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Design and Characterization of Transdermal films containing Ketorolac tromethamine

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1. Abstract: The objective of this work was to develop suitable film formulations of ketorolac tromethamine (KT) for transdermal use and to investigate the effect of film composition and permeation enhancers on the in-vitro release and skin permeation of the drug. Polyvinyl alcohol (PVA), sodium carboxymethylcellulose (NaCMC), and chitosan were used as film-forming polymers. The adhesive hydrophilic polymers plastoid® E35L (PL E35) and polyvinyl pyrrolidone (PVP) were added to improve bioadhesion. The permeation enhancers used were oleyl alcohol (OA), sodium glycocholate (NaGC) and propylene glycol (PG). Formulated films were characterized by measuring their mean thickness, mass, drug content, folding endurance and bioadhesion. In-vitro release was studied using the USP XXIII rotating paddle method and in-vitro permeation across hairless rat skin was studied using an in-vitro diffusion cell. Addition of PVP enhanced the drug release and permeation especially in case of chitosan, while Plastoid® E35L improved permeation only. Skin permeation of the drug was greatly improved by the addition of permeation enhancers, the rank of their effectiveness was: sodium glycocholate (Na GC) > oleyl alcohol (OA) > propylene glycol (PG). The results obtained showed that these polymeric films can be a promising therapeutic system for the transdermal delivery of ketorolac.

Key words: ketorolac tromethamine, polymeric films, transdermal delivery, penetration enhancers, adhesive.

2. Introduction:

Ketorolac tromethamine (KT) is a nonsteroidal agent with potent analgesic and moderate anti-inflammatory activity by inhibiting prostaglandin synthesis [1,2]. Unlike narcotic analgesics, ketorolac does not alter gastric motility or hemodynamic variables or adversely affect respiration, nor it is associated with adverse central nervous system effects, abuse, or addiction potential; therefore, ketorolac is a relatively more favorable therapeutic agent for the management of moderate to severe pain [3]. Ketorolac (as tromethamine salt) is administered intramuscularly and orally in divided multiple doses for short-term management of post operative pain (30 mg q. i. d. by IM injection and 10 mg q. i. d. as oral tablets). This frequent dosing, which results in unacceptable patient compliance, is required due to the short half-life of the drug (4-6 h) [2]. Although oral bioavailability of KT was reported to be 90% with a very low first-pass metabolism, its short biological half-life and many adverse effects, such as upper abdominal pain and gastrointestinal ulceration, restrict its oral use [1,4].

To avoid invasive drug therapy such as injections and to eliminate frequent dosing regimen

with oral administration, a transdermal drug delivery system has been studied as an alternative dosage form. Its high analgesic activity and low molecular weight make KT a good candidate for transdermal delivery.

In addition to the noninvasive therapy and maintaining the drug blood levels for an extended period of time, the transdermal delivery system has several advantages: it avoids first-pass metabolism, it is easy to discontinue the administration, and it reduces side effects. Despite these advantages, only a limited number of drugs can be administered percutaneously, due to low skin permeability of most drugs through the skin. The stratum corneum was recognized as an excellent barrier against skin penetration. To overcome this problem, vehicles, penetration enhancers, and electrotransport-facilitated transdermal systems have been attempted in the development of a transdermal delivery system of KT [3, 5-7]. However, the numbers or kinds of enhancers or vehicles used were very limited.

The purpose of the present study was to formulate self-adhesive transdermal films as delivery systems that would make it possible for KT to penetrate the skin at a high and constant rate. In order to achieve this purpose, three different film-forming polymers were used; also two adhesive polymers were added to the formulations to improve bioadhesion. The effect of film composition on the in-vitro release and skin permeation of the drug was investigated. Effect of three different permeation enhancers on the release and permeation of the drug was also studied in addition to the physical characteristics of the formulated films.

3. Material and Methods:

3.1. Materials:

Ketorolac tromethamine was generously donated from Amriya Pharmaceuticals Ind. (Alexandria, Egypt). Sodium carboxymethylcellulose (Na CMC) was obtained from Winlab Company (Maidenhead, Berkshire, England). Chitosan, oleyl alcohol (OA) and sodium glycocholate (NaGC) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Polyvinyl alcohol (PVA) was obtained from Fluka (Fluka chemical, Buches, Switzerland). Propylene glycol (PG) from El-Nasr Company (Abou-Zabal, Egypt). Polyvinyl pyrrolidone (PVP) was obtained from BDH Chemical (England). Plastoid® E35L (PL E35) was a gift from Rhöm (Darmstadt, Germany). Other chemicals were of reagent grade.

3.2. Methods:

3.2.1. Film Preparation:

Films containing KT were prepared by solvent casting method. The composition of the mixtures to be casted is reported in Table I. A solution of drug and plasticizer (glycerin) was added to the polymer water solution (except for chitosan, it was dissolved in glacial acetic acid) and to the adhesive Pl E35 (that is supplied as an aqueous solution that has a dry weight of 34% w/w) or to the PVP solution. In case of using enhancers, they were dissolved in the drug and plasticizer solution. The final solution was stirred overnight, and then left for 6 h to get rid of air bubbles. 10 ml of the drug polymer solutions were poured into a glass Petri dish and oven-dried at 60° C for 6 h. the films were stored in a desiccator for 24 h and then placed in a sealed container until time of use.

3.2.2. Film Characterization:

3.2.2.1. Drug Content:

The uniformity of drug distribution was evaluated by determining drug content at different places of the film. Pieces (5 cm^2) of five different places of the film were dissolved and subsequently diluted with phosphate buffer pH 7.4, filtered through 0.45µm Whatman filter paper and measured spectrophotometrically at 321 nm against blank.

3.2.2.2. Mass Uniformity and Thickness:

Each piece (five pieces of 5 cm^2 surface area) was measured for weight and thickness using a micrometer (Mitutoyo Co., Kanagawa, Japan) and the mean values were calculated.

3.2.2.3. Folding Endurance:

Folding endurance was determined by repeatedly folding each film at the same place till it broke or was folded up to 200 times without breaking [8].The experiments were performed in triplicate, and average values were reported.

3.2.2.4. In-Vitro Bioadhesion:

The bioadhesive strength was determined according to a previously published method [9] using hairless rat skin. A circular piece (surface area of 2 cm^2) was cut and glued with cyanoacrylate adhesive on the ground surface of a tissue holder made of Plexiglas. