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Influence of Tartaric Acid on the Bioadhesion and Mechanical Properties of Hot-Melt Extruded Hydroxypropyl Cellulose Films for the Human Nail

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ABSTRACT The objective of this study was to investigate the influence of tartaric acid (TTA) on the bioadhesive, moisture sorption, and mechanical properties of hot–melt-extruded (HME) hydroxypropyl cellulose (HPC) films containing polymer additives. Two Klucel® EF and LF batches (HPC, MW: 80000 and 95000, respectively) containing the model antifungal drug ketoconazole (one batch of each MW with and without TTA 4%) were prepared into films by HME using a Killion extruder (Model KLB-100). The bioadhesive properties of the HPC films, with and without TTA, were investigated ex vivo on the human nails. The parameters measured were work of adhesion and peak adhesion force (PAF). A statistically significant increase in both the area under the curve (AUC) and PAF was seen for the HME films containing TTA than those without TTA. Moisture content of hot-melt extruded HPC films was determined using thermogravimetric analysis (TGA). TGA data collected at the two-week interval (25°C/60% RH), measured higher moisture content for the TTA-containing films than those without TTA. Tensile strength and percent elongation were determined utilizing a TA.XT2i Texture Analyzer® equipped with a 50-kg load cell, TA-96 grips, and Texture Expert™ software. TTA functioned as an effective plasticizer, increasing percent elongation and decreasing tensile strength of the HPC films. TTA could potentially be a candidate for transnail applications in film devices prepared by hot-melt extrusion technology.

KEYWORDS Tartaric acid, Hot-melt extrusion, Bioadhesion, Mechanical properties, Thermogravimetric analysis (TGA), Nail

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INTRODUCTION

Tartaric acid (TTA, 2,3-Dihydroxybutanedioic acid) has been utilized for numerous applications in pharmaceutical dosage forms. It is widely used in food products and oral, topical, and parenteral pharmaceutical formulations

and is generally regarded as a nontoxic material (Vaughan, 2002). The chemical properties of this distinctive compound have suggested its use as a surface modifier, an acidifying agent, an acidulant and as a flavor enhancer (Vaughan, 2002). TTA has a melting point of approximately 170°C (Vaughan, 2002). These physical properties coupled with its chemical properties make TTA a potential candidate for hot-melt extrusion (HME) applications. The chemical structure is shown in Fig. 1.

Several studies have demonstrated the effects of TTA as a surface modifier (Repka et al., 2001; Mididoddi & Repka, 2004). The surface-active nature of TTA-containing films was demonstrated to provide better surface modification to the human nail than those without the compound (Mididoddi & Repka, 2004). Repka et al. conducted a study using polarized light microscopy (PLM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) to compare the morphology of the non-treated human nail with those treated with TTA for the partial assessment of topical treatment modalities for onychomycosis. These researchers reported disruption, and in some cases complete removal, of the dorsal surface of the human nail when treated with TTA. The dorsal surface morphology was found to change quite dramatically when subjected to surface modifier TTA, and they could observe the change in topography from the non-treated dorsal surface resulting in increased roughness and a consequent increase in surface area of the treated specimen (Repka et al., 2002). From the visualization of micrographs, these researchers concluded that the increase in surface area provides a greater opportunity for polymer chains to inter-diffuse and bond with the nail plate, improving bioadhesion and retention of a drug delivery system (Lee et al., 2000). Nomura et al. (1996) reported that TTA increased the nasal absorption of non-glycosylated recombinant human granulocyte colony-stimulating factor produced by Escherichia coli. Yagi et al. (1993) concluded that TTA enhanced the absorption of bumetanide, resulting in an increased bioavailability following rectal administration of Macrogol suppositories.

