Original Article

Preparation and Evaluation of Matrix Containing Lidocaine and Prilocaine for Using in Transdermal Films

Abstract

Background: Lidocaine and prilocaine are amide-type local anesthetic agents that are expectedly adequate to create a rapid pharmacological effect immediately after using transdermal delivery system. **Objective:** The aim of this study was to investigate the effect of hydrophilic and hydrophobic materials on drug release from different polymeric films containing lidocaine and prilocaine. **Materials and Methods:** Several films containing lidocaine and prilocaine were prepared using ethyl cellulose (EC) or hydroxypropyl methylcellulose (HPMC) polymers. The effect of propylene glycol (PG) and polyethylene glycol 4000 (as permeation enhancers) and triacetin or dibutyl phthalate (DBP) as plasticizer on tensile strength, moisture absorption, content uniformity, and drug release properties were investigated. *In vitro* permeations studies were carried out using Fransz diffusion cells and samples were analyzed by high-performance liquid chromatography for each drug. **Results:** DBP unlike triacetin had a dramatic effect on drug release rate and moisture absorption in HPMC films. The presence of PG on the formulations containing EC caused an increase in the moisture absorption and drug release and shifted the mechanism of release from Fickian diffusion to Case-II transport. PEG4000 was not a significant effect on these variables in the HPMC films. **Conclusion:** Hydrophilic additives like PG when used in an water-insoluble membrane act as a channeling agent and increase the rate of drug release because in dissolution medium they dissolve out of the film and leave channels from which drug can be released more rapidly.

Keywords: *Ethyl cellulose transdermal film, hydroxypropyl methylcellulose, lidocaine, prilocaine*

Maryam Kouchak[1, 2], Saeed Rezaee[3], Nasrin Moshabeh[1], Somayeh Handali[4]

[1]Nanotechnology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, [2]Department of Pharmaceutics, Faculty of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran, [3]Department of Pharmaceutics, School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran, [4]Medical Biomaterial Research Centre (MBRC), Tehran University of Medical Sciences, Tehran, Iran

Introduction

Transdermal drug delivery (TDD) offers a noninvasive approach to avoid the first-pass effect and can sustain plasma levels within the therapeutic window for extended periods[1]. TDS formulations are usually ointments, cream semisolid emulsions, or films.[2] Transdermal films are usually well accepted due to their ease of applying, advantages in keeping with the treatment schedule, and less interference with daily life. They represent a valuable alternative when oral administration is difficult. For example, when a patient is unable to swallow or may result in erratic absorption due to nausea and vomiting. Moreover, they are noninvasive drug delivery systems intended for application on skin to achieve systemic effects.[1,3-6] Unlike semisolids, patch does not need occlusive dressing. The choice of the most appropriate polymeric composition is essential for patch characteristics in terms of mechanical properties and drug release kinetics.[2] Lidocaine and prilocaine are amide-type local anesthetic agents that are expected to be adequate to create a rapid pharmacological effect immediately after topical administration.[7,8] Plasma protein binding lidocaine and prilocaine are about 66%–70% and 55%, respectively.[9,10] After oral administration, lidocaine undergoes extensive first-pass hepatic metabolism with a bioavailability of about 35% and has short half-life (1–2 h).[9,10] Moreover, half-life of prilocaine is short (0.76–1.35 h).[11] Eutectic mixture of lidocaine and prilocaine in a weight ratio of 1:1 has a melting point below the room temperature and in the mixture, two local anesthetics change from crystal to liquid form. EMLA cream (Eutectic Mixture of Local Anesthetics) is a 5% emulsion that contains eutectic mixture of lidocaine and prilocaine (2.5% each of them).[1] This eutectic mixture increases systemic absorption of the two anesthetics in comparison to applying them separately. This system is used for preparation of EMLA anesthetic single disk too. The disk contains an absorbent cellulose disk containing 1-g EMLA emulsion. The depth and duration time of dermal anesthetic effect of EMLA on intact skin depends on the time spent for topical administration. To

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Address for correspondence:
Dr. Somayeh Handali,
Medical Biomaterial Research Centre (MBRC), Tehran University of Medical Sciences, Tehran, Iran.
E-mail: handali_s81@yahoo.com

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obtain an adequate anesthesia for clinical procedures such as intravenous catheter insertion and intravenous cannulation, EMLA disk as a cover bandage should be applied for at least an hour and should be used in the split skin graft for at least 2 h. Satisfactory anesthesia is achieved 1 h after the application and reaches maximum effect at 2–3 h.[12]

The aim of this study was to provide a polymer matrix containing a eutectic mixture of lidocaine and prilocaine in order to apply in the skin films and study its mechanical properties and profile release of drug from them.

