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Delivery of Itraconazole from Extruded HPC Films

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ABSTRACT The treatment of onychomycosis by oral delivery is problematic due to the high concentrations required and if available, a topical transcuticular route would be preferred. Towards this end the hot-melt extruded hydroxypropylcellulose based films containing anti-fungal drug itraconazole and α–tocopherol topical treatment for onychomycosis were studied. DSC and X-ray measurements did not show a crystalline itraconazole phase indicating the drug is present in the amorphous state. The rate of itraconazole release trended directly with the degree of film hydration and inversely to the hydroxypropylcellulose molecular weight. This results from a higher degree of crystallinity of the HPC films which also changes the release kinetics from first order to zero order as a more tortuous path is created.

KEYWORDS Extrusion, HPC films, Itraconazole, Topical delivery, Transdermal delivery, Nail, Onychomycosis, Controlled release

INTRODUCTION

Onychomycosis

A significant percent of the world population has onychomycosis (*tinea unguium*), a fungal infection that causes the nails to thicken, discolor or split. This widespread problem occurs in approximately 1 in 5 people and accounts for half of all reported nail problems (Ghannoum et al., 2000; Repka et al., 2004). The majority of those infected include the elderly, diabetic, military personnel, farmers, ranchers, and those in the medical field. Men are primarily affected with smokers being prone to contracting the disease on their fingernails (Gupta et al., 1998). This disease also has a high rate of recurrence and is progressive.

Itraconazole

Itraconazole, the model drug used in this study, is currently one of the handful of drugs used to treat onychomycosis through oral administration. It is an imidizole antifungal agent whose mode of action is primarily by way of binding to proteins such as albumin in circulating blood where it eventually concentrates in fat cells, skin, and nails. It is a low aqueous solubility class II

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compound due to its weakly basic character with a pK_a of 3.7 and is used to treat the primary fungi of this disease, *Trichophyton rubrum* and *Trichophyton mentagrophytes* (Six et al., 2004). Itraconazole binds to the fungal p450 enzymes and stops the fungal cell's synthesis of ergosterol, the main component of the cell wall.

Disadvantages of Itraconazole Oral Delivery

Orally administered itraconazole has been found to be moderately effective against onychomycosis, however there are some issues that contribute to the common recurrence of the disease. Patient non-compliance is a serious issue in the treatment of this fungal disease since the patient must take an oral dose of itraconazole 2–3 times a day for 3–6 months. Patients are reluctant to take itraconazole due to side effects such as nausea and vomiting. In addition, oral delivery of itraconazole is plagued with other barriers that inhibit effective delivery to the affected site, the nail bed.

Due to the low solubility of the drug, significant concentrations are stored in fat cells, reducing the amount available for the targeted nail bed (Richardson & Warnock, 2003). Solubility is further decreased if the patient is taking antacids, which eliminate the acidic environment that itraconazole needs to be solubilized. Complications encountered that inhibit the oral bioavailability of the drug include: slow dissolution in the gastrointestinal (GI) tract, metabolism in the liver, low membrane permeability and complex formation as a result of interactions with the substances in the GI tract. Even prescribed dosages can overload the metabolic capability of the liver leading to damage of the liver and heart failure in some cases (http://www.drugs.com/MTM/itraconazole.html).

These factors have given impetus to formulation changes that improve solubility, including surfactants, inclusion complexation and solid dispersion techniques.

Topical Therapy

An additional approach to formulation changes is to apply the drug by site directed delivery or topical delivery. This is an alternative to oral and systemic treatments, which reduce the total drug dose to the patient. To address problems with oral delivery, HPC extruded patches are being studied in this research to effectively deliver itraconazole topically, by site directed delivery. This topical method would also reduce nontarget site toxicities by concentrating the dosage directly at the point of infection rather than indirectly (Chowdary & Rao, 2004).

For topical therapy of drugs, a polymer is typically used as a carrier of the active compound in which modification to the polymer can control the dosage form's release rate and location. The release of itraconazole can be modified by changing the polymer vehicle properties such as the molecular weight, crystallinity and hydrophilicity of the material and hence the miscibility of the contained drug in the film. Additional variations are derived from the preparation method of the film (e.g., hot-melt extrusion).

