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Stabilization of Hot-Melt Extrusion Formulations Containing Solid Solutions Using Polymer Blends

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ABSTRACT

This study was aimed at enhancing the physical stability of the drug clotrimazole (CT) and the polymer contained within hot-melt extrusion (HME) films using polymer blends of hydroxypropyl cellulose (HPC) and poly(ethylene oxide) (PEO). The HME films were investigated for solid-state characteristics, moisture sorption, bioadhesivity, mechanical properties, glass transition temperature, release characteristics, and physical and chemical stability of the drug and the polymer within the HME films. The solid-state characterization of the drug and the polymer was performed using differential scanning calorimetry, x-ray diffractometry, and dynamic mechanical analysis. A texture analyzer was used to study the bioadhesive and mechanical properties of the HME films. The physical and chemical stability of the films, stored at 25°C/60% relative humidity or in a desiccator, was studied for up to 12 months. CT was found to be in solid solution within all of the formulations extruded. The physical stability of the drug and PEO in the HME films increased with increasing HPC concentration, but the bioadhesivity and flexibility of the PEO films decreased with increasing HPC concentration. Films containing HPC:PEO:CT in the ratio of 55:35:10 demonstrated optimum physical-mechanical, bioadhesive, and release properties. In conclusion, polymer blends of HPC and PEO were used successfully to tailor the drug release, mechanical and bioadhesive properties, and stability of the HME films.

KEYWORDS: Solid solution, physical stability, hot-melt extrusion, polymers, physicochemical characterization.

INTRODUCTION

Interest in novel drug delivery systems such as transdermal and transmucosal patches has grown tremendously in the past 2 decades because they offer several advantages over conventional dosage forms. The 2 main designs of transdermal patches are the reservoir type and the matrix (drug-in-adhesive) type of patches. In recent years, the matrix/drug-in-adhesive patches have become the most popular form of transdermal/transmucosal systems. The traditional and most common method of manufacturing matrix-type patches is by solvent casting. However, hot-melt extrusion (HME) technology is currently being explored and used in the pharmaceutical field because it offers several advantages over traditional processing methods.[1] HME may be used to disperse drugs in a given matrix at the molecular level, thus forming solid solutions. It is well documented that the solid solution approach is commonly used for delivery of poorly soluble drugs because of its role in increasing the dissolution, absorption, and therapeutic efficacy of drugs.[2] Also, in the case of transdermal drug delivery systems, at least part of the incorporated drug must be in solution since only drug in solution diffuses from the polymeric patch and is available for absorption. It is often a challenge to formulate a stable solid solution, since the crystalline state is thermodynamically more stable than amorphous systems.[3]

Clotrimazole (CT) is a practically water-insoluble antifungal agent with a melting point of 146ºC to 147ºC.[4] Hydroxypropyl cellulose (HPC) is a non-ionic water-soluble thermoplastic polymer. It is an amorphous polymer that softens between 100°C and 150°C based on its molecular weight (MW).[5] HPC has been extensively used or explored in conventional and HME dosage forms. Poly(ethylene oxide) (PEO) is a thermoplastic semicrystalline polymer with a melting point ranging from 60°C to 75°C and a glass transition temperature of –67°C.[6,7] Initial studies were performed to characterize HME films containing CT and either HPC or PEO.[8,9] These experiments reported that HPC films, because of relatively high glass transition temperatures, exhibited brittle fracture and were found to be stiff, with a high elastic modulus and a very low percent elongation (less than 5%). In contrast, PEO films, because of their negative glass transition temperature (–67°C)[6,7] and the chemical structure of PEO, were flexible, with a low elastic modulus and exceptionally high percent elongation. CT incorporated into both of the polymeric films was found to be in solid

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solution postextrusion (day 1), as indicated by differential scanning calorimetry (DSC) and x-ray diffractometry (XRD). However, CT incorporated into HPC films was found to be more stable (no recrystallization observed for 6 months in films stored at 25°C/60% relative humidity [RH], as indicated by DSC and XRD profiles) than CT incorporated into PEO films (CT recrystallization was observed after storage for 3 months at 25°C/60% RH). Moisture had a significant effect on the mechanical properties of HPC films at all of the tested RHs. In contrast, moisture content within the PEO films had no significant effect on the mechanical properties of films stored below 60% RH. PEO films exhibited higher bioadhesivity than HPC films because of the extremely flexible PEO structure, which can result in stronger interpenetration of the polymer and mucin chains.

In earlier studies it was determined that release of the drug from both of the films (HPC or PEO) followed a zero-order profile (erosion), irrespective of the MW.[8,9] Release profiles demonstrated only 40% and 80% of drug release at the end of 30 hours in the case of films prepared from higher-molecular-weight polymers—Klucel MF (HPC, 850 000 Da) and Klucel GF (HPC, 370 000 Da), respectively—in comparison to 100% release from the lower-molecular-weight films—Klucel JF (HPC, 140 000 Da). Hence, Klucel JF was chosen for further studies.[8]

Evaluation of HPC or PEO films containing CT indicated that HPC films exhibited better stability and sustained-release properties than PEO films. However, PEO films demonstrated more desirable mechanical and bioadhesive properties than HPC films.[8,9] Therefore, the current research focuses on enhancing the physical stability of drug and the polymer PEO contained within the HME films using polymer blends containing optimized proportions of HPC and PEO. Such mucoadhesive HME films have potential application in delivering drugs that have low bioavailability when administered orally, especially drugs with low solubility or extensive first-pass metabolism. Hence, the physical stability of the solid solution of the drug is critical when these films are aimed at enhancing the bioavailability of the drug, since the solid solutions have a propensity to convert to their native crystalline forms, which are relatively less soluble.