Materials and Methods

Hydroxypropyl methylcellulose (HPMC, 50 cPs), ethyl cellulose (EC, 100 cPs), polyethylene glycol 4000 (PEG 4000), DBP, and triacetin were purchased from Merck (Germany). Lidocaine and prilocaine were obtained from Shahid Rezakhani Co. (Tehran, Iran) and Orgamol (Evionnaz, Switzerland), respectively. Propylene glycol (PG) was purchased from Sepidaj Co. (Tehran, Iran). All other materials used in this study were of analytical reagent grade.

Preparation of Hydroxypropyl Methylcellulose Matrixes

The films were prepared using casting/solvent evaporation method. HPMC was dispersed in hot distilled water under stirring to form a homogeneous mixture. The prepared gel was placed in refrigerator to remove air bubbles. Polymer solution, PG, and DBP or triacetin as plasticizers were mixed. Lidocaine, prilocaine, and PEG 4000 were dissolved in ethanol (96% v/v) and added to the mixture. The prepared solution was poured in a Petri dish and allowed to dry at 40–45°C for 24 h. The compositions of different formulations are shown in Table 1.

Preparation of Ethyl Cellulose Matrixes

Drugs, EC, PG, and triacetin were dissolved in a mixture of methanol and dichloromethane (1:1 v/v). The films were prepared using casting and solvent evaporation as mentioned above. Compositions of different formulations of films are shown in Table 2.

Characterization of the Films

Physical appearance

Each formulation was visually inspected for film formation capability, ease of separation from the mold, transparency, and presence of bubble.

Moisture absorption

The films were kept in an oven at 50°C to reach a constant weight. The pieces of each film (3.14 cm^2) were cut, weighed accurately, and held in a desiccator containing saturated potassium bromide (84% RH) for a week. The samples were taken out and reweighed. The moisture absorption was calculated as the difference between final and initial weight with respect to initial surface area.

Tensile strength

The tensile strength properties of the films were evaluated using a texture analyzer (WDW, Japan). The specimens (3 × 5 cm^2) were positioned between two mounting clamps and were pulled by the top clamp at a rate of 50 cm/h. The tensile strength at break was calculated.[13,14]

Drug content analysis

To determine content uniformity of HPMC films, samples (1 cm × 1 cm) were precisely cut from three random sites in each film and placed into dialysis bag and hang in 20-mL distilled water for 24 h. The bag was removed and the concentration of drugs was measured by high-performance liquid chromatography (HPLC) (Waters, USA). To determine content uniformity of EC films, samples were immersed in 4 mL of methanol and the volume was made up to 100 mL with distilled water. The solution was filtered and the drug content was measured by HPLC.

Chromatographic separation was performed using a C18 column (25 cm, 4.6 mm) maintained at 25°C, using mobile phase phosphate buffer (pH 8) and methanol (70:30 v/v) and

Table 1: Compositions of different formulations of films prepared using HPMC

Formulation	HPMC 10% (g)	PEG (g)	Triacetin (g)	DBP (g)	PG (g)	Ethanol96% v/v (mL)	Lidocaine (g)	Prilocaine (g)
HP_1	10	–	0.5	–	2	10	0.16	0.16
HP_2	9	0.1	0.5	–	2	10	0.16	0.16
HP3	7	0.3	0.5	–	2	10	0.16	0.16
HP_4	5	0.5	0.5	–	2	10	0.16	0.16
HP_5	10	–	–	0.5	2	10	0.16	0.16

Table 2: Compositions of different formulations of the films prepared using EC

Formulation	EC (g)	Triacetin (g)	PG (g)	Dichloromethane (mL)	Methanol (mL)	Lidocaine (g)	Prilocaine (g)
E_1	1.5	0.5	–	5	20	0.16	0.16
E_2	1.5	0.5	2	5	18	0.16	0.16
E_3	1.5	0.5	4	5	16	0.16	0.16

flow rate of 0.8 mL/min. The injection volume was 50 µL and the UV detector was set to 220 nm.