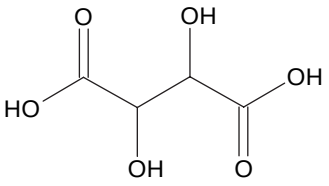

FIGURE 1 **Physical Properties and Structure of TTA.**

Onychomycosis refers to a fungal infection that affects the toenails or the fingernails. It may involve any component of the nail unit, including the nail matrix, the nail bed, or the nail plate. Onychomycosis has received much attention recently due to increased incidence of nail infections and problems associated with its therapy (Myoung & Choi, 2003). Negative aspects associated with oral systemic antifungal therapy for onychomycosis include its limited success rate, toxicity, high cost of medication, and increased microbe resistance (Murdan, 2002). Although current topical therapy does not lead to systemic side effects or drug interactions, its efficacy is questionable, which is likely due to poor penetration of drugs into and through the nail plate. The nail is comprised of dead corneocytes without nuclei or organelles and filled with α-keratin, constituting almost the entire dry weight of the nail (Quintanar-Guerrero et al., 1998). Indeed, the nail plate is a relatively thick and dense structure that inhibits adequate penetration of most drugs indicated for fungal nail.

HME continues to spark much attention in the pharmaceutical field (Follonier et al., 1994; Repka et al., 1999). 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, pellets (Young et al., 2002), sustained release tablets (Crowley et al., 2002; Crowley et al., 2004), and transdermal and transmucosal drug delivery systems (Aitken-Nichol et al., 1996; Repka et al., 2001; Repka et al., 2003; Repka et al., 2004). In HME drug delivery systems, the active compound is embedded in a carrier formulation comprised of one or more meltable substances and other functional excipients. Poorly water-soluble drugs (including most antifungal agents) that demonstrate a low bioavailability are prime candidates for this technique.

Few, if any, studies have been reported in the literature concerning the bioadhesion and mechanical properties of TTA incorporated into hydrophilic films produced by HME techniques. Satisfactory bioadhesion is essential for the successful application of a bioadhesive drug delivery system for transnail delivery. In addition, due to the unique properties of TTA as a surface modifier and having potential modified release

properties, transdermal and transmucosal applications are also possible. The objective of this investigation was to study the influence of tartaric acid on the bioadhesion and mechanical properties of HPC hot-melt extruded films. In addition, these studies can direct evaluation and further investigation of delivery systems for the treatment of onychomycosis.

MATERIALS

Hydroxypropyl cellulose (HPC) (Klucel® EF; MW, 80000 and Klucel® LF; MW, 95000) was kindly gifted by the Aqualon Company (Wilmington, DE). Poly(ethylene oxide) (PEO) (MW, 100000) was obtained from Aldrich Chemical Company (Milwaukee, WI). Noveon® AA-1 (Polycarbophil) was obtained from Specialty Chemicals (Cleveland, OH). Tartaric acid (TTA) was obtained from Spectrum Chemicals, Inc. (Gardena, CA).

METHODS

Preparation of HME Films

Two Klucel® EF (HPC, MW:80000) film batches (250 g) containing the model antifungal drug ketoconazole (one without and one with TTA 4%) and two Klucel® LF (HPC, MW:95000) film batches (250 g) containing the same drug (one without and one with TTA 4%) were prepared by HME using a Killion extruder (Model KLB-100). The extruder was preheated to processing temperatures based on previous studies. 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 40°C–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°C–160°C. Homogenous films were obtained with a thickness range of 0.23–0.33 mm. The extrudate was collected in rolls, labeled, and sealed in 5-mil, opaque, foil-lined polyethylene bags (25°C/60% RH). Initial testing was commenced after 7 days of storage.

Bioadhesion Testing

Tip nail pieces were obtained from fingers of healthy volunteers (University of Mississippi, IRB # 03–045) using nail clippers. Bioadhesion tests were performed on Klucel® EF films (without and with TTA 4%) using a Texture Analyzer® (TA.XT2*i*, Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK) (Fig. 2(a)) equipped with Texture Expert™ software. The extruded films used in this work were wetted with 300 μL of nanopure water for approximately 10 sec to allow the polymer chains to fully hydrate prior to testing. The films were then applied to human nail samples, ex vivo. Each nail sample was placed and secured on a slotted die-cut fixture (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), or work of adhesion.