Materials and Methods

HPC (Klucel JF, MW 140 000 Da; Klucel GF, MW 370 000 Da; and Klucel MF, MW 850 000 Da) was kindly donated by Aqualon Division, Hercules Inc (Wilmington, DE). PEO (PolyOx WSR N-80 [PEO N-80], MW 200 000 Da; PolyOx WSR N-750 [PEO N-750], MW 300 000 Da) was kindly donated by Dow Chemical Co (Midland, MI). Butylated hydroxytoluene, potassium dibasic phosphate, and CT were obtained from Spectrum Chemical (Gardena, CA). Sodium iodide, calcium nitrate sodium chloride, and methanol (high-performance liquid chromatography [HPLC] grade) were purchased from Fisher Chemicals (Fair Lawn, NJ).

HME Process

The drug and the polymers were geometrically diluted and dried in an oven (Isotemp Incubator 625D, Fisher Scientific, Rockville, MD) at 40°C to 50°C for 24 hours and then blended for content uniformity in a V-blender at 100 rpm for 15 minutes. The resultant blend was fed into a single-screw extruder (Killion, Model KLB 100, Davis-Standard, Pawcatuk, CT) equipped with a 1-inch-diameter screw and a 6-inch flex-lip die. The die opening was adjusted to 0.005 inches (0.127 mm), and the screw speed was set at 60 rpm. The various formulations and the extrusion parameters are indicated in Table 1. Lower-MW PEO N-80 (15%) was added to formulation 5 (F5) since PEO N-750 could not be extruded because of its high viscosity. The residence time of the materials within the extruder was ~2 to 3 minutes. The extruded films were cooled to room temperature by passing over a chill roll. The films were measured for thickness using an electronic digital caliper. Films were then rolled, labeled, and stored in 5-mil (1 mil = 0.001 inches)

Table 1. Formulation and Extrusion Parameters for HME Films Containing Polymer Blends*

Formulation		F1	F2	F3	F4	F5
Formulation	HPC JF (% wt/wt)	90	75	55	35	0
	PEO N-750 (% wt/wt)	0	15	35	55	PEO N-750 (75%) + PEO N-80 (15%)
	Clotrimazole (% wt/wt)	10	10	10	10	10
Extrusion temperature (°C)	Zone 1	120	120	120	125	125
	Zone 2	130	130	130	135	135
	Zone 3	140	140	140	145	145
	Die/melt	140	140	140	145	145
	Screw speed (rpm)	60	60	60	60	60

*HME indicates hot-melt extrusion; HPC, hydroxypropyl cellulose; PEO, poly(ethylene oxide).

polyethylene bags and placed in a desiccator until they were analyzed.

Moisture Sorption

Saturated salt solutions at 25°C were used to maintain a constant humidity in sealed humidity chambers. Such constant humidity chambers at 25°C, maintained at 6 different RHs—<4% (Drierite), 14% (LiCl), 33% ($MgCl_2$), 50% ($Ca(NO_3)_2.4H_2O$), 75% (NaCl), and 86% (KCl)—were used to equilibrate the films. Thermogravimetric analysis (TGA) was performed using a Pyris 1 TGA (PerkinElmer, Shelton, CT) equipped with Pyris Manager software to determine the equilibrium moisture content (EMC) and ensure equilibration of the HME films stored at the aforementioned RHs. Samples weighing 8 to 10 mg were obtained and heated from 25°C to 90°C at 40°C/min and then held at 90°C until there was no significant loss of weight (<0.1%/hr). Studies were performed at 2 different time points (1 and 2 weeks). Water vapor sorption isotherms were plotted from the EMC values of the extruded film samples equilibrated (at 2 weeks) at 6 different RHs.

Bioadhesion Studies

A texture analyzer (TA.XT2*i*, Texture Technologies Corp, Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK) equipped with a 5-kg load cell, TA-303 indexable adhesive test rig, and TA-57R stainless steel probe and Texture Expert software was used to study the bioadhesive properties of the HME films.[10] Rabbit intestinal mucosa was used as a biological substrate. The films were wetted with artificial saliva (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8 g of NaCl in 1 L of distilled water adjusted with phosphoric acid to pH 6.8 ± 0.05)[11] for ~30 seconds and placed on the slotted die-cut fixture that is secured on the lower base of the instrument. The mucosal substrate, pre-equilibrated with the artificial saliva, was attached to the probe with a cyanoacrylate adhesive. The probe lined with mucosa was set to approach the film with a speed of 1 mm/s and apply a force of 3.5 N for 30 seconds. The test speed used was 0.1 mm/s. Following the application of force, the probe was withdrawn at a speed of 0.5 mm/s until the film detached from the mucosa. The peak adhesive force and the area under the curves were used to evaluate the bioadhesive strength of the HME film formulations.

Dynamic Mechanical Analysis

A Pyris Diamond Dynamic Mechanical Analyzer (PerkinElmer) was used to study the glass transition temperatures of the HME films containing HPC and/or PEO. The tests were performed at a frequency of 1 Hz, and the temperature was ramped up at 5°C/min. The loss modulus (M″) and the storage modulus (M′) were used to evaluate the mechanical properties, and tan δ (M″/M′) was used to determine the Tg of the films.

During dynamic mechanical analysis (DMA), a sinusoidal tensile strain is applied to one end of the film and the resultant stress is measured at the other end, that is, the DMA method uses small sinusoidal deformation as the probe to modulus and damping (tan δ). Thus, the complex tensile modulus of the film sample (M*) and its components (M′ and M″), as well as tan δ (M′/M″), can be measured. Changes in these parameters are studied as a function of temperature and impressed frequency. The transitions are displayed as peaks on the loss modulus (the imaginary part of the complex modulus) or tan δ versus temperature curves.

