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European Journal of Pharmaceutics and Biopharmaceutics 59 (2005) 189–196
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Characterization of cellulosic hot-melt extruded films containing lidocaine

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Received 16 February 2004; accepted in revised form 7 June 2004
Available online 1 September 2004

Abstract

Hot-melt extrusion technology was used to produce thin films containing a model drug, lidocaine, and the cellulosic polymers hydroxypropyl cellulose (HPC) and hydroxypropyl methyl cellulose (HPMC). Two film formulations were extruded and compared, one containing only HPC and the other containing HPC:HPMC (80:20). Thermal analysis of the films using differential scanning calorimetry (DSC) suggested that the drug existed in the amorphous condition, which was confirmed by wide angle X-ray diffractometry. Sustained release of the drug was observed from both of the polymer matrices. Dissolution profiles suggested that HPMC retarded the drug release from HPC:HPMC (80:20) films. However, the mechanism of drug release from both of the films was predominantly diffusion of the drug through the polymer matrices. Incorporation of HPMC also increased both adhesive strength and work of adhesion as compared to the HPC-only films.

Keywords: Hot-melt extrusion; Lidocaine; Texture analyzer; Muco-adhesive films; Hydroxypropyl cellulose; Hydroxypropyl methyl cellulose

1. Introduction

Local delivery of drugs to the tissues of the oral cavity has a number of applications including treatment of periodontal disease [1], dental analgesia [2], bacterial and fungal infections (oral candidiasis) [3–5], aphthous ulcers and dental stomatitis. Dosage forms for local action have included ointments, gels, buccal tablets and lozenges. However, use of these dosage forms carry an inherent risk that a high percentage of the drug may be excluded from absorption or partitioning into the target tissues by swallowing of the tablet or lozenge, or by salivary clearance of the drug from the delivery system. In addition, these dosage forms act only for a short duration thus decreasing the dosing interval. Therefore, it is desirable to develop alternative dosage forms that remain in the oral cavity in intimate contact with the mucosa thereby releasing the drug for a prolonged period of time. In addition, for dental analgesia, it would be advantageous to have not only prolonged release of the anaesthetic but also an initial burst release so as to obtain therapeutic levels sufficient for immediate pain relief.

Ishida et al. [2] have formulated a muco-adhesive tablet containing lidocaine for both immediate and sustained release. However, this current research focuses on developing a film dosage system, which has advantages over the muco-adhesive tablet including decreased thickness, increased flexibility and better comfort of the dosage form, thereby increasing patient compliance. In addition, in ongoing research, films are produced using hot-melt extrusion (HME) technology, which may yield drug in the form of a solid dispersion or solution, thereby increasing the solubility of poorly soluble drugs.

Several authors have developed film formulations utilizing solvent cast methods [6–9]. The films, however, were not intended for sustained release of the drug. Moreover, it is well known that the solvent cast method suffers from several disadvantages over the HME method. Gutierrez-Rocca demonstrated that polymeric

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doi:10.1016/j.ejpb.2004.06.008

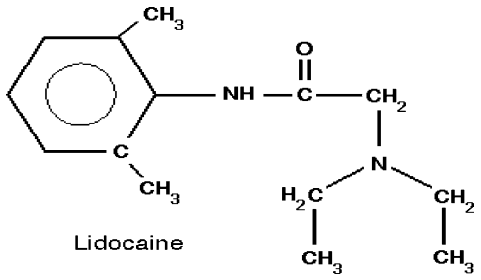

Fig. 1. Chemical structure of lidocaine.

films prepared by a solvent cast method turned brittle during the storage, as indicated by decrease in the percentage of elongation due to the evaporation or loss of the residual solvent in the film with time [10]. In addition, HME has several advantages including it being a solvent-free, continuous, less time and energy consuming process.

Aitken-Nichol and coworkers investigated the viability of HME technology for the production of thin, flexible, acrylic films for topical drug delivery [11]. These researchers showed that lidocaine HCl was able to plasticize the acrylic polymer and that the drug was completely dispersed at the molecular level within the extruded films. Solubilized drug molecules were shown to plasticize the polymer by increasing the average polymer chain spacing. A process utilizing hot-melt technology for the production of thin films was also described by Repka et al. [3]. These researchers investigated the properties of hot-melt extruded films containing clotrimazole for intra-oral drug delivery.