Thermogravimetric Analysis (TGA)

Three samples of each HME film weighing 5–8 mg were loaded into the pan of the thermogravimetric analyzer (Perkin-Elmer Pyris 1 TGA) and heated from 25°C to 120°C at 10°C/min and then held at 120°C under constant nitrogen purge. The test was terminated when no significant loss of weight (< 0.1%/hr) was observed.

Mechanical Testing

Mechanical properties of HME films were determined utilizing a TA.XT2*i* Texture Analyzer® (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK) equipped with a 50-kg load cell, TA-96 grips (Figure 2(b)) and Texture

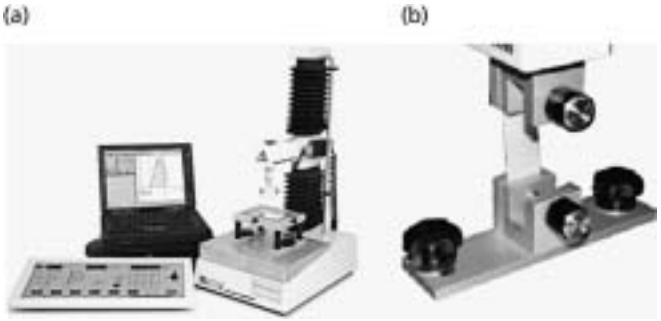

FIGURE 2 (a) TA.XT2*i* Texture Analyzer (from Texture Technologies Corp.) and (b) TA-96 Grips for Mechanical Testing.

Expert™ software. Film samples, 50 mm in length, having uniform width of 10 mm and free from physical imperfections, were held between the two grips (TA-96). The grip separation was set at 30 mm. The crosshead speed was 2 mm/sec (strain rate), and the data acquisition was terminated when the film failed. The Texture Expert™ software generates the stress-strain curves and calculates the tensile strength and percent strain (percent elongation). These parameters can be defined and calculated by the following equations. The tensile strength can be defined as the maximum stress (σ_{max}) sustained by the material and is calculated from 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

$$\sigma_{\max} = \frac{F_{\max}}{A} \tag{1}$$

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 change in the length of the sample to the original sample.

$$\%\ \text{Elongation (or \% strain)} = \frac{\Delta L}{L} * 100 \tag{2}$$

Statistical Analysis

For all studies, statistical analysis was determined utilizing one-way analysis of variance (ANOVA). A statistically significant difference was considered when $P < 0.05$.

RESULTS AND DISCUSSION

Results of force-deflection profiles for HME films containing HPC are depicted in Figs. 3–5. The deflection measurements of the pofiles 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. 3 and 4 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