In vitro release study

Release of lidocaine and prilocaine from HPMC and EC films in PBS (pH 7.4) as the receiver medium was evaluated by Jacketed Franz cells using dialysis membrane as a diffusion barrier at 37°C. The concentration of released drugs was assayed using HPLC. Also, the process was performed for HP_{11} film without lidocaine and HP_{11} film without prilocaine. Dissolution efficiency (DE) was determined as follows:

$$DE = \frac{\int_{t=0}^{t=T} y \times dt}{y_{100} \times t} \times 100 \quad (1)$$

where y is the percentage of dissolved product and DE is the area under the dissolution curve between time points $t = 0$ and $t = T$ expressed as a percentage of the curve at maximum dissolution, y_{100}, over the same time period (T). Moreover, to study the release kinetics drugs from films, the Korsmeyer–Peppas semiempirical was applied and the release data were fitted as follows[15,16]:

$$M_{t}/M_{\infty} = K_{kp} t^{n} \quad (2)$$

where $M_t/M\infty$ is the fractional drug released at time t, K_{kp} is a constant incorporating characteristics of the drug and the macromolecular network system, and n is diffusional release exponent which is indicative of the transport mechanism.[16,17]

Statistical Analysis

All data were expressed as means with regard to ± standard deviation. The statistical analysis was performed using paired *t*-test, analysis of variance (ANOVA), and Tukey's test to assess the significance of the differences among the various formulations.

Results and Discussion

All of films showed excellent properties in terms of film formation, ease of separation, appearance uniformity, and lack of bubbles. HP [Figure 1] and E_1 [Figure 2A] films showed transparency, whereas E_2 and E_3 films were turbid [Figure 2B and 2C].

Physical properties evaluation

Physical properties of the films are shown in Table 3. According to the results, all of the formulations (except formulation E_1) could absorb the moisture. The values for all formulations were between 31×10^{-4} and 53×10^{-4} g/cm^2. Unlike HPMC, the EC is a hydrophobic polymer and does not have affinity with water absorb.[18,19] Sanpa *et al*.[20] reported that the moisture absorption of film containing HPMC was more than the film containing EC. ANOVA statistical test is used to compare water absorption capacity of the EC films. These films presented significantly

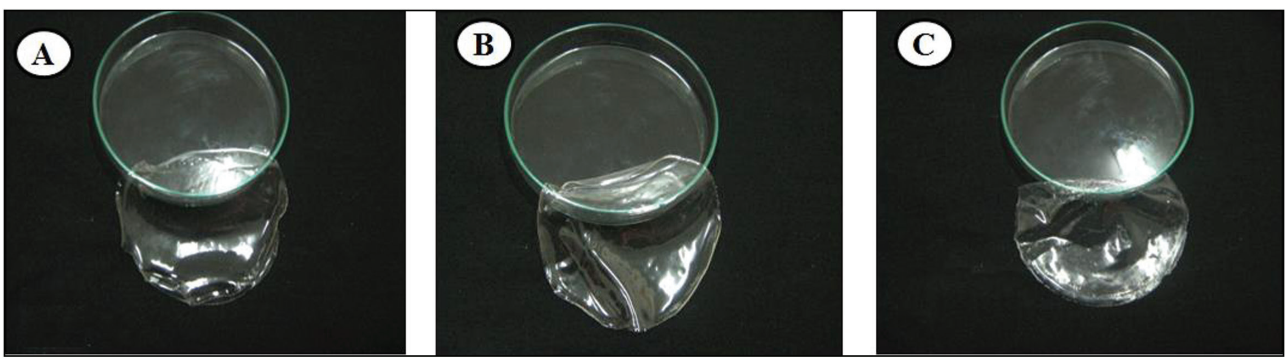

Figure 1: Appearance of an HPMC film: (A) HP_2, (B) HP_4, and (C) HP_5

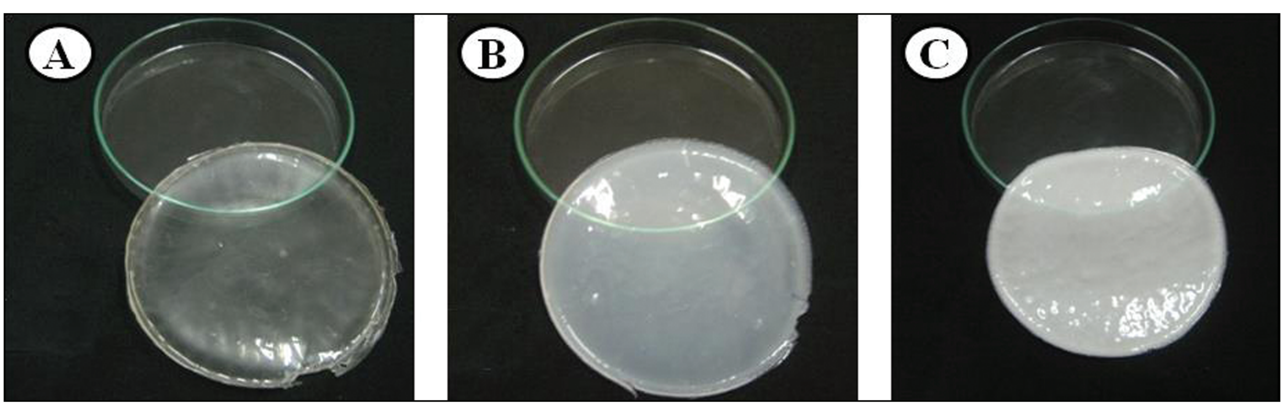

Figure 2: Appearance of the EC films: (A) E_1, (B) E_2, and (C) E_3

different capacity ($P < 0.05$). Formulation E_1 was not able to absorb moisture, but the presence of PG as a hydrophilic plasticizer[21] in other EC films gives them hydrophilic property. In the water environment, PG dissolves and creates water-filled channels that accelerate the penetration of water into the polymer. Moisture absorption values of the HPMC films were compared with Tukey's test. No statistically difference ($P > 0.05$) was found between the triacetin-containing films (HP_1–HP_4), but HP_5 film containing DBP (a hydrophobic plasticizer) significantly absorbed less moisture than the others ($P < 0.05$). A highly water-soluble compound such as triacetin in an HPMC matrix generates an additional osmotic gradient, thereby resulting in a faster rate of polymer swelling.[18]

As shown in Table 3, $HP_{1,}$ $HP_{2,}$ HP_3, and HP_4 formulations had similar tensile strength. It was found that the tensile strength of HP_5 which had a hydrophobic plasticizer (DBP) was more than other formulations. During gel preparation the hydrophilic plasticizer (triacetin) in $HP_{1,}$ HP_2, HP_3, and HP_4 competes with HPMC molecules to bind to active site which joins polymer molecules to each other. Reducing the number of polymer–polymer contacts leads to a decrease in the rigidity of the three-dimensional structure formed on drying and a decrease in mechanical strength of the films.[22] The results indicated that adding PEG4000 to HP_2, HP_3, and HP_4 formulations had no effect on their tensile strength.

E_1 formulation showed relatively good tensile strength but its texture is brittle. The mechanical properties play an important role in the patch final performances as they should possess an adequate flexibility to avoid breaking.[2] The addition of PG in E_2 and E_3 formulations caused to produce more flexible films. In the presence of a solvent, the mobility of the polymer chains is enhanced, resulting in a gradual transformation of a glassy matrix to a rubbery state.[18] E_2 film had high tensile strength, but E_3 film showed lower tensile strength. The later film has a high ratio of PG because of liquid nature.

Drug content analysis

According to the results of Table 4, distribution of both drugs in various parts of the films was uniform.

Table 3: Physical properties of the films (mean ± standard deviation, $n = 3$)

Formulation	Moisture absorption (g/cm²)	Tensile strength (Mpa)
HP_1	10^{-4} ± 0.002×53	0.054
HP_2	10^{-4} ± 0.0016×42	0.056
HP_3	10^{-4} ± 0.0018×42	0.055
HP_4	10^{-4} ± 0.0014×42	0.054
HP_5	10^{-4} ± 0.00*×31	1*
E_1	0.00 ± 0.00**	1.103
E_2	10^{-4} ± 0.00×31	2.059
E_3	10^{-4} ± 0.0017×53	0.676

*Significant difference with other HPMC films

** Significant difference with other EC films

In vitro drug release

Table 5 shows the DE values for the drugs released from the films and their main parameters (K_{kp} and n) for Korsmeyer–Peppas equation. The DE values of the HPMC films were compared with Tukey's test. The results indicated that substitution of a part of HPMC by PEG 4000 in the structure of the films had no effect on the release rate of drugs from HP_1–HP_4 films [Figure 3]. These two polymers showed the same behavior with regard to moisture absorption, mechanical strength, and drug release. Concerning the results of Tukey's test, DE values for the film containing DBP were less than those for the films containing triacetin ($P < 0.05$). Hydrophobic nature of DBP increased the diffusion barrier property of HPMC films and reduced moisture absorption, dissolution rate, and drug release.