In the current study, lidocaine (Fig. 1), a topical anaesthetic was chosen as a model drug due to its applicability in dental analgesia, and its reported high-thermal stability [12]. The objective of this study was to investigate the effect of a nonthermoplastic polymer, hydroxypropyl methyl cellulose (HPMC), incorporated into hot-melt extruded hydroxypropyl cellulose (HPC) films for the potential development of oral muco-adhesive dosage forms. Bioadhesive and release profiles, solid-state characteristics of the drug within films, and drug stability were studied to accomplish this objective.

2. Materials and methods

2.1. Materials

Lidocaine, polyethylene glycol 3350 NF and butylated hydroxytoluene (BHT) were purchased from Spectrum quality products, Inc. (New Brunswick, NJ, USA). Klucel® GF (HPC, MW 370,000) was gifted by Aqualon Division, Hercules, Inc. (Delaware, USA). Methocel K-15 HPMC (15k cps) was purchased from Aldrich chemical company, Inc. (Milwaukee, WI, USA). Noveon AA-1 (polycarbophil) was purchased from Noveon, Inc. (Cleveland, OH, USA). PolyOx N-80 (Polyethylene oxide, MW 200,000) was a generous gift from the Dow chemical company (Midland, MI, USA).

2.2. Methods

2.2.1. Preparation of the polymer films by the HME technique

Polymeric film matrices were prepared by HME technology utilizing a single-screw Killion extruder (KLB-100). The formulations and the extrusion conditions are presented in Table 1. All of the powders were blended in a V-blender for 20 min to ensure content uniformity of the drug within the films. These powders were dried in the oven at 50 °C for 24 h to remove moisture that has been adsorbed by the polymers. These dried and blended powders were extruded at temperatures ranging from 140 to 156 °C. The screw speed was adjusted to 50 rpm. The extruded films were stored in foil-lined 5-mil polyethylene bags and placed in a dessicator to prevent moisture adsorption by the films.

2.2.2. Drug content determination within the HME films

Film samples were accurately weighed, dissolved in methanol, and sonicated until the films were completely dispersed. These samples were then centrifuged and the supernatant was filtered using 0.45 μ nylon filters to remove the polymer debris present within the sample. The percentage of lidocaine in the film was calculated using HPLC (Millennium™ software) equipped with Waters 2487 Dual λ absorbance detector and Waters 600 pump. A Luna C18 Phenomenex column with dimensions of 250×4.6 mm (5 μ) was used. The mobile phase used was 80% methanol and 20% 25 mM dibasic potassium phosphate and the flow rate was adjusted to 1 ml/min. The injection volume and wavelength selected were 20 μl and 220 nm, respectively. Retention time of lidocaine was approximately 6.4 min. Drug concentration in these samples was determined by measuring the peak area of the sample curve and comparing it with the peak areas of the calibration curve ($R^2 = 0.9979$). The percent theoretical of the drug in the films stored at 25 °C and 60% RH was determined after 1 week, 3 months and 6 months post extrusion.

Table 1
Formulation ingredients and processing conditions of hot-melt extruded films containing HPC:HPMC 80:20 or 100:0

Hydroxypropyl cellulose (GF), Klucel®	Matrix forming polymer
Hydroxypropyl methyl cellulose (K15M), Methocel®	Polymer—release retardant
Polycarbophil, Noveon® (AA-1)	Bioadhesive polymer
Poly(ethylene oxide), Polyox® (N-10)	Polymer—processing aid
Polyethylene glycol 3350	Plasticizer
Butylated hydroxy toluene	Antioxidant
Lidocaine	10%
Zone 1—barrel	140 °C
Zone 2—barrel	140 °C
Zone 3—barrel	143 °C
Die/melt temperatures	156 °C/150 °C
Screw speed	50 rpm

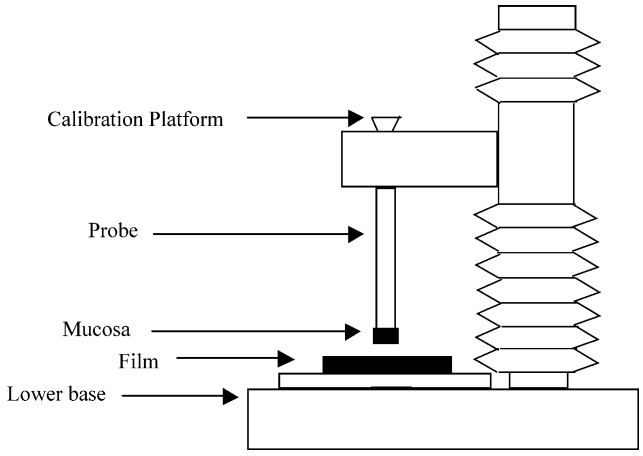

Fig. 2. Schematic diagram of the Texture Analyzer TA.XT2*i* used to perform the bioadhesion studies.