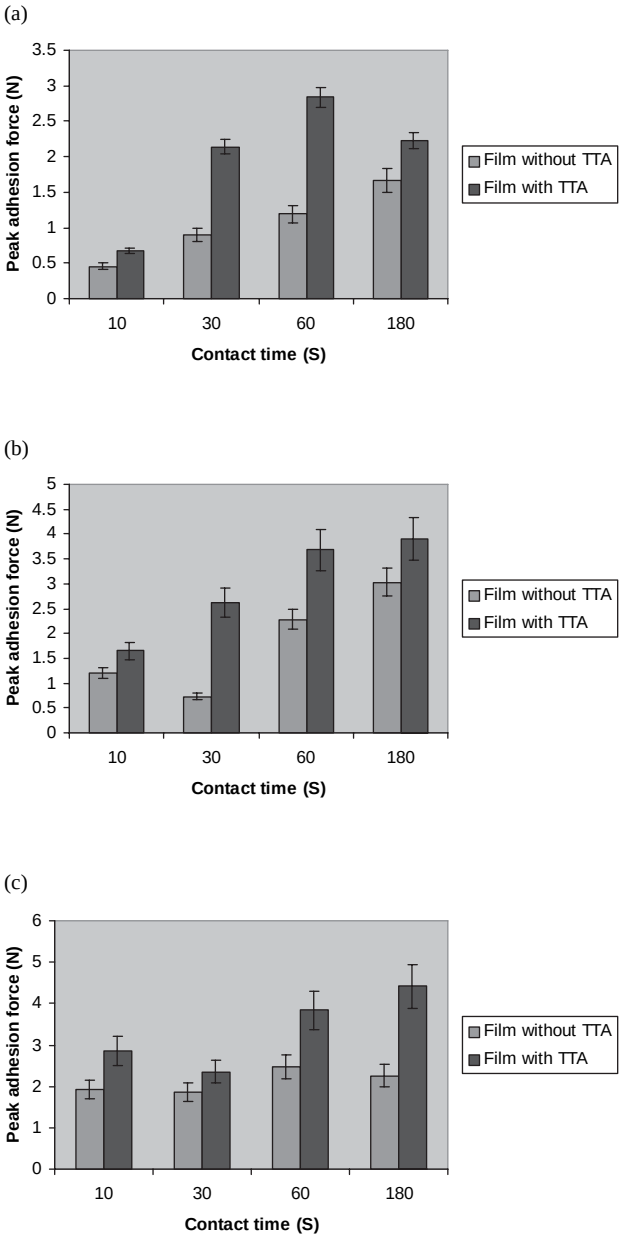

FIGURE 3 **Influence of Contact Time on Peak Adhesion Force of HME Films Containing Ketoconazole on Human Nail: (a) Contact Force—0.1 N, (b) Contact Force—0.5 N, and (c) Contact Force—1.0 N.**

the marked differences between the TTA-incorporated film and the HPC film without TTA. It can be inferred from these two figures that, at all contact forces employed, both the AUC and PAF were higher for the HPC films containing TTA. As can be seen in Fig. 3(a), for a contact time of 30 sec (0.1 N contact force), the PAF was, approximately, 2.5-fold higher for the TTA-containing film than the film without TTA. Indeed, PAF was statistically higher for the TTA-containing films at all contact forces and at all contact times tested. The area

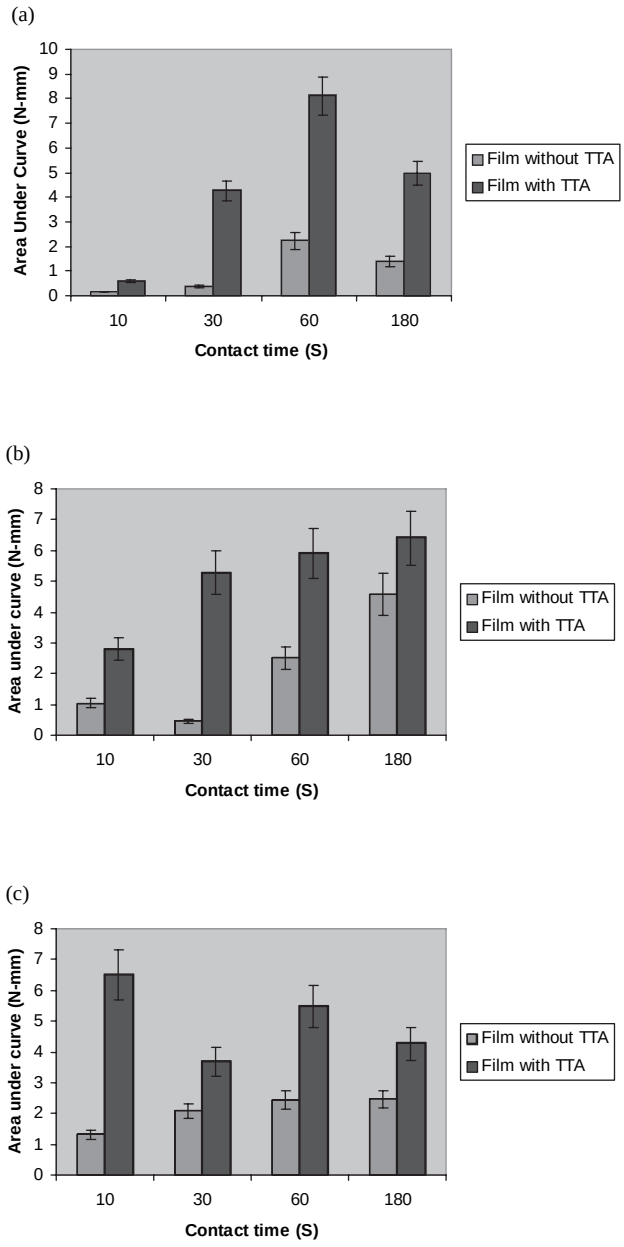

FIGURE 4 **Effect of Contact Time on Work of Adhesion of HME Films Containing Ketoconazole on Human Nail: (a) Contact Force—0.1 N; (b) Contact Force—0.5 N; (c) Contact Force—1.0 N.**