The *in vitro* release data were fitted into Korsmeyer–Peppas equation to determine the mechanism of drug release from the films. Peppas found that equation 2 can be used to express drug release from swellable polymers system (e.g., systems based on HPMC, poly (vinyl alcohol), etc.) as long as these systems swell gently in contact with the penetrant. In the Korsmeyer–Peppas model, the exponent n characterizes the transport mechanism of drugs as described in Table 6. For Fickian release from a thin film, n is equal to 0.50. The second limiting case, Case- II transport, is defined by n equal to 1.00. For these two limiting cases, the constant K_{kp} has physical significance, that is, $K_{kp} = 4(D/\pi l^2)^{1/2}$ for Fickian diffusion, and $K_{kp} = 2k_0/C_0 l$ for Case-II transport. Here, D is the drug diffusion coefficient, l is the initial film thickness, k_0 is defined as the Case-II relaxation constant, and C_0 is a constant drug concentration on the surfaces of the thin film during release process. Many release processes from swellable polymers fall between these two limiting cases. Anomalous release behavior is intermediate between diffusion-controlled and relaxation-controlled (and/or erosion-controlled) release and defined by values of n between 0.50 and 1.[17] For lidocaine and prilocaine release from HP_1–HP_4 films, n values were equal or near 1 so the mechanism of drug release follows Case-II transport. The relaxation and swelling characteristics of HPMC and PEG 4000 matrices influence drug release kinetics so as for a time-independent pattern to be created. HP_5 films show exponential value (n) between 0.5 and 1, indicating a coupling of diffusion and relaxation mechanisms, so-called anomalous diffusion.[17]

Table 4: Content uniformity of the films (mean ± standard deviation, $n = 3$)

Formulation	Prilocaine (%)	Lidocaine (%)
HP_1	100.73 ± 1.88	103.69 ± 1.24
HP_2	98.31 ± 0.79	102.601 ± 1.96
HP_3	103.73 ± 2.40	104.08 ± 1.19
HP_4	103.24 ± 1.17	104.02 ± 1.75
HP_5	107.13 ± 2.66	103.44 ± 1.63
E_1	102.61 ± 1.91	104.14 ± 1.63
E_2	102.87 ± 0.069	100.70 ± 2.73
E_3	100.62 ± 1.24	99.80 ± 1.44

Table 5: DE_{3h} and kinetic parameters of drug release from the formulations (mean ± standard deviation)

Formulation no.	Prilocaine				Lidocaine			
	DE_{3h} %	R^2	K_{kp}	n	DE_{3h} %	R^2	K_{kp}	n
HP_1	43.50 ± 2.60	0.99	2.23	0.80	28.16 ± 2.81	0.98	2.40	0.87
HP_1*	40.16 ± 2.26	0.99	2.42	0.88	–	–	–	–
HP_1**	–	–	–	–	29.23 ± 1.22	0.99	2.35	0.85
HP_2	34.20 ± 1.53	0.97	2.84	1.04	23.99 ± 0.086	0.98	2.75	1.01
HP_3	35.33 ± 2.85	0.96	2.57	0.94	24.10 ± 4.12	0.97	2.53	0.93
HP_4	30.59 ± 1.069	0.99	2.46	0.90	25.36 ± 4.26	0.97	2.88	1.05
HP_5	16.21 ± 3.04	0.98	2.14	0.76	10.69 ± 1.61	0.99	1.87	0.62
E_1	19.38 ± 3.30	0.98	1.80	0.58	13.60 ± 2.68	0.98	1.66	0.51
E_2	17.65 ± 0.99	0.92	2.91	1.07	12.28 ± 0.74	0.95	2.27	0.82
E_3	22.65 ± 1.49	0.99	3.00	1.09	16.93 ± 0.48	0.97	2.74	1.01