2.2.3. Bioadhesion studies

TA.XT2*i* Texture Analyzer (Scarsdale, NY)/Stable Microsystems (Godalming, Surrey, UK), (Fig. 2) equipped with Texture Expert™ software was used to study the bioadhesive properties of the extruded films. The films were wetted with artificial saliva adjusted to a pH of 6.8 ± 0.05 for approximately 1 min and placed on the lower base of the instrument. Rabbit intestinal mucosa was used as a biological substrate and was attached to the probe with cyanoacrylate adhesive. The mucosa was equilibrated with the artificial saliva before the bioadhesion testing commenced. In this method, the probe mounted with the mucosa approached the film with a speed of 1 mm/s and applied a force of 3.5 N for 30, 60 or 120 s and then withdrew with a pre-set speed of 0.5 mm/s. The Texture Expert™ software recorded the data when the probe started withdrawing from the film. The peak adhesive force and the area under force distance curve (work of adhesion) obtained from the texture profile were used to assess the bioadhesivity of the extruded films.

2.2.4. Differential scanning calorimetry studies

A Perkin-Elmer Pyris-1 differential scanning calorimeter (DSC) was used to study the crystallinity of the drug in the extruded films and the physical mixtures of the formulations. Approximately 3–4 mg of each sample of pure drug, physical mixture and extruded film were hermetically sealed in a flat bottomed aluminum pan and heated over a temperature range of 20–200 °C at a linear heating rate of 10 °C/min.

2.2.5. Wide angle X-ray diffraction studies

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

2.2.6. Dissolution studies

A Hanson SR8-plus dissolution system was used to attain the dissolution profiles of the HME films. The dissolution studies were performed according to USP 23 apparatus 5, paddle over disc method. Nine hundred milliliters of simulated saliva solution, which consisted of phosphate buffer saline solution at 37 °C, was used as the dissolution medium. Artificial saliva was prepared by dissolving 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 the phosphoric acid to pH 6.8 ± 0.05 [13]. The paddle rotation speed was adjusted to 50 rpm. Five-milliliter samples were withdrawn at predetermined time intervals and fresh medium was used to replace sample volume. The dissolution samples were centrifuged and then analyzed using a UV–Visible spectrophotometer at 220 nm.

2.2.7. Data analysis

Statistical differences in bioadhesive profiles were determined by a one way ANOVA. A $P < 0.05$ was considered statistically significant. A Student's *t*-test on GraphPad Prism® statistical software, and $f1$ and $f2$ factors of SUPAC suggested by FDA were used for determining the differences in the dissolution data [14]. The level of significance was set to $P < 0.05$ for the *t*-test and the dissolution profiles were considered similar when $f1$ was less than 10 and $f2$ was greater than 50.

3. Results and discussion

3.1. Preparation of hot-melt extruded films

Both formulations produced homogenous films with an average thickness of 0.60 mm (SD 0.01) (27.5 mil, 1 mil = 25.4 μm). The two final formulations and the processing conditions for the preparation of the sustained-release dosage forms containing lidocaine are listed in Table 1. HPC was chosen as the primary matrix-forming polymer since it is the only water-soluble cellulose derivative that is thermoplastic [15]. HPC has a softening temperature in the range of 100–150 °C, depending on its molecular weight. Therefore, the films processed for investigation were extruded at temperatures ranging between 140 and 156 °C. HPMC, a cellulosic polymer, was included in one of the formulations in an attempt to modify the drug release rate of the matrix [16]. PEG 3350 acts as a plasticizer and allows for the reduction of the extrusion temperatures, which potentially improves the stability of the active compound and improves the flexibility of the films obtained by the extrusion process. Also, plasticizers provide die lubrication, reduce melt viscosity and improve melt uniformity [17]. A low molecular weight PEO was also incorporated to facilitate the film processing. BHT was included in

the formulations to prevent the oxidative degradation of the polymers and the drug.

The polymers HPC, HPMC and polycarbophil used for extrusion of the matrix films are hygroscopic. Therefore, all of the powders were dried in an oven at 50 °C for 24 h prior to extrusion to reduce the residual moisture content. Water present in the system may cause changes in the physical and chemical properties of the final product by inducing chemical degradation, dissolution rate changes and flow and compaction property alterations of the powders [18]. Also, volatilization of the moisture from the polymer blends containing high residual moisture content during the hot-melt process results in physical deformities in the extruded film. The polymers that were chosen for the preparation of films produced in this study were hydrogels. These hydrogels swell when they come in contact with water and thus themselves act as bioadhesives without requiring a separate adhesive layer.