under the curve, for a contact time of 30 sec (Fig. 4(a)), for the TTA-containing film, was 12-fold higher than the film without TTA. This increase in bioadhesion for TTA-containing films can be explained by the fact that the surface-active nature of TTA-containing films was demonstrated to provide better surface modification to the human nail, thereby increasing its PAF and AUC when compared to HPC films without TTA (Repka et al., 2002). Surface properties of a substrate have shown to significantly influence polymer-substrate interactions, such as force of adhesion and adhesive toughness (Felton et al., 2000). These results confirm the significance of previous work by Repka et al., where the dorsal surface morphology of the human nail was found to change quite dramatically, when subjected to the surface modifier, TTA. These researchers observed the change in topography from the non-treated dorsal surface, resulting in increased roughness and a consequent increase in surface area of the treated specimen (Repka et al., 2002). Another supporting explanation for the different bioadhesion profiles between the two films is that the polycarbophils contain a large number of carboxylic acid groups, which provide the ability to form a greater number of hydrogen bonds with the increased surface area of the human nail tested with TTA-containing films (Mortazavi, 1995).

In comparison, the bioadhesion appeared to be less influenced by the change in contact force. Increasing the contact force from 0.1 to 0.5 N, or 0.5 to 1.0 N, did not demonstrate a statistically significant increase in the work of adhesion at all contact times studied. Almost similar observations were obtained when the bioadhesion was quantified using the PAF. These findings indicate that the contact time is more critical in affecting the bioadhesion process than the contact force used. The contact time may affect the degree of hydration and swelling, which in turn will influence the adhesion to the human nail (Ponchel et al., 1987). These results are in agreement with the work of Wong and co-workers who found that the contact time was more critical in affecting the bioadhesion of polymers utilizing a model tissue (Wong et al., 1999).

A contact force of 0.5 N and a contact time of 180 sec were employed to study the effect of probe speed on the work of adhesion and PAF. This setting was chosen based on the previous study of Wong and co-workers on both Carbopol® 974P and Methocel® K4M tablets (Wong et al., 1999). Fig. 5 shows the influence of probe speed on PAF and work of adhesion for the films. A statistically significant increase in both the PAF and the AUC was seen for the HME films containing TTA than for the films without TTA. This increase in PAF and AUC can also be attributed to the increased roughness and a consequent increase in surface area of the nail (Repka et al., 2002).

TTA has been demonstrated to function well as a plasticizer when incorporated into HPC films at the 3% level and has been chemically stable at various processing temperatures. Fig. 6 demonstrates the influence of TTA on the tensile strength and percent elongation of the extruded films. The tensile strength determined for HPC films with TTA was lower when