Mechanical Properties

A TA.XT2*i* Texture Analyzer equipped with a 50-kg load cell, TA-96 grips, and Texture Expert software (Texture Technologies Corp/Stable Micro Systems) was used to evaluate the mechanical properties of the HME films. Film samples that were 50-mm long, had a uniform width (~10 mm) and thickness (0.5 mm), and were free from physical imperfections were held between 2 grips (TA-96). The grip separation was set at 30 mm. A thin sheet of rubber was attached to the surface of the grips via double-sided tape to prevent the film from being cut by the grooves of the grips. The crosshead speed was 2 mm/s (strain rate), and the data acquisition was terminated when the film failed. Data from the film samples that failed at, and not between, the clamps were not used in the evaluation of the mechanical properties. All of the tests were performed at an RH of 24% ± 2% and a temperature of 24°C ± 1°C. The stress, percent strain (percent elongation), and Young's modulus were recorded. The Texture Expert software was used to generate the stress-strain curves and calculate the tensile strength and percent strain (percent elongation). The tensile strength is defined as the maximum stress (σ_{max}) sustained by the material and is calculated as the ratio of the maximum force applied during a tension test carried to break (F_{max}) and the original cross-sectional area of the sample (A), given as

$$\sigma_{max} = \frac{F_{max}}{A} \quad (1)$$

Tensile strength is expressed in megapascals (1 MPa = 1 N/mm^2 = 9.807 kg/mm^2). Elongation at break (strain) is calculated from the ratio of the change in the length (ΔL) of the sample to its original length (L):

$$\%Elongation = \frac{\Delta L}{L} \times 100 \quad (2)$$

The elastic modulus, E (Young's modulus), was calculated from the slope of the initial linear part of the stress-strain curve and expressed in MPa:

$$E = \frac{Stress}{Strain} \quad (3)$$

In Vitro Release Studies

Release studies were performed using a Hanson SR8-Plus dissolution test system (Chatsworth, CA) according to the US Pharmacopeia 28 apparatus 5, paddle-over-disk method. Nine hundred milliliters of 1% wt/vol sodium lauryl sulfate (SLS) at 37°C was used as the dissolution medium to maintain the sink conditions, and the paddle rotation speed was 50 rpm. Samples were collected at predetermined time intervals, filtered using a 0.45-micron nylon syringe filter, and analyzed by HPLC. The studies were performed in triplicate. The release data were fitted to 3 models—first order, square root, and zero order—to describe the drug release kinetics from the matrices. The Kopcha model was used to determine the release mechanism of the drug and to calculate the individual erosion and diffusion contributions to the release.

All of the results are reported as the average of 3 replicates ± SD. The mechanism of drug release was assessed by fitting the initial 60% of fractional release of drug from the films' data into a generalized expression developed by Ritger and Peppas,[12] as shown in Equation 4:

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

Here M_t/M_∞ is the fraction of drug released at time t; k is the constant incorporating characteristics of the polymer and drug; and n is the diffusional exponent indicative of the release mechanism of the drug.

If n = 0.5, release is by Fickian diffusion; if n = 1, release is by polymer dissolution or erosion; and if 0.5 < n < 1, release is anomalous (ie, by both diffusion and erosion). The drug release profiles were also fitted into an equation (Equation 5) developed by Kopcha et al[13] to account for the diffusion and erosion contributions to the drug release:

$$M = At^{1/2} + Bt + C \quad (5)$$

In Equation 5, A is the diffusion term, B is the erosion term, and C is a term related to physical parameters. If C is small in relation to A and B, then it would represent the experimental as well as the curve-fitting error. A large positive number suggests an initial burst release. A large negative number indicates a lag time before release from the matrix:

- A/B = 1; diffusion and erosion are equal
- A/B < 1; erosion predominates over diffusion
- A/B > 1; diffusion predominates over erosion

HPLC Analysis

Random samples (n = 3) were taken from different areas of the films stored at different conditions and analyzed for drug content. The chromatographic system consisted of a Waters Alliance HPLC equipped with a 2695 separation module with an online degasser, Waters 2996 photo diode array detector, and Waters Empower chromatography software (Waters, Milford, MA). All injections were performed by an autosampler, and the injection volume was 20 µL. A Waters Nova-Pak phenyl column with dimensions 150 × 4.6 mm and a particle size of 3 µm was used. The mobile phase used was 80:20 methanol:25 mM KH_2PO_4. The flow rate used was 1 mL/min, and the detection wavelength was 215 nm.

Stability Studies

HME films stored in stability chambers (Caron 6030 Environmental Test Chamber, Caron Products and Services, Marietta, OH) at 25°C/60% RH for 6 months in an unpackaged condition and at 25°C/Drierite (desiccant) were analyzed using HPLC to determine the chemical stability of the drug. The physical stability of the polymer and the drug was evaluated using DSC and XRD, respectively, on the stored samples. All samples stored at 25°C in the presence of the desiccant in sealed chambers for 2 weeks contained less than 1% moisture as measured by TGA.

DSC

DSC was used to study the crystallinity and solid-state physical stability of the HME films pre- and postextrusion. The DSC thermograms were recorded using a Pyris 1 DSC equipped with Pyris Manager software (PerkinElmer). Accurately weighed amounts (10-15 mg) of either the films or the physical mixtures of PEO, HPC, and CT (10%) were hermetically sealed in a flat-bottomed aluminum pan and heated from 25°C to 170°C at a linear heating rate of 10°C/min. Samples stored at 25ºC/60% RH were evaluated in triplicate at 3 different time intervals (1 day, 6 months, and 12 months) postextrusion to study the physical stability of PEO.

XRD

The crystallinity of the drug was analyzed using XRD. The studies were performed on a D-8 Advance X-Ray

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Diffractometer (Bruker AXS, Madison, WI) equipped with a Sol X detector and Diffrac Plus software. The generator voltage and current were 40 kV and 40 mA, respectively. The 2-theta scanning range was from 5° to 50°. The step size was 0.02°, and the dwell time at each step was 1 second.

Statistical Analysis

Statistical differences were determined using either Student *t* test or 1-way analysis of variance (ANOVA). Statistica (version 5.5, Stat Soft, Tulsa, OK) and JMP (version 5.1, JMP, Cary, NC) software were used for data analysis. A difference was considered to be statistically significant when $P < .05$.