3.2. Drug content determination

The HPLC analysis of the extruded film samples showed only one peak (no degradation peak) corresponding to that of the standard lidocaine peak. The percentage of the drug in these samples was determined be in the range of 99% (Table 2). 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. In addition, no significant degradation of lidocaine was observed even after storage at 25 °C for 6 months. This could be attributed to the high thermal stability of lidocaine and a short residence time of the drug inside the barrel of the extruder. Its high stability is due to the steric hindrance towards attack on the amido group exhibited by the two ortho methyl groups. Lidocaine has a melting point range between 68 and 69 °C and is extremely resistant in aqueous solutions to heat, acid and alkali but is expected to decompose by hydrolysis [12]. Since the formulations were thoroughly dried in an oven at 50 °C for 24 h to minimize the moisture content, the chances of drug hydrolysis were minimized.

3.3. Bioadhesion studies

Bioadhesion studies using Texture Analyzer revealed that the hot-melt extruded HPC:HPMC films had a greater area under the curve (work of adhesion) and a higher peak adhesive force than that of the HPC films. The peak force and work of adhesion results for the HPC and HPC:HPMC films with an applied force of 3.5 N as a function of time are depicted in Fig. 3. Bioadhesion profiles demonstrated that with an increase in the time of application of the force, the peak adhesive force as well as the overall work of adhesion increased for both of the formulations. Analysis of the bioadhesion results showed that the HPMC incorporated films demonstrated a statistically higher ($P<0.05$) peak force and work of adhesion than the HPC-only films at all the contact times tested.

Table 2
Drug content post extrusion in HME films containing lidocaine

Formulation	1 week	3 month	6 month
HPC	98.77±2.3	98.22±1.6	97.51±1.9
HPC:HPMC (80:20)	99.50±2.8	99.13±2.4	98.96±3.3

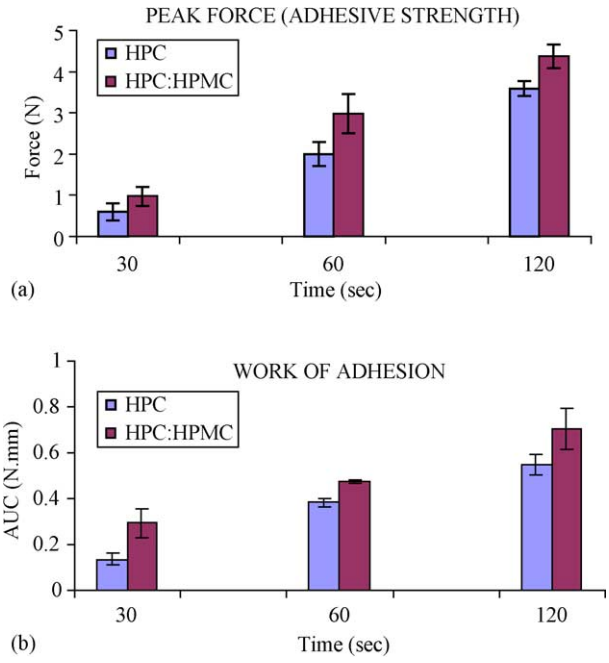

Fig. 3. (a) Peak force (adhesive strength) and (b) work of adhesion of HPC and HPC:HPMC films measured using Texture Analyzer and rabbit intestinal mucosa as a substrate ($n=5$).

According to one of the theories involved in the adhesion of the polymer to the tissue, hydration of the polymer causes the mobilization of the polymer chains and results in the interpenetration and physical entanglement of these chains with the mucin complex [13]. HPC and HPMC contain hydroxyl groups, which are most likely responsible for the bioadhesion. The interaction of these hydrophilic polymers with mucin may also be as a result of hydrogen bonding. However, the HPMC-containing films exhibited higher detachment force and work of adhesion than the films containing only HPC. This is explained by the fact that HPMC is relatively more hydrophilic than HPC, hydrates faster, and interacts with mucin chains more quickly due to increase in chain mobility of the polymer. These findings are consistent with those of other investigations [19]. The increase in adhesiveness of both the formulations with the increase in contact time is likely due to increased interpenetration and entanglement of the polymer and mucin chains, which results in formation of a greater number of secondary covalent bonds between the entangled chains. These findings are consistent with the findings of Wong et al. [20].