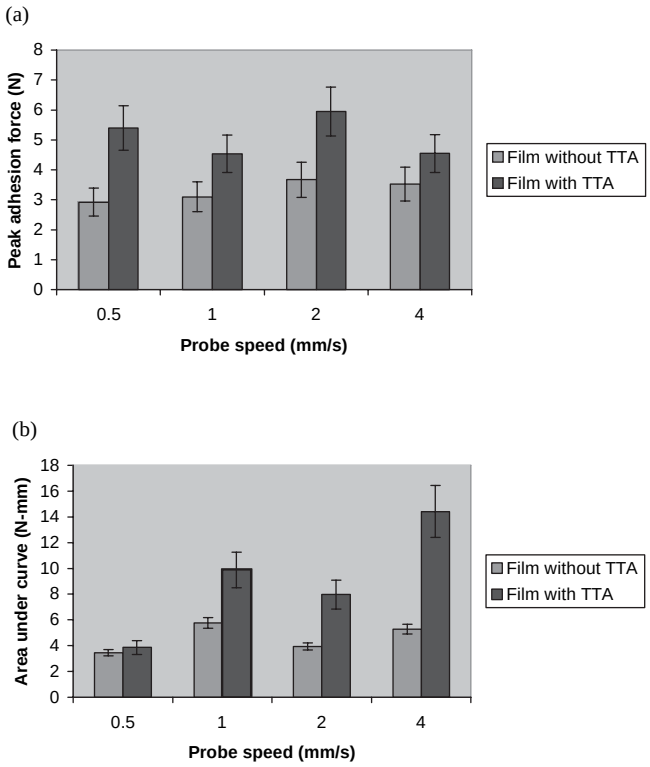

FIGURE 5 **(a) Effect of Probe Withdrawal Speed on Peak Adhesion Force of HME Films Containing Ketoconazole on the Human Nail. (b) Effect of Probe Withdrawal Speed on Work of Adhesion of HME Films Containing Ketoconazole on the Human Nail.**

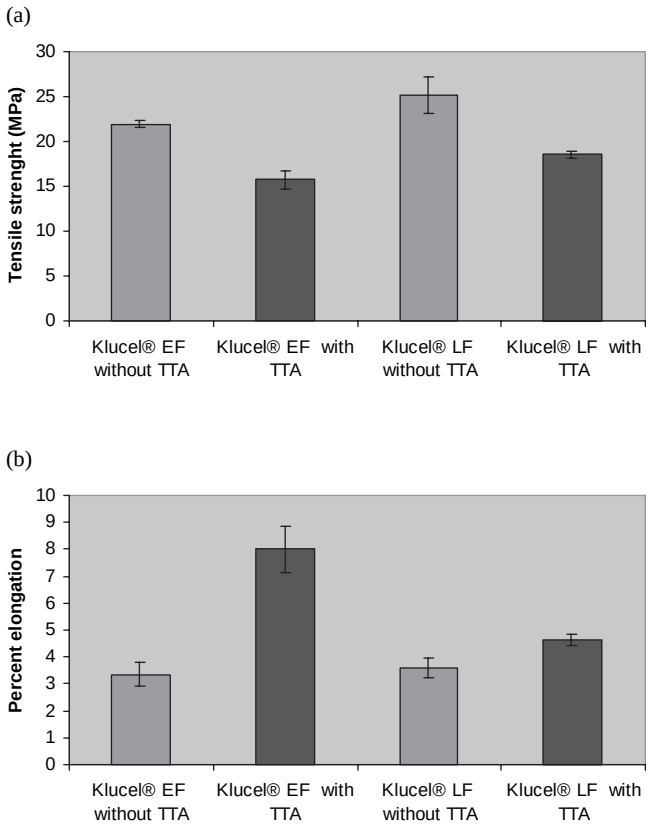

FIGURE 6 **(a) Influence of Tartaric Acid on the Tensile Strength of Hot-Melt Extruded Hydroxypropyl Cellulose Films. (b) Influence of Tartaric Acid on the Percent Elongation of Hot–Melt-Extruded Hydroxypropyl Cellulose Films.**

compared to that of the films without TTA. Conversely, percent elongation was significantly higher for films containing TTA than the films without TTA. The effectiveness of a plasticizer is related to its ability to disrupt the intermolecular forces of the polymer, which in the present study is HPC (Repka et al., 2001). Greater disruption of these forces would hence produce a film with greater ductility, thereby producing a greater percent elongation and lower tensile strength upon mechanical testing. These properties have been demonstrated in this study. Repka et al. (2001) found similar results with a hot–melt-extruded HPC film incorporated with chlorpheniramine maleate in the case of tensile strength and percent elongation. The change in tensile properties is also explained by the linear nature of the cellulose structure and consequent crosslinking by TTA incorporated into the film. The linear cellulose strands are interconnected by bonding of three reactive hydroxyl groups present on each anhydroglucose monomer unit of the HPC chain. Therefore, the TTA-containing film interacts with the cellulose backbone structure by hydrogen bonding and other intermolecular forces that are not as rigid as the covalent bonds of the more linear cellulose structure, effectively crosslinking the HPC (Aqualon, 1997). Thus, there is more latitude for elongation.