Results and Discussion

HME

Films containing different proportions of HPC, PEO, and CT were extruded into thin films. The formulations and extrusion parameters are listed in Table 1. Films containing only PEO N-750 could not be extruded because of its high viscosity. Hence, PEO N-80 (15%) was incorporated to aid in the processing of F5.

The thickness of the films was found to be 0.54 mm (±0.02 mm). The films were uniform, and the opacity of the films increased as the concentration of PEO increased. PEO, unlike HPC, is a semicrystalline polymer, and the crystalline regions are usually dense and hence impart opacity to the PEO films.

Water Sorption Studies

The water vapor sorption isotherms of HME films containing CT and polymer blends are represented in Figure 1. The EMC was significantly affected by the polymer composition. The EMC of the polymer-blended films decreased as the percentage of PEO incorporated within the films increased (F1 > F2 > F3 > F4 > F5) because of low water sorption properties of PEO at RHs lower than 70%. Determining the moisture uptake by the polymer films is important in defining the storage conditions, to predict and enhance the physical-mechanical and chemical stability of the film matrices.

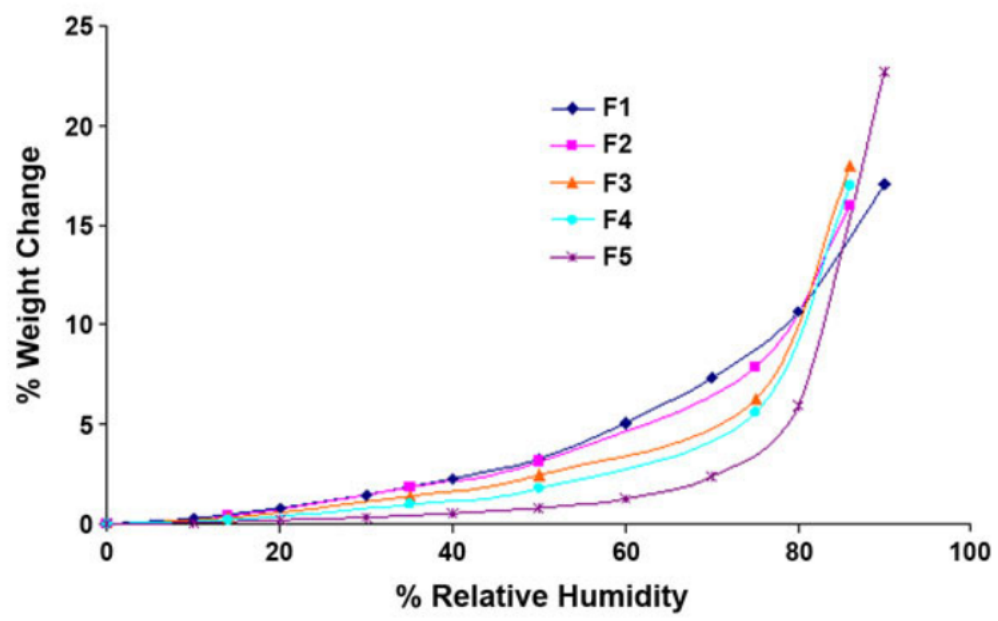

Figure 1. Water vapor sorption isotherms of hot-melt extrusion film formulations.

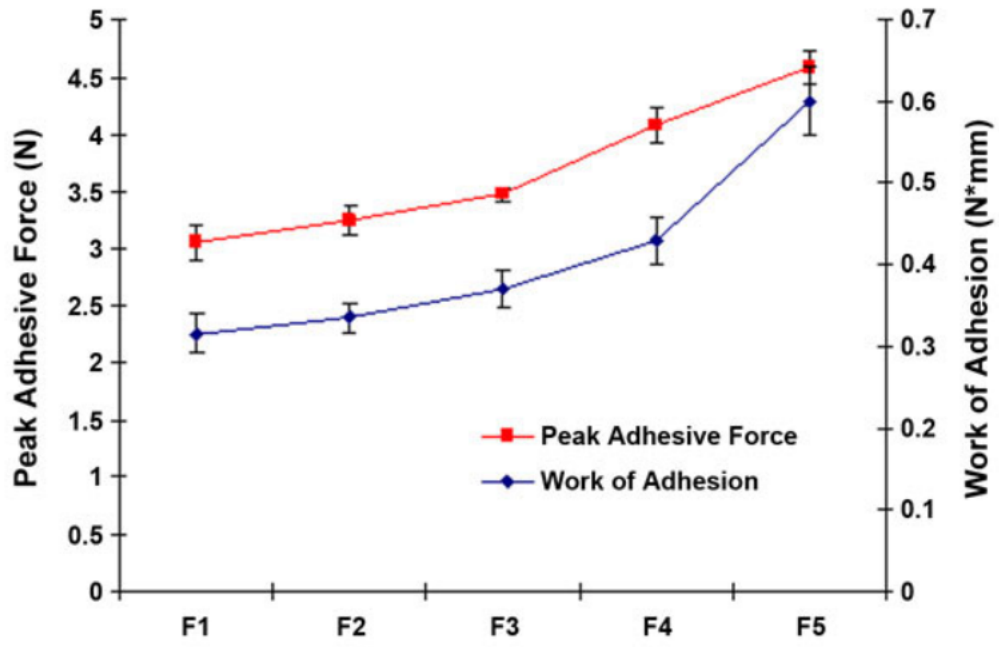

Figure 2. Peak adhesive force and work of adhesion of hot-melt extrusion film formulations.

Bioadhesion Studies

The peak adhesive force (PAF) and the work of adhesion area under curve (AUC) obtained are illustrated in Figure 2. It was observed that the bioadhesion increased with an increase in PEO concentration (F1 < F2 < F3 < F4 < F5).

Statistical analysis was performed by ANOVA and also by comparing all of the formulation pairs by the Tukey-Kramer HSD (honestly significant difference) test. Statistical analysis was also performed to compare each formulation with the control formulation using Dunnett's test, which determines whether means are different from the mean of a control group. F1 was considered to be the control group. The statistical analysis revealed that F1 and F2 were not significantly different, indicating that incorporation of 15% PEO into the HPC films did not increase the bioadhesive properties of HPC films significantly. However, concentrations greater than 15% PEO increased the bioadhesion of HPC films significantly.