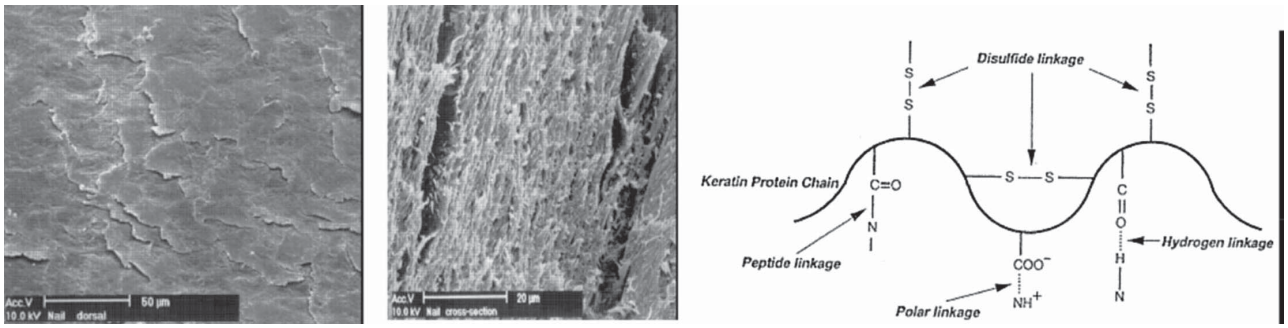
Topical Considerations

Since onychomycosis affects the nail bed, in order to employ topical delivery of itraconazole through the nail plate, the nail structure must be thoroughly understood. The nail is made up of 25 layers of dead, keratinized cells of which 80% are the harder hair type keratin and 20% are the softer skin-type keratin. The cells are bound by intercellular links such as cystine rich proteins having hydrogen bonding, disulfide linkages, and ionic bonding (Fig. 1c; Murdan, 2002).

There are three main keratin layers with the thickness ratio of the layers being dorsal:intermediate:ventral 3:5:2. The top dorsal surface is made up of cells that overlap to form a smooth hard surface (Fig. 1a). The intermediate layer is softer and accounts for the bulk of the nail and is made up of hair-like keratin filaments. These filaments are oriented perpendicular to the growth axis and combine into "keratin sandwiches" that swell and deswell, acting as a hydrogel, with 10–30% water depending on the environment (Fig. 1b). The ventral layer is closest to the nail bed and is the thinnest layer.

In actual use, it is expected that these extruded films will be applied to the nail once the dorsal layer has been filed or otherwise compromised, allowing the drug to diffuse most efficiently to the nail bed.

Hot melt extrusion (HME) has recently shown to be a viable method for preparing drug delivery systems and has benefits over film cast delivery systems in that, solvents are unnecessary and there are fewer processing steps. Additionally, compressibility of the active ingredi-



a) b) c)

FIGURE 1 **(a)Dorsal layer of the nail, (b) Cross section of the nail illustrating keratin sandwiches and c.) bonds involved in the nail structure.**

ent is not needed, particles are more uniformly dispersed due to intense mixing, and bioavailability is improved. This enhanced bioavailability has been shown to be a result of the molecular level solubilization of the drug in the polymer carrier (Rambali et al., 2003).

During the HME process, the drug, thermoplastic polymers, and other excipients are fed into a heated barrel consisting of either a single rotating screw or two screws, which aid in transferring the polymeric-drug blend to the end of the heated barrel. The polymer melts at the elevated temperature and the molten mass is continually pumped through a die attached to the end of the heated barrel. The molten mass rapidly cools as it passes over a chilling apparatus and is collected using a wind-up roll in the case of films (Repka et al., 2004). Since HME precludes the use of solvents, especially water, the potential for drug degradation in the solid state is minimized.

Hydroxypropyl cellulose (HPC), a thermoplastic, water-soluble polymer was used in this study as a sustained release matrix forming polymer. As supplied HPC is an amorphous non-ionic polymer that is a hydrogel and swells to a large extent in water. However, when extruded the HPC crystalline domains form which retards gel layer formation. This property of the polymer can be advantageous when fabricating a delivery system for poorly soluble drugs.

An appropriate choice of polymer molecular weight (chain length) may result in a desired erosion rate and hence a release rate that provides predictable salivary or blood levels of the drug. The molecular weight of HPC, along with processing conditions can be used to alter the crystallinity of the resulting films. Controlling crystallinity in the HPC films allows for tuning of the hydration rate of the HPC matrix and hence the release rates of a drug such as itraconazole. Bioavailability of the model drug was found to be improved when it is dispersed at the molecular level by extrusion techniques, implying that this is a promising method of delivering compounds that are highly hydrophobic (Repka et al., 2002).

The goal of this project involves improving treatment modalities for onychomycosis. The purpose of the present study is to explore a potential topical drug delivery approach using HPC hot-melt extruded films as an alternative to toxic systemic delivery systems. The work reported here addresses the release rate of itraconazole as a function of HPC molecular weight, and also correlates to the resulting thermal and mechanical properties of the HME films.

EXPERIMENTAL

Materials

Hydroxypropyl cellulose (HPC) (Klucel® grades EL, LF, JF, GF, and MF) was kindly supplied by the Aqualon Company, Wilmington, DE. Itraconazole was obtained from Hawkins Chemical Inc., Minneapolis, MN. Diethylamine, α-tocopherol and sodium lauryl sulfate (SLS) were obtained from Spectrum Chemical Mfg. Corp., Gardena, CA. Acetonitrile was purchased from Fisher Scientific, Pittsburgh, PA.

METHODS

Preparation of Films

A single-screw Randcastle Microtuder® (Model RCP-0250) was used to prepare thin polymer films containing itraconazole, α-tocopherol and HPC

grades that spanned the MW range of 80 to 850 kDa. The films were prepared from a blend of the components: 5 wt. % α-tocopherol (vitamin E), 10 wt. % itraconazole, and 85 wt. % HPC. Screw speed was controlled to afford films with a size of 45 mm in width by 0.1 mm in thickness.

α-Tocopherol and the polymer were geometrically diluted through dry blending and dried in an oven at 55°C for 24 hr and then introduced into a V blender and mixed at 100 rpm for 15 min. The resultant blend was fed into the extruder. The extrusion parameters are given in Table 1.

Thermogravimetric Analysis (TGA)

Weight loss as a function of temperature was measured using a TA Instruments Q500 TGA at a heating rate of 10°C/min and a nitrogen flow of 40 mL/min. Water loss was determined by calculating the weight change that occurred at less than 100°C at which point the weight loss profile begins to plateau. The degradation temperature (T_d) was calculated using the onset function in Universal Analysis Software (2002) where two points are selected, one at a plateau point before weight loss and the other at the point maximum in the derivative peak. The TGA temperature was calibrated with nickel and the weight calibration was performed in the range of 200 mg to 1 g with a pan weight of slightly over 200 mg. Platinum sample pans were used with a typical sample size of 10–12 mg.

Dynamic Scanning Calorimeter (DSC)

Thermal properties were measured using a Q1000 DSC from TA Instruments with nitrogen flow of 22 mL/min at a heating rate of 10°C/min and a scan range from 25°C to 150°C. Thermal properties resulting from the first heat were reported. Calibration was performed using indium and zinc standards and heat flow calibration was established using sapphire standards. Values reported for the melting (T_m) and crystallization temperatures (T_c) are those at the minimum and maximum of endothermic and exothermic peaks, respectively.

TABLE 1 Formulation and Extrusion Conditions for Preparation of HME films

Polymer	80 kDa	95 kDa	140 kDa	370 kDa	850 kDa
Feed zone (°C)	150	150	150	150	151
Compression zone (°C)	150	150	150	150	150
Metering zone (°C)	155	155	155	155	155
Die (°C)	155	155	155	155	155
Screw speed	41	41	41	42	43

Wide Angle X-Ray Diffraction (XRD)

XRD was performed on the powders and films in order to determine the relative crystallinity using a Rigaku Ultima III X-ray diffractometer with a Cu-K_∞ radiation source and a λ of 1.54 Å. A scan rate of 5°/min was used with a sampling width of 0.1 mm and a 2θ range of 2–30. The measurement was performed with a tube current of 44 mA and a tube voltage of 40 kV.

High Performance Liquid Chromatography (HPLC)

Drug quantification was performed on a HPLC system consisting of a Waters 600 pump and a dual wavelength Waters 2487 UV detector. The analytical column used was a 150 × 4.6 mm ID, Inertsil ODS-2 column (Alltech Associates Inc.,) with a particle size of 5 μm.

Random samples ($n = 4$) were taken from all of the batches immediately after extrusion and at predetermined intervals analyzed for drug concentration using HPLC. The samples were weighed and dissolved in 10 mL of acetonitrile, sonicated for 10 min or until the entire film was dissolved. After being centrifuged for 18 min at 4000 rpm, the supernatant was removed and filtered using a 0.45 μm nylon filter and injected into the chromatographic system. The mobile phase for HPLC was prepared by mixing HPLC grade acetonitrile, nanopure water and diethylamine in the ratio of 70:30:0.05. This mixture was vacuum filtered using a 0.2 μm nylon filter in a millipore vacuum filtration assembly. The filtered solvent mixture was then degassed using a vacuum assembly, simultaneously stirred using a magnetic stirrer until no bubbles were observed. Chromatography was performed with the filtered degassed mobile phase at a flow rate of 1.0 mL/min

and an injection volume of 20 μL. The effluent was monitored at 261 nm.

For the calibration curve, stock solution of itraconazole at a concentration of 500 μg/mL was prepared in clean and dry volumetric flask by dissolving an appropriate amount of analyte in acetonitrile. Other calibration standards were prepared by serially diluting the stock solutions with acetonitrile. A calibration curve was prepared by plotting the area under the curve of the peak against the concentration.

Stability Tests

Stability testing provides evidence on how the quality or quantity of an active substance varies with time under the influence of variety of environmental factors, such as temperature and humidity and enables recommended storage conditions, re-test periods and shelf-lives to be established. Stability studies were performed on films stored in an unpackaged condition at 25°C/60% RH. Films were analyzed for the drug content using HPLC at time zero, 3 and 6 months to determine the stability of the drug within the HME films.

In Vitro Release Studies

Release studies were performed using a Hanson SR8-Plus™ dissolution test system according to USP XXVIII Apparatus 5, paddle over disk method. Nine hundred milliliters aqueous solution containing 0.5–1.0% SLS at 37°C was used as dissolution media and the paddle rotation speed was 75 rpm. Samples were collected at predetermined time intervals, filtered using a 0.45 μ nylon syringe filter and analyzed using HPLC. These studies were performed in triplicate. The release studies were fitted to first-order, square root, and zero-order models, to ascertain the drug release kinetics from the matrices.

RESULTS AND DISCUSSION

Stability Studies

The drug content remaining in the films stored at 25°C/60% RH for 3 and 6 months is illustrated in Figure 2. The post-extrusion content remaining in the five films ranged from 84.5% (±1.7) of itraconazole added to the blend for the Klucel® MF (MW: 850 kDa) film to 94.2% (±3.0) for the Klucel® JF (MW: 140 kDa) film. In spite of extruding the films at temperatures well above melting point of itraconazole there was less than 10% degradation of the drug observed in three of the film batches. This is due to the high thermal stability of itraconazole and short residence time of the drug inside the barrel of the extruder.

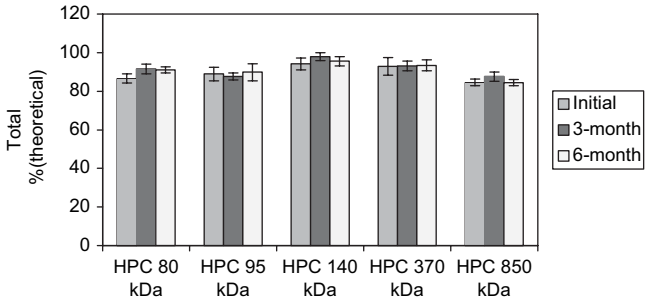


FIGURE 2 **Retained itraconazole in HPC films.**

In Vitro Release Studies

Approximately 52% (±0.8) and 43% (±0.1) of drug was released at the end of 10h from the 370 kDa and 850 kDa films, respectively; whereas 80% (±2.0) release occurred from 80 and 95 kDa films at the same time interval (Fig. 3). The release profile was only carried out to 10 hr for the lower molecular weight films 80 and 95 kDa, this is due to the plateau of drug release at this point as the films were mostly dissolved. The films prepared from the 140, 370, and 850 kDa HPC samples all retained visual mechanical integrity until 25 hr and continued to demonstrate drug release.