*Lidocaine free HP_1 film
**Prilocaine free HP_1 film

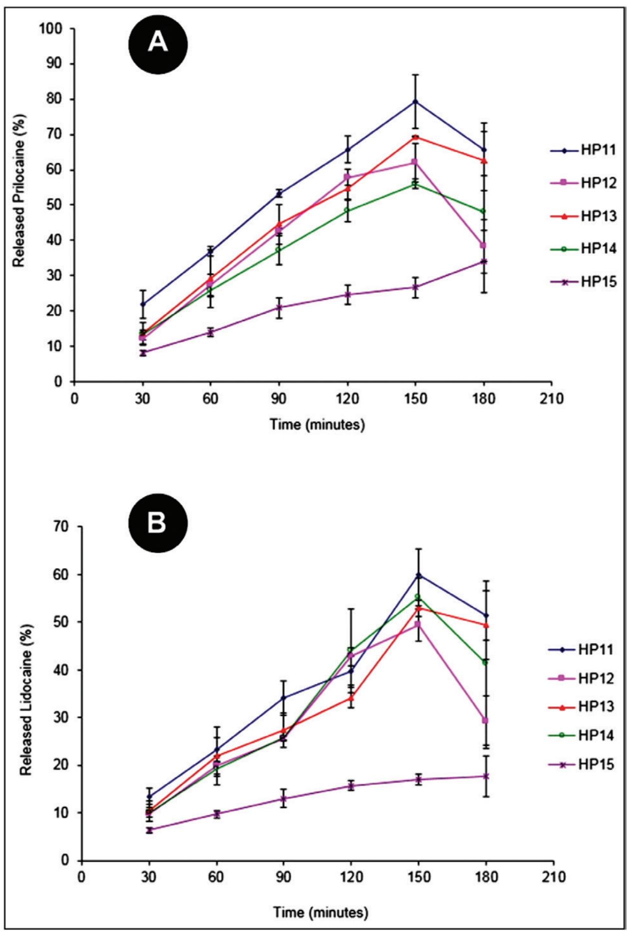

Figure 3: Release profiles of (A) prilocaine and (B) lidocaine from HPMC films

The n values for E_1 (0.511 and 0.588 for lidocaine and prilocaine, respectively) appear to indicate that diffusion is the dominant mechanism of drug release from this formulation. In contrast, the *in vitro* release profiles of E_2 and E_3 with comparatively higher exponential (n) values (close to 1) can be best expressed by zero-order kinetics. These formulations contained PG which dissolves in the water environment, resulting in matrix erosion and creates a time-independent

Table 6: Drug release mechanisms and diffusion exponent for polymeric controlled delivery systems of thin film[23,24]

Diffusional release exponent (n)	Overall solute diffusion mechanism
0.5	Fickian diffusion
$0.5 < n < 1$	Anomalous (non-Fickian) diffusion
1	Case-II transport (zero-order or time-independent release)
$n > 1$	Super Case-II transport

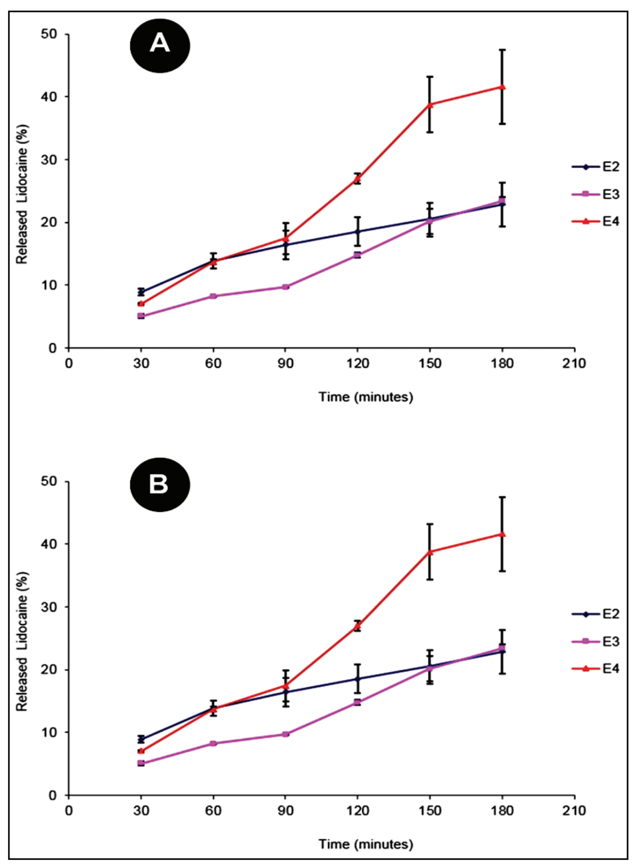

Figure 4: Release profiles of (A) prilocaine and (B) lidocaine from EC films

drug release. On the contrary, in the presence of PG as a pore agent, drug diffusion is accelerated and for poorly water-soluble drugs, dissolution will be the rate-determining step of drug release. If a saturated drug solution is maintained in matrix for a long time, the system poses a zero-order release.