It can be observed from Figure 2 that F5, containing only PEO, had a higher peak adhesive force and work of adhesion than did F1, which had only HPC. An important feature of a mucoadhesive polymer is the ability to form physical bonds, principally by entanglement with the substrate molecules (mucin). The linear flexible chains of the PEO molecule have extremely high segmental mobility

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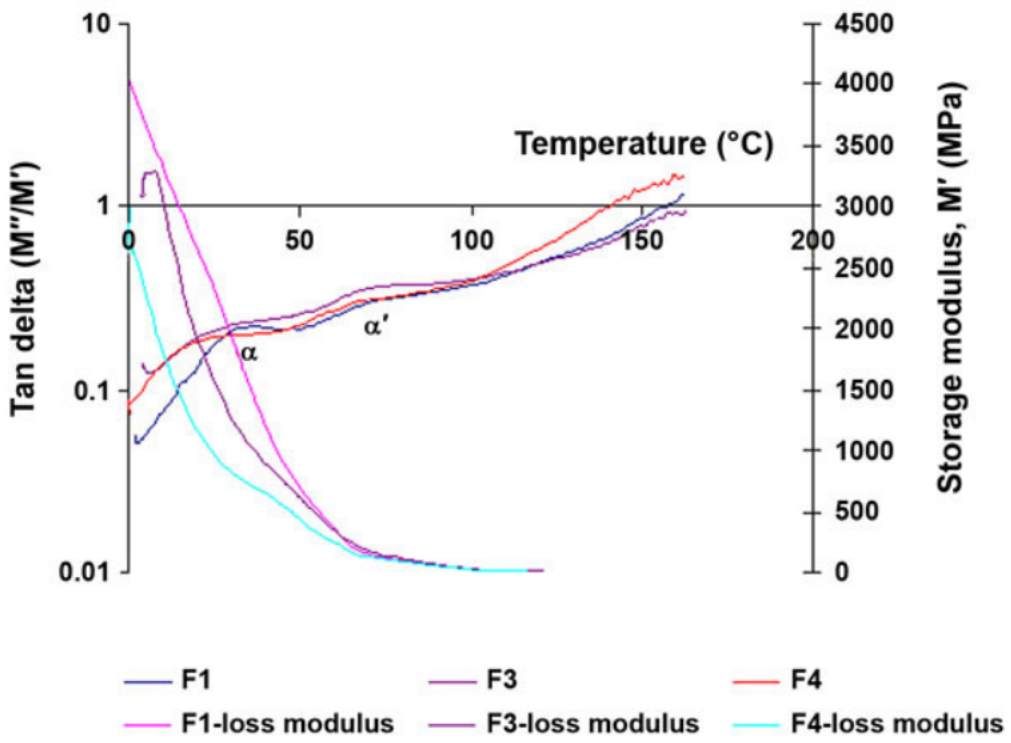

Figure 3. Glass transition temperatures of hot-melt extrusion film formulations stored at 25°C/Drierite for 1 week postextrusion (determined by dynamic mechanical analysis).

because of the ether linkages, which make for a very flexible backbone, and hence penetration into the substrate networks is deep and relatively rapid.[14] This interpenetration results in an intimate contact and hence enhances bioadhesion.

Although HPC has a greater number of hydrogen bonding groups (6 OH groups) than PEO (which has an -O- in each unit and an OH at the end of each chain), PEO films demonstrated higher bioadhesion than HPC films. This can be explained by the fact that PEO hydrates faster, takes up more water (Figure 1, 90% RH), and swells more than HPC. The swollen polymers maximize the space between polymer molecules, increasing chain flexibility, which leads to more entanglements, interpenetration, and consequently adhesion strength.[15] Recently reported studies by Bouckaert and Remon[16] challenged the importance of hydrogen bonding between the mucoadhesive and the glycoprotein of the mucus. These researchers demonstrated that the physical mechanisms of mucoadhesion (ie, interpenetration and entanglement) are of greater importance than secondary bond (H-bond) interactions. Hence, it can be concluded that the contribution of the flexible nature of PEO chains (increased segmental mobility and hence increased entanglements and/or penetration) to bioadhesion was higher than the contribution of the hydrogen bonding nature of the HPC molecule, which resulted in higher bioadhesion of PEO films than of HPC films. It can also be observed from Figure 2 that the PAF and AUC increased with increasing PEO concentration. The increase was significant at PEO concentrations of 35%, 55%, and 90% (F1-F3, F1-F4, F1-F5) but was not significant at 15% PEO (F1-F2), indicating that 15% PEO was not adequate to increase the bioadhesion of the blended films.

Determination of Glass Transition Temperatures by DMA

The onset of cooperative motion of the polymer chain segments, glass transition, is designated as α transition. At the glass transition temperature, M′ decreases drastically (a peak is observed for tan δ); the magnitude of this decrease is much higher for amorphous than for semicrystalline polymers.[17]

The interpretation of the transitions recorded by DMA is not always straightforward and is still under debate in the literature. There are several studies reporting difficulty in determining the glass transition temperature of HPC using DSC[18] as well as DMA.[19] HPC's complex morphological structure perhaps accounts for the difficulty in determining a Tg and the wide range of Tg values that have been reported.[17,18]

Representative graphs were plotted to illustrate the calculation of the Tg of the HME films containing polymer blends and stored at 25°C/Drierite (Figure 3). The first transition peak observed (20°C-35°C) was considered to be the glass transition temperature since there was a corresponding decrease in storage modulus observed at that temperature. The primary glass-rubber transition, which is often referred to as α transition, is characterized by a large decrease in storage modulus (from glassy state ~10^{10} dyn/cm^2 to rubbery state 10^7 dyn/cm^2).[17] There was a second transition peak observed at ~70°C to 75°C. A transition at a higher temperature than the α transition's is usually a α' transition, which occurs between the Tg and Tm (melting temperature) and corresponds to the molecular motion within the crystals or crystalline relaxations.[19] Since the second transition was observed between the glass transition temperature and the melting point of HPC (>150°C), it can be considered the crystalline relaxation of the polymers.