3.4. Differential scanning calorimetry studies

Differential scanning calorimetry (DSC) studies of the pure drug produced an endotherm representing its melting point at 69 °C indicating that lidocaine is a crystalline drug (Fig. 4). Both PEG 3350 and PEO are semi-crystalline polymers due to their linear and regular structures melting in the range of 60–70 °C. In the solid state, these polymers consist of an intimate mixture of ordered crystals and randomly structured amorphous regions. In the physical mixtures—lidocaine, HPC, HPMC, PEG 3350, PEO and other additives produced a single melting peak in the range of 65 °C (Fig. 4). In addition, no peak representing lidocaine was observed. This may be explained by the fact that lidocaine is being solubilized in the melted PEO and PEG 3350. This hypothesis was confirmed by the DSC

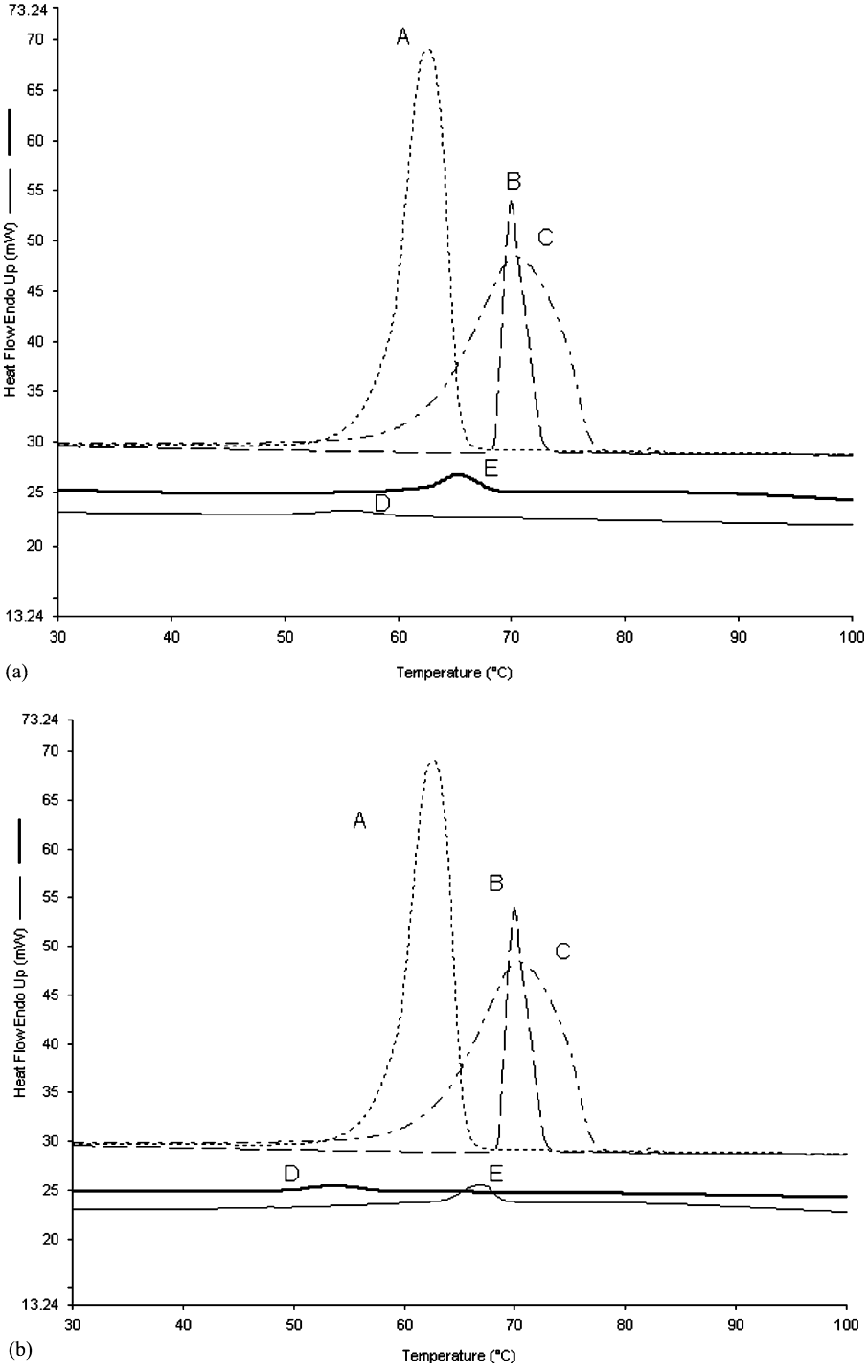

Fig. 4. Differential scanning calorimetry profiles of different components in hot-melt extruded films: (a) HPC film; and (b) HPC:HPMC film. (A) PEG3350; (B) Lidocaine; (C) PEO; (D) HME film; (E) Physical mixture.