The data in Table 1 demonstrated the influence of TTA on the moisture content of the extruded films. After storage for two weeks (25°C/60% RH), the films containing TTA exhibited a 44–51% increase in water content. As illustrated in Table 1, the Klucel® EF film containing TTA showed an increase in moisture content from 2.11% (film without TTA) to 3.24% (film with TTA). In addition, the Klucel® LF film containing

TABLE 1 **Moisture Content of Hot-Melt Extruded Hydroxypropyl Cellulose Films Determined by Thermogravimetric Analysis**

	Film	Moisture content (%)
1	Klucel® EF without TTA	2.11
2	Klucel® EF with TTA	3.24
3	Klucel® LF without TTA	2.14
4	Klucel® LF with TTA	3.05

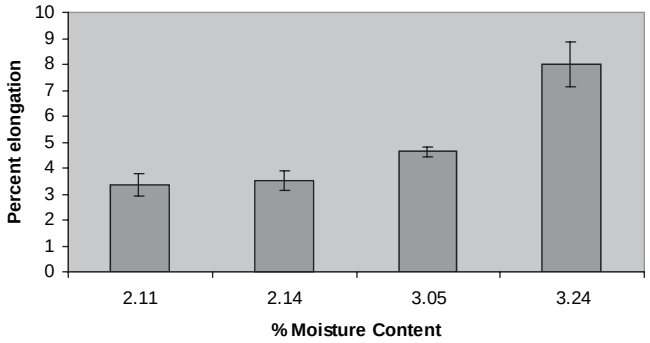

FIGURE 7 **Percent Elongation of Hot-Melt Extruded Hydroxypropyl Cellulose Films as a Function of Moisture Content.**

TTA showed an increase in moisture content from 2.14% (film without TTA) to 3.05% (film with TTA). The higher moisture content attained for films with TTA is potentially due to TTA's moisture absorption properties. Perez-Rodriguez et al. found similar results with polytartaramides, i.e., polyamides obtained from tartaric acid. P6DMLT is a modified nylon 6,4 polytartaramide that absorbs up to 20% of water when exposed to a humid atmosphere (Perez-Rodriquez et al., 2000).

The effect of moisture on the percent elongation of the films is depicted in Fig. 7. There was a significant increase in the percent elongation of the films with increasing moisture content. This observation was anticipated due to the plasticizing effect of the adsorbed water such that the polymer backbones have an opportunity to change their configurations before the material breaks. The small size of the water molecule allows it to penetrate and weaken polymeric intermolecular attractions and increase the polymer's free volume (Zuelger & Lippod, 2001). This allows the polymer molecules to move more easily, thereby increasing flexibility (Gutierrez-Rocca & McGinity, 1993; Wheatley & Steuernagel, 1997). Repka et al. (2000) found similar percent elongation results with hot-melt extruded HPC films. The stress-strain curves also indicated that the tensile strength increased as a function of molecular weight. This may be due to increased chain entanglement with an increase in molecular weight, which can endure higher imposed stress (Rowe, 1983).

CONCLUSIONS

The hot-melt extrusion process was shown to be a promising technology for preparing films containing HPC with TTA as an additive. Addition of TTA within the film formulations significantly influenced the bioadhesion and mechanical properties tested. Force-deflection profiles obtained from nail adhesion experiments indicate that the surface active nature of TTA-containing films was demonstrated to provide better surface modification to the human nail, thereby increasing its PAF and AUC (a two- to three-fold difference) when compared to HPC films without TTA. The HPC films containing TTA exhibited a lower tensile strength and a higher percent elongation than those films without TTA. TGA data collected at the two-week interval (25°C/60% RH), measured higher moisture content for the TTA-incorporated films than the films without TTA. TTA functioned as an effective plasticizer, increasing percent elongation and decreasing tensile strength. Results of this investigation, coupled with nail permeability and other studies, are relevant to ongoing development of improved formulations for topical drug delivery.

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