From the obtained glass transition temperatures (Table 2) it can be observed that the Tg decreased with increasing PEO concentration. This can be explained by the low glass transition temperature of PEO itself, which is approximately –67°C. PEO is an extremely flexible molecule because of the presence of the ether linkages and the CH_2 groups.[20] The glass transition temperatures were also found to decrease at higher moisture content (when stored at 60% RH) in all of the film formulations. It is well documented that

Table 2. Glass Transition Temperatures of HME Films Containing Clotrimazole and Polymer Blends as Determined by Dynamic Mechanical Analysis*

Formulation	Tg (°C) at 25°C/Desiccator	Tg (°C) at 25°C/60% RH
F1	33.23	29.31
F3	26.76	25.32
F4	22.33	20.80

*HME indicates hot-melt extrusion; RH, relative humidity.

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Table 3. Mechanical Properties of HME Films Containing Polymer Blends (Mean ± SD) (n = 6)*

Formulation	Tensile Strength (MPa)	Elastic Modulus (MPa)	Elongation at Break (%)
F1	65.5 ± 2.3	19.9 ± 1.2	3.4 ± 0.1
F2	60.0 ± 1.8	13.3 ± 0.9	7.5 ± 0.7
F3	55.3 ± 2.0	10.1 ± 1.0	10.4 ± 1.1
F4	45.2 ± 1.5	9.3 ± 0.6	29.7 ± 3.2

*HME indicates hot-melt extrusion.

water acts as a plasticizer and enhances the mobility of the polymer chains, thus decreasing the Tg. HPC films containing CT, when dry/<1% moisture, had a glass transition temperature of 33.23°C. Thus, water (with a very low Tg, –134°C) or PEO (with a Tg of approximately –67°C) increasingly and continually reduces the Tg of the film system as its concentration in the solid increases.[21]

Mechanical Properties

Mechanical properties are important when one considers oral mucoadhesive film dosage forms since these properties not only reflect the softness, flexibility, and durability of the films but also can be used as in vitro test measurements to detect batch-to-batch variations or deformities in the extruded films. The stress-strain values are provided in Table 3. The stress-strain curve of F1 (0% PEO, 90% HPC, 10% CT) indicated brittle failure with low percentage elongation (3.4%), high Young's modulus (19.9 MPa), and high tensile strength (65.5 MPa). The brittleness is essentially due to F1's high glass transition temperature (33.23°C as calculated by DMA). A good correlation was observed between the glass transition temperatures and the flexibility of the films, which is in agreement with the reported literature.[22] With increasing PEO concentration, the films demonstrated a decrease in Young's modulus and hence an increase in flexibility. This is clearly reflected in the measured glass transition temperatures (using DMA). The glass transition temperatures of F1, F2, and F3 were above the storage or testing temperature, and hence brittle failure was observed. However, in F4, where the recorded Tg was 22.3°C, ductile behavior was observed; the films had a low tensile strength and Young's modulus, and a higher percent elongation. The ductile behavior of F4 (90% PEO, 0% HPC, 10% CT) can be explained by the fact that the testing/storage temperature (25°C) was higher than the glass transition temperature of the film formulation (22.3°C). Hence, the segmental mobility of the polymer is very high when its glass transition temperature is below the testing temperature. At temperatures below Tg, the polymer maintains the disordered nature of the melt but lacks the molecular mobility and is understood to be in a glassy state. At temperatures above Tg, the polymer is easily deformed because of the partial flexibility of the chains. There is therefore a drastic change in the rigidity and, in general, in the mechanical properties of the polymers at Tg.[7] This high flexibility of F4 can also be attributed to the oxygen group (-O-) present in the polymer backbone, which tends to reduce chain stiffening and impart flexibility.[20]

Release Studies

The release profiles suggest that a sustained release of drug was observed from all of the tested HME film formulations (Figure 4). However, the release rate decreased with increasing PEO concentration, except in the case of F5, which had 10% PEO N-80 incorporated into the film since the formulation containing only PEO N-750 had high viscosity and could not be homogeneously extruded. PEO N-80 has low MW, which might have caused an increase in the erosion rate of the matrix. However, with the exception of F5, there was a decrease in the release rate with an increase in the PEO concentration. This can be attributed to the high viscosity of PEO N-750 (5% solution 600-1200 mPa) in contrast to HPC JF (5% solution 150-400 mPa). When the dissolution data were fitted to 3 different models, the kinetics of drug release was determined to be zero order. The analysis of the dissolution data using the Kopcha model and the Peppas model suggested that the mechanism of release was solely by erosion from all of the films, irrespective of the ratio of HPC to PEO. The ratio A/B (Kopcha model coefficients) was less than 1, and the release exponent n (Peppas model) was 1 for all of the tested films (Table 4). Zero-order release

