adhesive for an extended period of time [24]. Fig. 8 shows the influence of probe speed on PAF and work of adhesion for a contact force of 0.5 N and a contact time of 180 s. These parameters were chosen based on the previous study of Wong and co-workers on both Carbopol® 974P and Methocel® K4M tablets [11]. A statistically significant increase in both the PAF (Fig. 8a) and the AUC (Fig. 8b) was seen for the 'etched' nails compared to that of the 'control' which can be attributed to the increased roughness and a consequent increase in surface area of the nail [9].

In the present study, it was found that wetting of the film was essential for the establishment of intimate contact between the HME film and nail to develop strong adhesive bonds. Moreover, an increase in degree of hydration may increase the chain segment motility, which could lead to increase interdiffusion of polymer and tissue [25]. In the measurement of *in vitro* bioadhesive strength, the contact time for wetting the film was relatively short (10 s).

From an interfacial point of view, it was determined that certain contact force was required to develop a satisfactory intimate molecular contact between the bioadhesive system and biological substrate, such that adequate interaction could be achieved to allow strong adhesion. In the present study, it was observed that at a contact force above 1.0 N, no significant increase in both PAF and AUC was observed, suggesting that there was a 'ceiling' contact force for maximum intimate contact, above which there was no further contribution to the adhesion process. Hence, too

Table 2
Calculated (a) solubility parameters and (b) interaction parameters for ketoconazole, HPC and PEO

	δ_t (Hoftyzer/ Van Krevelen)	δ_t (Hoy method)	δ_t Average value
(a)			
HPC	21.27	23.58	22.43
PEO	20.19	27.96	24.08
Ketoconazole	20.09	18.80	19.45
(b)			
$\Delta\delta_t$ (HPC–PEO)	1.68		
$\Delta\delta_t$ (HPC–ketoconazole)	2.98		
$\Delta\delta_t$ (PEO–ketoconazole)	4.63		

high a contact force may not be advantageous, and may damage the film without achieving better contact [11].

3.6. Calculated solubility parameters of ketoconazole, HPC and PEO and their relationship to the experimental results

Table 2 shows the interaction parameters and calculated solubility parameters for ketoconazole, HPC and PEO. The difference between the calculated solubility parameters of the polymers and drug predicts that PEO/ketoconazole and HPC/ketoconazole are likely to be miscible. Thus, the Hansen solubility parameter calculated using the approaches of Hoftyzer/Van Krevelen and Hoy supports the results of DSC, SEM and XRD given that these three techniques proved that melt cooled mixtures of drug and polymer were amorphous.

4. Conclusions

HME continues to demonstrate its applicability for production of various dosage forms including thin drug-incorporated films. Drug loaded films containing up to 20% ketoconazole were successfully prepared by HME processing. DSC, SEM and XRD techniques demonstrated that melt cooled mixtures of the drug and the two polymers were amorphous. HPLC studies indicate that the theoretical post-extrusion content of ketoconazole remaining in the six film batches ranged from 90.3% (±2.2) to 102.4% (±9.0) for up to 6 months and from 83.9% (±3.6) to 91.6% (±3.0) for up to 12 months. It should be noted, however, that optimum packaging is the subject of future studies. The bioadhesive measurements of HME films onto the human nail could be influenced by instrument variables such as contact force, contact time and speed of probe removal from the tissue. Both the work of adhesion and PAF appeared suitable for evaluating the bioadhesivity of the films. Bioadhesion studies of HPC films tested on 'etched' nails demonstrated significantly higher PAF and AUC than that of non-treated 'control' nails. The results of these studies indicate that the development of these films would be relevant as potential dosage forms for onychomycosis and other fungal infections.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejpb.2006.08.013.