thermograms of the physical mixture of PEO and lidocaine in addition to that of the physical mixture of PEG 3350 and lidocaine. After the HME process, the matrix films exhibited an endotherm corresponding to PEO and PEG 3350 at approximately 56 °C. A 7–9 °C shift to the left was observed in the melting endotherm (Fig. 4) and also there was a decrease in the intensity of the PEO–PEG peak when compared to the intensity of the peaks in the respective physical mixtures. This may be due to a decrease in crystallinity of the PEO and/or PEG after extrusion. Very few polymers will crystallize completely from melts where the molecules are initially highly entangled [21]. There was no peak of lidocaine observed in the hot-melt extruded films. Thus, lidocaine may be solubilized in the melted PEO or PEG 3350 during the heating cycle of the DSC studies or the drug may indeed be present in its amorphous state in the polymer matrix. X-ray diffraction studies were performed to further investigate the solid state of lidocaine within the hot-melt extruded films.

3.5. Wide angle X-ray diffraction

The results of the DSC studies are supported by the wide-angle X-ray diffraction (XRD) patterns and observations. X-Ray diffraction patterns of the lidocaine, the physical mix and the extruded HPC and HPC:HPMC (80:20) films are illustrated in Fig. 5a and b, respectively. The XRD-profile of the lidocaine illustrates its crystallinity. The highest crystalline peaks of lidocaine are observed at approximately 2θ angles, 10 and 12.5. The crystallinity of PEO and PEG 3350 is also shown in their respective XRD profiles. The XRD profile of the physical mixture also demonstrated the crystalline peaks, however the intensity was lessened. This is due to the presence of relatively low concentrations of crystalline compounds in the physical mixture. The extruded films showed one broader peak, which is characteristic of amorphous compounds. There was no crystalline pattern corresponding to that of lidocaine observed. These data, coupled with the DSC study results, indicate that lidocaine is in the solid-solution state within the polymer matrix.

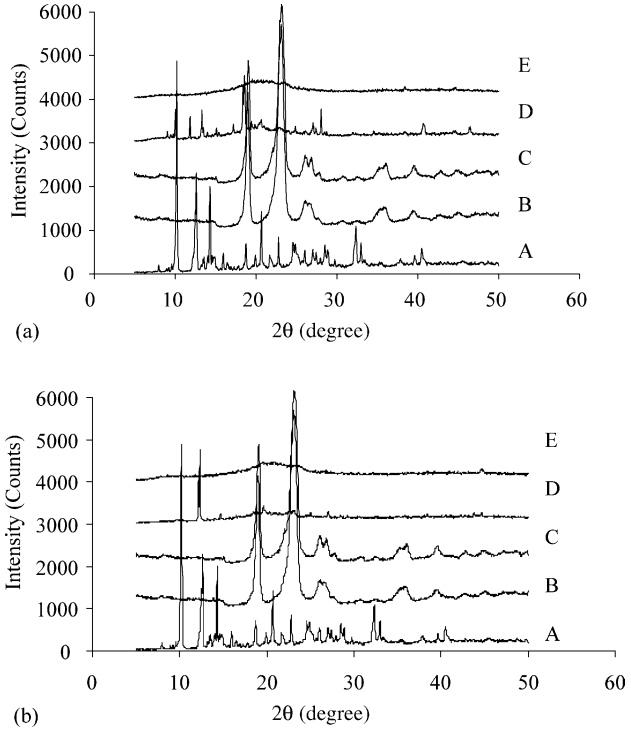

Fig. 5. Wide angle diffraction patterns of different components in hot-melt extruded films: (a) HPC films; and (b) HPC:HPMC films. (A) Lidocaine; (B) PEG3350; (C) PEO; (D) Physical mixture; (E) HME Film.