The release profiles in Fig. 3 show a clear retardation as the HPC molecular weight increases beyond 95 kDa. Such release profiles suggest that the process is

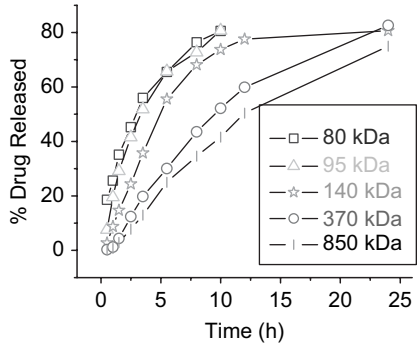


FIGURE 3 **Release profiles of itraconazole from HPC films.**

carrier controlled and the physical properties of the drug are of minimal importance and imply that the release of the drug from the HME HPC films can be tailored by altering the molecular weight without affecting the mechanism of release.

The release data were fit to three different models, the kinetics of drug release for the HPC film of 80 kDa was found to be 1st order indicating that the concentration behind the poly(tetrafluoroethylene) (PTFE) membrane in the Hanson dissolution test decreases significantly over time. The 95 kDa film was found to have the kinetics of Higuchi-square root kinetics in which diffusion is controlled by the matrix of the film, in which there is a diffusion layer present. The three films of higher molecular weight HPC, 140, 370, and 850 kDa, respectively, were determined to have zero-order release rates (Fig. 4). In zero order kinetics there is a constant supply of drug or a saturated concentration behind the PTFE membrane in the Hanson dissolution test. The zero-order kinetics is desirable for controlled release dosage forms as a constant concentration of drug is released over time (Cleary et al., 2002).

To observe the solubility of drug in the films, X-ray diffraction was used to assess the reactants in comparison to the final film (Fig. 5). The data suggests that there is drug content uniformity within the films because there are no sharp crystalline peaks resulting from itraconazole in the final film. However it cannot be determined from this data if α-tocopherol is homogeneously distributed (Fig. 6). This solubility of itraconazole in the films can also be observed in the DSC spectra of an extruded film and the components of the film.

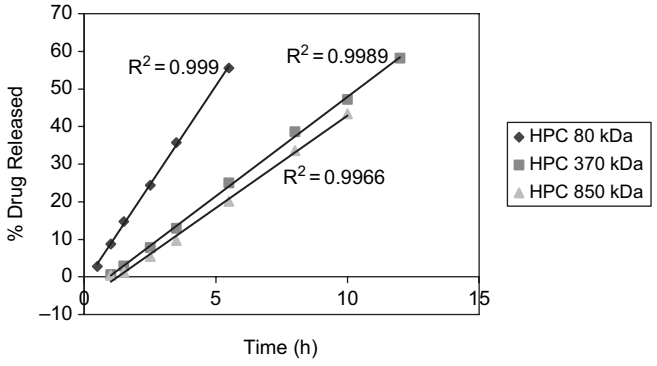


FIGURE 4 **HPC 140, 370, and 850 kDa drug release plots fit to zero order kinetics.**

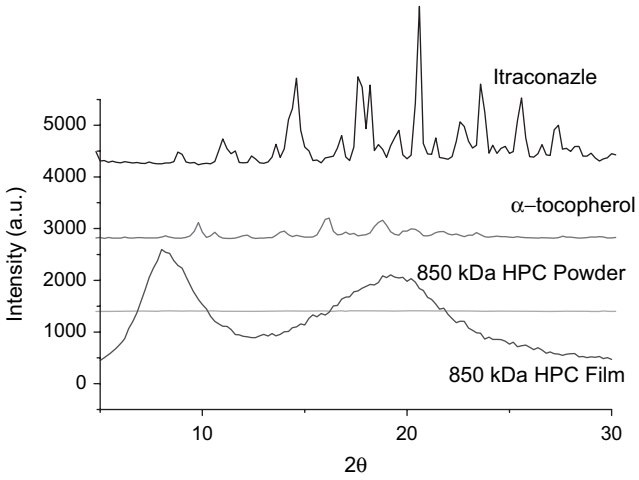


FIGURE 5 **X-ray diffraction spectra of HPC film, HPC powder, α-tocopherol, and itraconazole.**

With no endotherm attributable to itraconazole in the extruded film, it is assumed to be solubilized within the film and no longer in a separate crystalline drug phase. However, there is a thermal event in the final film indicative of α-tocopherol. The endotherm is small as it makes up only 5% of the total components in the film. The melting temperature is lower however, dropping from 80°C alone to 60°C in the film indicating some degree of mixing.