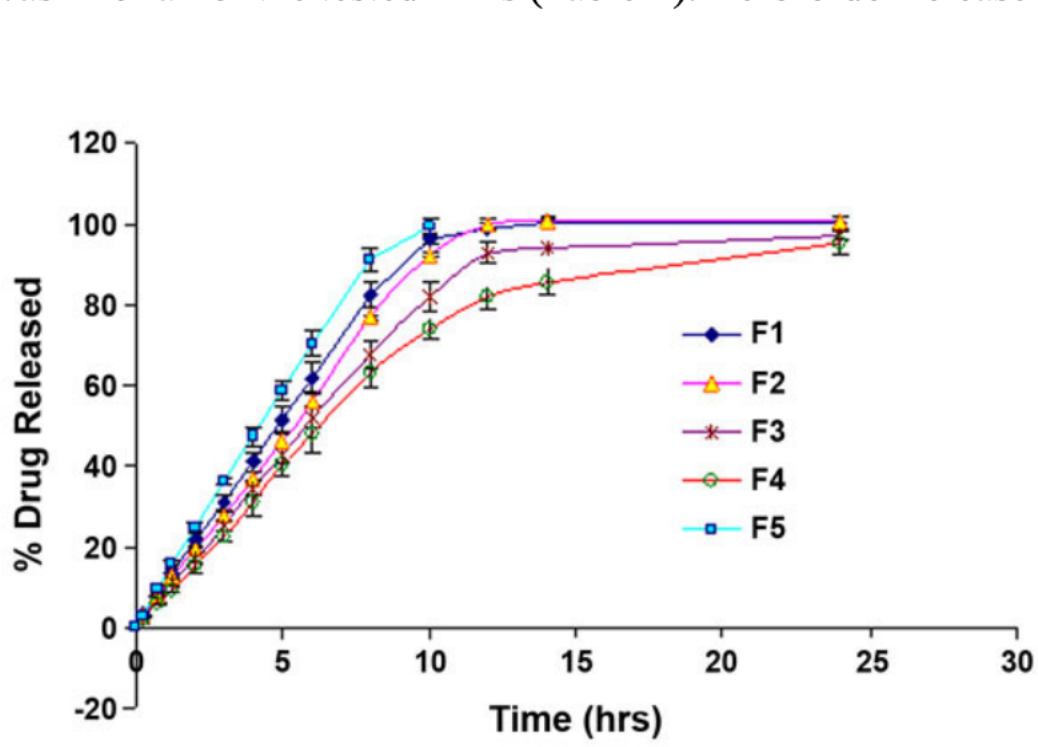

Figure 4. Release profiles of hot-melt extrusion film formulations.

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Table 4. Calculated Model Coefficients for the Release of Clotrimazole From HME Films Containing Different Proportions of HPC and PEO*

	Kopcha Model (Equation 5)				Peppas Model (Equation 4)
Formulation	A ($mgh^{-1/2}$)	B (mgh^{-1})	C (mg)	A/B	n (release exponent)
F1	–0.28	10.28	0.80	–0.03	1.04
F2	–3.10	10.31	2.39	–0.30	1.01
F3	0.67	8.29	–0.16	0.08	1.00
F4	3.34	6.76	–2.13	0.49	0.98
F5	2.12	10.89	–0.27	0.19	0.98

*HME indicates hot-melt extrusion; HPC, hydroxypropyl cellulose; PEO, poly(ethylene oxide).

is consistent with the physical nature of CT, which is practically insoluble in water, and with the release of the drug from the individual polymers.

Chemical Stability: HPLC

There was no significant drug degradation observed in any of the formulations (F1, F2, F3, F4, F5) stored at 25°C/ Drierite for 12 months. Also, no significant drug degradation occurred in F4 and F5 stored at 25°C/60% RH for up to 6 months. However, there was significant degradation of CT observed within F1, F2, and F3 after storage for 6 months. (No packaging was used in any of the tests.) The drug incorporated within F4 and F5 was chemically more stable than the CT incorporated within F1, F2, and F3, evidently because of the lower moisture content in the formulations containing higher PEO concentrations since the degradant products were identified as (*o*-chlorophenyl)diphenyl methanol (CPDM) and imidazole and quantitated via HPLC analysis. It has been reported that CT undergoes acidic hydrolysis, resulting in CPDM and imidazole.[10]

Polymer Stability: DSC

The DSC thermograms of F1 and F5 were discussed in earlier studies.[8,9] The thermogram of F3, pre- and postextrusion, appears in Figure 5. As discussed previously, DSC could not be used to study the solid state of CT within the films containing PEO because of its solubilization in the PEO melt during the heating phase of DSC (PEO melts at a lower temperature than CT). It was also discussed earlier that the PEO transitioned from the extended-chain form to the folded-chain form upon HME and then slowly transitioned back into the extended-chain crystal form.[23-25] The transition of PEO from the extended-chain crystallites into the folded-chain crystallites postextrusion, indicated by a decrease in the melting point (Tm = 71.2°C), was observed in all of the formulations. The decrease in the melting point of the PEO postextrusion could also be partly due to PEO-CT interactions. The melting point of the PEO in F4 and F5 from day 1 postextrusion to after 12 months' storage at 25°C/60% RH increased from 59.6°C to 69.9°C (10°C), indicating the slow conversion of the unstable folded-chain crystallites of PEO into the more stable extended-chain crystallites, but in the case of F2 and F3 the increase in the melting point observed was not significant (it increased only 3.5°C for F2 and F3). Another plausible explanation for the increase in the melting point of PEO in F4 and F5 upon storage may be weakening of the interactions, which in turn may be due to F4's and F5's low Tg. F2 and F3 consisted of 75% and 55% HPC, respectively. From the DMA studies it was observed that F2 and F3 had glass transition temperatures of 31°C and 28°C, respectively, in contrast to F4, whose Tg was determined to be 20.8°C, which is below the storage temperature (25°C). F5 (PEO-only and CT-only containing films) was expected to have a glass transition temperature lower than 20°C, since PEO has a Tg in the range of –57°C to –67°C, as reported in the literature.[6,7] Hence, unlike with F4 and F5, F2's and F3's high Tg did not allow the transition of PEO from the folded-chain to the extended-chain form. Also, their high Tg may have prevented any weakening of the PEO-CT interactions and hence no observed change in the melting point upon storage, thus preventing recrystallization of CT (see XRD results).