3.6. Dissolution studies

A statistically significant difference ($P < 0.05$) in percentage release of the drug from the HPC film and the HPC:HPMC (80:20) film was observed (Fig. 6). However, $f1$ (difference factor) value of 9.2 and $f2$ (similarity factor) value of 57 suggest that the difference may not be significant. After 10 h the percent drug released from the HPC films and the HPC:HPMC films was 85.2 ± 2.6 and 75.8 ± 1.5, respectively. The presence of 1/5 proportion of HPMC in the HPC:HPMC formulation retarded the release rate of the drug from the HPC:HPMC film compared to that of the film containing only HPC (after 3 h). This is explained by the fact that HPMC has a higher swelling ability than HPC. The thickness of the swollen gel layer in HPMC containing films would be higher than that of only HPC films resulting in an increase in the diffusion pathway for the drug molecules for the more swellable polymer (HPMC) than that for the relatively less swellable or non-swellable polymer (HPC). Thus, the increased diffusion pathway slowed the lidocaine release from the HPMC incorporated matrix.

Three main models describe the drug release kinetics from the polymer matrix systems: the zero-order model, the first-order model, and the Higuchi square root law model [22,23]. The zero-order kinetics was not applicable for the developed formulations, as the amount released vs. time

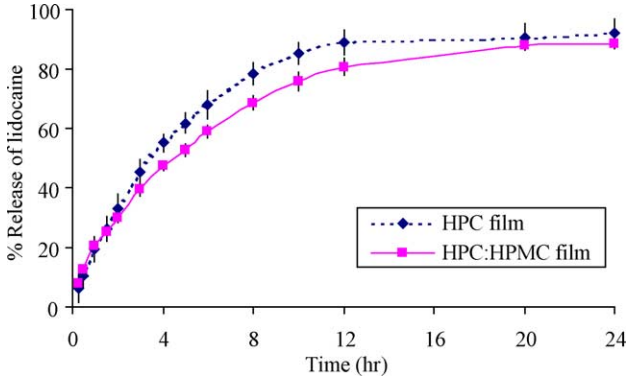

Fig. 6. In-vitro release profile of lidocaine from HPC and HPC:HPMC polymer matrices in artificial saliva at pH 6.8 ± 0.05 (USPXXIII apparatus 5, paddle over disk method; RPM = 50, $n = 3$).

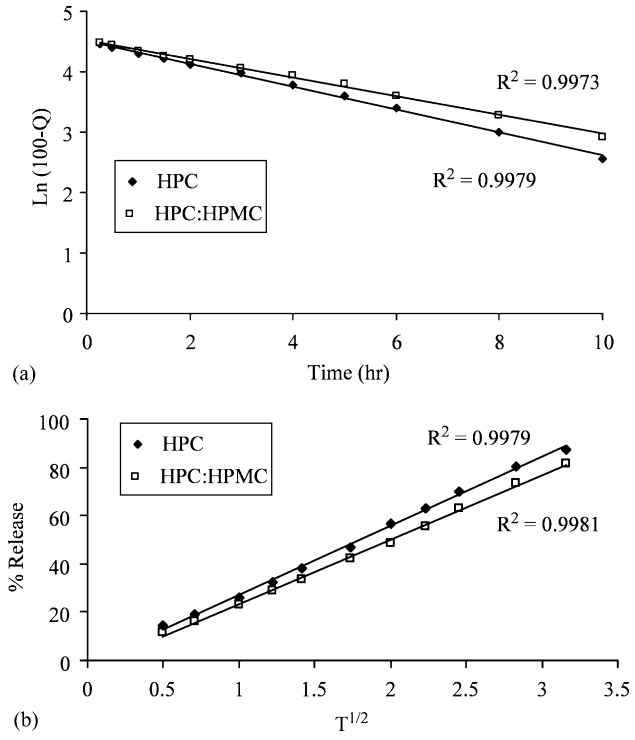

Fig. 7. Release of lidocaine from the hot-melt extruded formulations: (a) first-order release kinetics; and (b) Higuchi release kinetics, in artificial saliva at pH 6.8 (±0.05) after 10 h (USPXXIII apparatus 5, paddle over disk method; RPM = 50, $n = 3$).