As shown in Figure 4, drug release from EC films (with and without PG) is accompanied by some delay. These lag times are related to required time to dissolve water-soluble materials of matrix (triacetin and PG) in the water environment to produce channels that accelerate the diffusion of the drugs out of the films. In comparison with other formulations, HP_1 and HP_5 showed the highest and the lowest rate of drug release, respectively. To study the effect of eutectic mixture of lidocaine and prilocaine on pattern of release, two formulations similar to HP_1 containing just prilocaine or lidocaine were prepared and their drug release were evaluated [Table 5 and Figure 5]. Paired *t*-test was used to compare drug release profiles of HP_1 formulation films with lidocaine free or prilocaine free corresponding films. Both paired groups showed the same release behavior ($P > 0.05$). No significant differences were found between DE and kinetics mechanism of prilocaine and lidocaine released from HP_1 and the same formulations containing only one drug ($P > 0.05$).

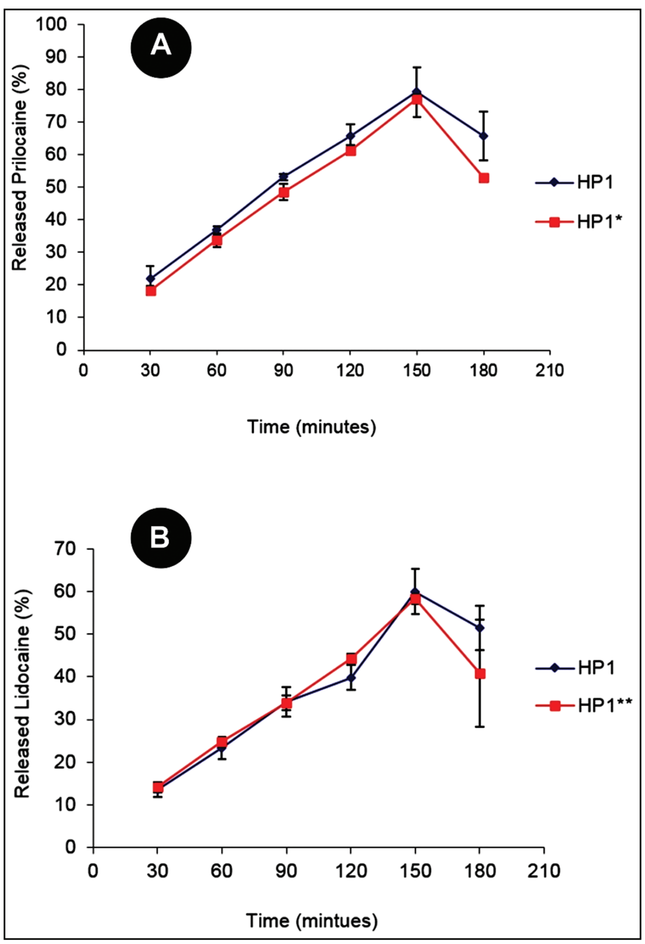

Figure 5: Release profiles of (A) prilocaine from HP_1 and lidocaine free HP_1* and (B) lidocaine from HP_1 and prilocaine

Conclusion

The presence of PG on the EC films caused an enhancement of the moisture absorption and the rate of drug release and shifted the mechanism of release from Fickian diffusion to Case-II transport. However, existence of PEG 4000 as a hydrophilic polymer in the structure of the HPMC films had no effect on these parameters. DBP could increase tensile strength of HPMC films, although it reduced the moisture absorption and their drug release rate. According to the results of the study, eutectic mixture could not increase the release rate of drugs. Thus, further studies are needed in order to investigate the effect of this mixture on the absorption rate of two anesthetics.

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Conflicts of interest

There are no conflicts of interest.

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