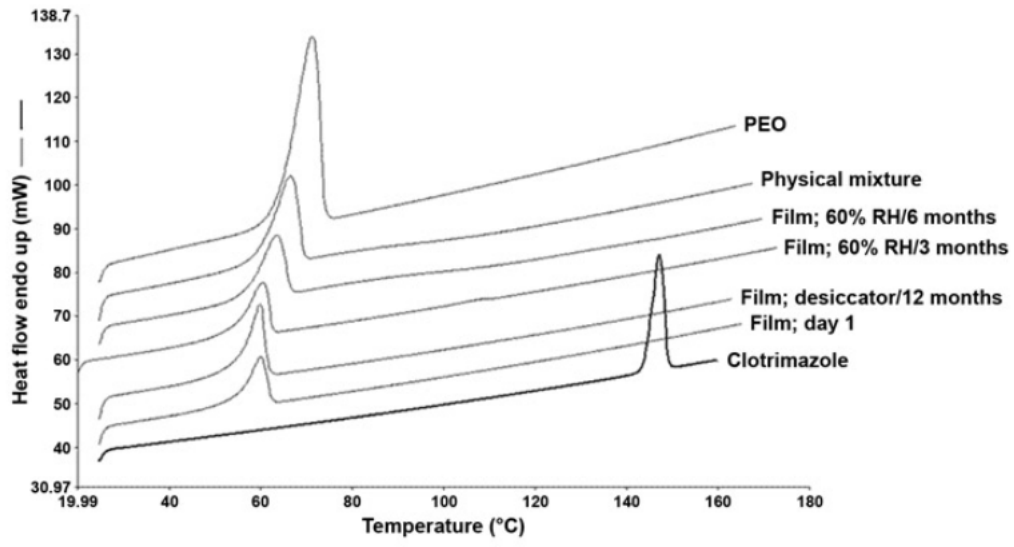

Figure 5. Differential scanning calorimetry thermograms of drug, polymer, physical mixture, and hot-melt extruded formulation F3. PEO indicates poly(ethylene oxide).

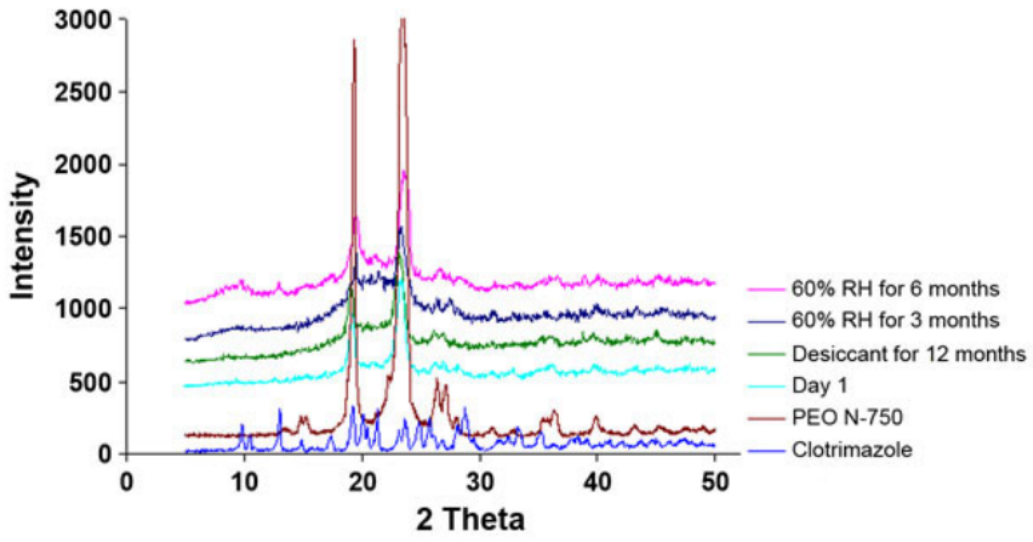

Figure 6. X-ray diffractometry patterns of formulation F3 stored at 25°C and various RHs. RH indicates relative humidity; PEO, poly(ethylene oxide).

Solid-State Stability of CT: XRD

The XRD profile of F3 stored at various conditions is depicted in Figure 6. The drug was found to be in solid solution within all of the formulations 1 day postextrusion.

The physical stability of the films increased as the proportion of HPC:PEO increased (F1 > F2 > F3 > F4 > F5). As previously reported,[9] the films containing only PEO (F5) exhibited poor physical stability. Recrystallization of CT was observed within 3 months when the films were stored at either 25°C/Drierite or 25°C/60% RH.

There were no crystalline peaks corresponding to CT observed in F4 after up to 3 months' storage at 25°C/Drierite. However, recrystallization of CT was observed (peaks corresponding to CT at $2\theta = 9.6, 14.6, 21.1$) after 3 months of storage at 25°C/60% RH and after 6 months of storage at 25°C/Drierite. This physical instability of the drug can be partially explained using the DSC thermograms, which indicated the slow transition of the metastable PEO crystallites into the stable form and/or possible PEO-CT interactions. The slow chain-unfolding process and/or the weak PEO-CT interactions might have resulted in the recrystallization of CT. The nature of the chain-unfolding process can be explained by the fact that F4's glass transition temperature was determined to be 20.80°C (below the storage temperature) when F4 was stored at 25°C/60% RH. At temperatures below Tg, the polymer maintains the disordered nature of the melt but lacks the molecular mobility and is understood to be in a glassy state. At temperatures above Tg, the polymer is easily deformed because of the partial flexibility or segmental mobility of the chains.[7] The relatively higher stability of CT incorporated in F3 may be primarily due to the fact that F3's Tg (25.32°C) is slightly higher than the storage temperature. In addition, F3 was physically stable for 12 months when stored at 25°C/Drierite, where its Tg was determined to be 26.76°C. F1 and F2 were stable for 12 months at 25°C/Drierite and for more than 6 months at 25°C/60% RH (data not shown).

CONCLUSIONS

Polymer blends of HPC and PEO were used successfully to tailor the drug release, mechanical and bioadhesive properties, and stability of polymeric matrices. The glass transition temperature of the polymers plays an important role in determining the physical stability of the solubilized drug. HPC was found to enhance the physical stability of PEO and CT. Films containing HPC:PEO:CT in the ratio of 55:35:10 (F3) demonstrated the optimum physical-mechanical, bioadhesive, and release properties while maintaining the physical and chemical stability of the drug within the films.

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