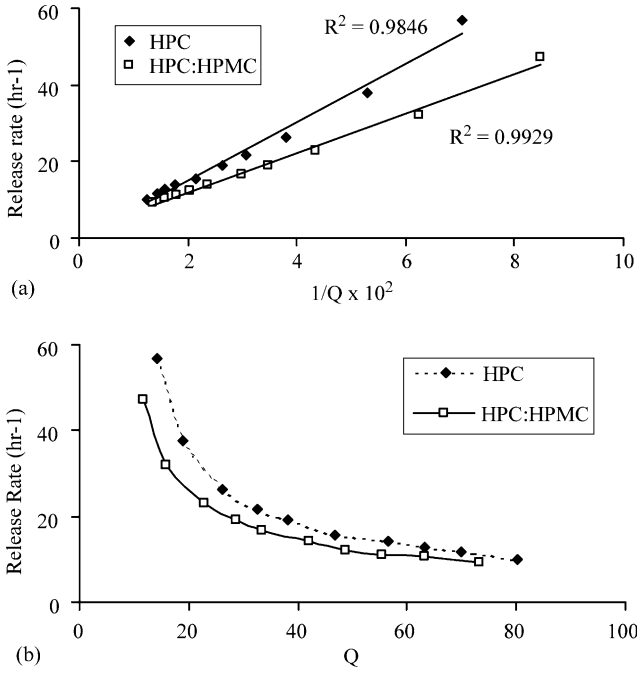

Fig. 8. Release of lidocaine from the hot-melt extruded formulations according to the differential rate treatment: (a) Higuchi release kinetics; and (b) first-order kinetics, in artificial saliva at pH 6.8 (±0.05) (USPXXIII apparatus 5, paddle over disk method; RPM = 50, $n = 3$).

when plotted with the obtained dissolution data were non-linear. The results of kinetic release profiles can be modeled using both first-order and Higuchi release kinetics (Fig. 7a and b, respectively). Therefore, the actual mechanism of the drug release was ascertained by applying the differential rate treatment model proposed by Schwartz et al. According to this model, for the square root law, the release rate is inversely proportional to the total amount of the drug released (Q), and for the first-order model, the release rate is proportional to Q [23,24].

Upon application of the differential rate model, it was observed that the mechanism of drug release in both of the formulations followed Higuchi release kinetics with release rate linear to $1/Q$ (Fig. 8a) and consequently did not obey first-order release kinetics (Fig. 8b). This is also supported by the fact that high molecular weight HPC and HPMC were utilized in the development of these polymer matrices, and as discussed previously, such type of polymer matrices exhibit diffusion as the dominant release mechanism with no distinct erosion of the polymer matrix [22].

Drug molecules are released from hydrocolloid matrices by the following three mechanisms [25]: (a) water induced relaxation of the polymer matrix, (b) erosion of the polymer gel layer surrounding the matrix dosage form, and (c) diffusion of drug molecules through the swollen gel layer. The relative significance of these three mechanisms depends on the properties of the drugs and polymers [26].

Drug release mechanism can generally be expressed by the following equation:

$$Q = k \times t^n \quad (1)$$

In this equation, n is the diffusional exponent for the drug release, K is the dissolution rate constant and Q is the cumulative amount of drug release in a certain time interval (t).

The release from the hydrogels and the more viscous pseudo-hydrogels follows square root of time law kinetics (Higuchi), and the mechanism involved is Fickian diffusion ($n = 0.5$). The release from the low molecular weight and less viscous polymers (shorter chain length) occurs by the dissolution of the polymer and follows zero order kinetics and the mechanism involved is erosion or relaxation controlled ($n = 1$). However, if the release from the polymer system involves both diffusion and erosion, the mechanism involved is non-Fickian diffusion (anomalous transport), and n is between 0.5 and 1 [27]. The dissolution data for both of the film formulations when fitted into Eq. (1) provided n values of 0.54 and 0.51 indicating Fickian diffusion. The cellulose ether derivatives are classified as pseudo-hydrogels as they swell infinitely by absorbing water and concomitantly dissolve from the surface of the system. The drug release from the pseudo-hydrogels systems occurs by diffusion of the molecules across the polymer matrix and also by the erosion of the polymer from the surface. However, the viscosity of the gel determines the mechanism of the drug release from these pseudo-hydrogels. In the current research, the polymer systems utilized

were highly viscous (i.e. high molecular weight), which do not erode for all practical purposes and thus the drug release corresponds to that of the conventional (crosslinked) hydrogels, which are insoluble in water. The drug release mechanism in these types of systems is predominantly diffusion.

4. Conclusions

HME was used successfully to extrude HPC and a combination of HPC:HPMC into thin uniform films with no significant drug degradation. DSC and XRD studies demonstrated that lidocaine is in solid solution within the extruded films. Incorporation of HPMC into the HPC matrix resulted in retardation of drug release. In addition, there was also a significant increase in the bioadhesive properties of the HME films containing the combination of HPC:HPMC. Films exhibited an initial burst effect that would be advantageous for rapid onset of action, followed by a sustained release of the drug for prolonged analgesia effects. The development of these films would be relevant as potential dosage forms for dental procedures and other topical applications.

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