X-ray measurements were made to look at how the crystallinity of the films differs as a function of HPC molecular weight and how extrusion changed the properties of HPC. The crystallinity of the received powders was very low, with only weak diffraction patterns evident in the x-ray measurements (Fig. 7a). Within the samples received, crystallinity appears to decrease with increasing MW. This is contrary to the trend found for the extruded samples. The film diffraction patterns (Fig. 7b.) show two trends. First the degree of crystallinity is much higher than the as received powders and second, the crystalline content in the films is contrary in comparison to the powders.

These observations are most likely the result of powder formation in which the materials were forced to cool very fast resulting in less time for the crystal domains to organize, with less mobility at higher molecular weights. Once extruded, the HPC films have a much higher degree of crystallinity compared to the powders and it can be seen from the two main ordering or crystalline regions at $2\theta = 10$ and 20°, that as the molecular weight of HPC increases in the films, there is increase in crystallization. Crystalline lamella

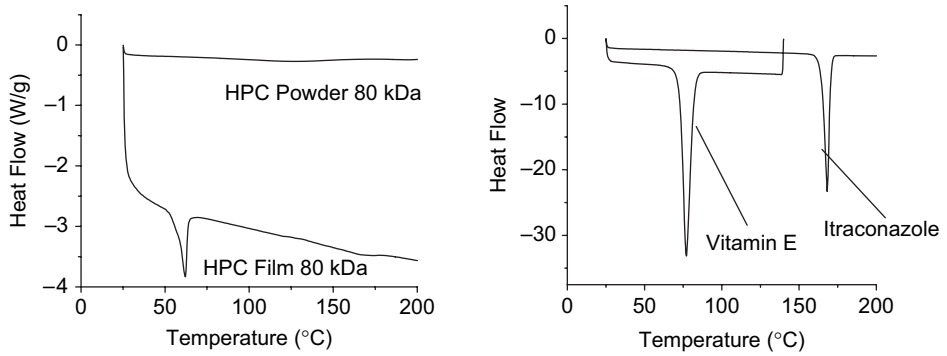


FIGURE 6 **DSC spectra of HPC powder, HPC film, α-tocopherol, and itraconazole.**

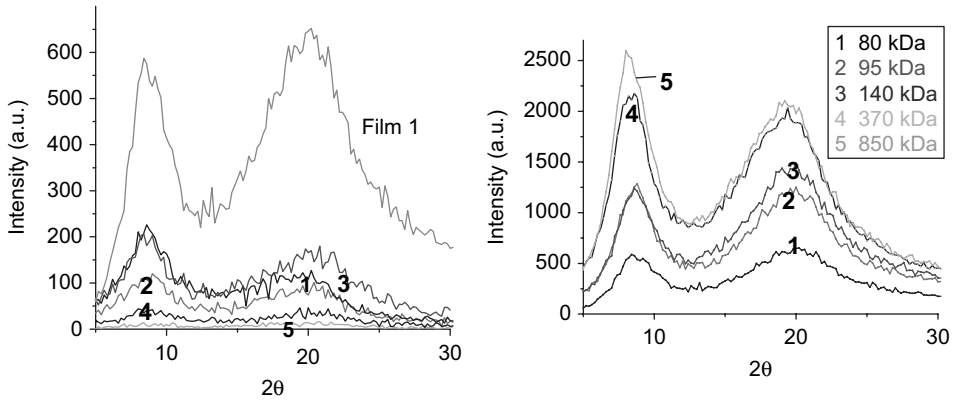


FIGURE 7 **X-Ray diffraction patterns of a.) HPC films and b.) corresponding powders (film 1 shown for comparison component).**