References

[1] M.M. Crowley, A. Fredersdorf, B. Schroeder, S. Kucera, S. Prodduturi, M.A. Repka, J.W. McGinity, The influence of guaifenesin and ketoprofen on the properties of hot-melt extruded polyethylene oxide films, Eur. J. Pharm. Sci. 22 (2004) 409–418.
[2] C. Aitken-Nichol, F. Zhang, J.W. McGinity, Hot melt extrusion of acrylic films, Pharm. Res. 13 (1996) 804–808.
[3] Y. Myoung, H. Choi, Permeation of ciclopirox across porcine hoof membrane: effect of pressure sensitive adhesives and vehicles, Eur. J. Pharm. Sci. 20 (2003) 319–325.
[4] S. Murdan, Drug delivery to the nail following topical application, Int. J. Pharm. 236 (2002) 1–26.
[5] M.A. Repka, J.W. McGinity, F. Zhang, J.J. Koleng, Encyclopedia of pharmaceutical technology, in: J. Boylan (ed.), Marcel Dekker, New York, 2002.
[6] M.A. Repka, T.G. Gerding, S.L. Repka, J.W. McGinity, Influence of plasticizers and drugs on the physical–mechanical properties of hydroxypropylcellulose films prepared by hot-melt extrusion, Drug Dev. Ind. Pharm. 25 (1999) 625–633.
[7] F. Zhang, J.W. McGinity, Properties of sustained-release tablets prepared by hot-melt extrusion, Pharm. Dev. Technol. 4 (1999) 241–250.
[8] M.A. Repka, P.K. Mididoddi, S.P. Stodghill, Influence of human nail etching for the assessment of topical onychomycosis therapies, Int. J. Pharm. 282 (2004) 95–106.
[9] M.A. Repka, J. O'Haver, C.H. See, K. Gutta, M. Munjal, Nail morphology studies as assessments for onychomycosis treatment modalities, Int. J. Pharm. 245 (2002) 25–36.
[10] A.K. Dash, Determination of the physical state of drug in microcapsule and microsphere formulations, J. Microencapsul. 14 (1997) 101–112.
[11] C.F. Wong, K.H. Yuen, K.K. Peh, An in-vitro method for buccal adhesion studies: importance of instrument variables, Int. J. Pharm. 180 (1999) 47–57.
[12] C.A. Lyman, T.J. Walsh, Systemically administered antifungal agents. A review of their clinical pharmacology and therapeutic applications, Drugs 44 (1992) 9–35.
[13] B.C. Hancock, P. York, R.C. Rowe, The use of solubility parameters in pharmaceutical dosage form design, Int. J. Pharm. 148 (1997) 1–21.
[14] M.M. Crowley, F. Zhang, J.J. Koleng, J.W. McGinity, Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion, Biomaterials 23 (2002) 4241–4248.
[15] Y. Kambe, Thermal behaviour of poly(ethylene oxide) as revealed by differential scanning calorimetry (1980) 352–255.
[16] Y.K. Godovsky, G.L. Slonimsky, N.M. Garbar, Effect of molecular weight on the crystallization and morphology of poly(ethylene oxide fractions), J. Polym. Sci. 38 (1972) 1–38.
[17] A. Kovacs, A. Gonthier, C. Straupe, Isothermal growth, thickening, and melting of poly(ethylene oxide) single crystals in the bulk, J. Polym. Sci. 50 (1975) 283–325.
[18] S. Prodduturi, R.V. Manek, W.M. Kolling, S.P. Stodghill, M.A. Repka, Solid-state stability and characterization of hot-melt extruded poly(ethylene oxide) films, J. Pharm. Sci. 94 (2005) 2232–2245.
[19] J.D. Menczel, M. Jaffe, W.E. Bessey, Films, in: E.A. Turi (Ed.), Thermal Characterization of Polymeric Materials, Academic Press, San Diego, California, 1997, pp. 1955–2089.
[20] M.A. Repka, S. Prodduturi, S.P. Stodghill, Production and characterization of hot-melt extruded films containing clotrimazole, Drug Dev. Ind. Pharm. 29 (2003) 757–765.

[21] M.A. Repka, K. Gutta, S. Prodduturi, M. Munjal, S.P. Stodghill, Characterization of cellulosic hot-melt extruded films containing lidocaine, Eur. J. Pharm. Biopharm. 59 (2005) 189–196.
[22] S. Prodduturi, R.V. Manek, W.M. Kolling, S.P. Stodghill, M.A. Repka, Water vapor sorption of hot-melt extruded hydroxypropyl cellulose films: effect on physico-mechanical properties, release characteristics, and stability, J. Pharm. Sci. 93 (2004) 3047–3056.
[23] Aqualon., Physical and Chemical Properties, Klucel®, Hydroxypropylcellulose, (1997) 2–6.
[24] S.A. Mortazavi, An in-vitro assessment of Mucus adhesive interactions, Int. J. Pharm. 124 (1995) 173–182.
[25] P.K. Gupta, S.H.S. Leung, J.R. Robinson, Bioadhesive/mucoadhesives in drug delivery to the gastrointestinal tract, in: V. Lenaertsand, R. Gurny (Eds.), Bioadhesive Drug Delivery Systems, CRC Press, Boca Raton, 1990, pp. 65–92.
[26] S. Klick, P.G. Muijselaar, J. Waterval, T. Eichinger, C. Korn, T.K. Gerding, A.J. Debets, C.S. Griend, C. Beld, G.W. Somsen, G.J. Jong, Toward a generic approach for stress testing of drug substances and drug products, Pharm. Technol. 29 (2005) 48–66.