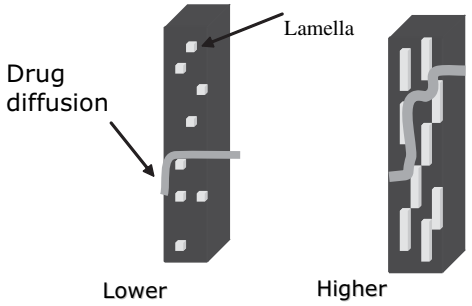


FIGURE 8 **Influence of crystal lamella on drug diffusion pathways.**

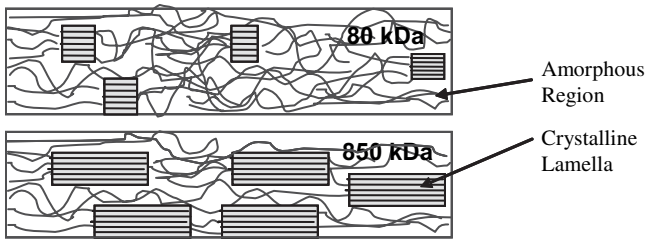


FIGURE 9 **Differences in amorphous ordering of 80 kDa HPC films compared to that of 850 kDa films.**

are also increasing in size as a function of molecular weight as can be seen from the broader peaks with increasing HPC molecular weights. This formation of larger and more crystalline lamella in the films would result in a more tortuous path for drug diffusion and would most likely result in zero order release kinetics. However, the lower molecular weight films with less crystallinity and smaller lamella provide a more facile route for the entrapped host, resulting in 1st order and Higuchi square root kinetics (Figs. 8 and 9).

Thermal Properties

In order to understand how the hydrophilicity of the HPC has changed by combining it with α-tocopherol and itraconazole along with increasing the overall crystallinity post extrusion, the HPC powders and final extruded films water uptake was measured after 5 days and after 3 months at 60% RH by TGA. HPC powders and films were dehydrated by placing them in a desiccator under vacuum containing P_2O_5 for 48 hr. These results are summarized in Table 2.

TABLE 2 Water content of HPC powders, $\%H_2O$ (±0.2%)

Condition/film	80 kDa	95 kDa	140 kDa	370 kDa	850 kDa
Dehydrated powder	1.2	1.3	1.1	1.3	1.1
Powder 5 d	1.3	2.4	1.6	1.4	2.5
Powder as received	1.8	2.6	1.8	2.1	3.1

From the data in Table 2, it can be inferred that as the HPC powder molecular weight increases (crystallinity decreases as determined by XRD) hydrophilicity increases. The same method was applied to the HPC films. (Table 3)

It can be observed from these TGA measurements that the hydrophilicity decreases with increasing HPC molecular weight and with increasing crystallinity content causing more difficulty for water vapor to penetrate due to the higher content and larger crystalline lamella. In terms of utilizing these films (patches) for the desired application, higher molecular weight HPC films with higher crystallinity will absorb water at a slower rate and release itraconazole with zero order kinetics.

In order to determine if the extrusion process degrades the HPC to produce modified molecular weight films, the degradation temperature was measured of the powder HPC before being extruded and post extrusion. The onset point of the degradation temperature of the powders, as seen by taking the intercept of the lines tangent to the weight loss curve, was compared to that of the films by TGA to determine if modification occurred during extrusion. These results are summarized in Table 4.

Using the *t*-test, it was determined that processing did not affect the degradation temperature of HPC powder (Table 4). This indicates that there was little to no degradation of the HPC upon extrusion.

TABLE 3 Water content of HPC extruded films $\%H_2O$ (±0.2%)

Condition/film	80 kDa	95 kDa	140 kDa	370 kDa	850 kDa
Dehydrated film	0.38	0.80	0.55	0.60	0.57
Film 5 d RH	1.0	1.1	0.98	1.9	1.2
Extruded film as received	3.0	2.8	1.4	1.8	1.2

TABLE 4 T_d of HPC powder component and subsequent extruded films

Form	80 kDa	95 kDa	140 kDa	370 kDa	850 kDa
Powder (±0.2)	374.6	375.9	377.3	377.3	383.3
Film (±0.2)	374.7	378.4	378.5	380.8	380.8

CONCLUSION

HME is a viable technology to produce thin, stable, and homogenous drug-incorporated HPC films. Data from these studies indicate that the matrices produced via HME utilizing various Klucel® HPC grades can be used for the controlled-release of poorly water-soluble drugs. Studies are in progress to increase the initial drug content by preventing the formation of solid bridge at the throat of the hopper. "Starve feeding" or a force-feeding/controlled feeding device will be used in future research for the extrusion of HPC.

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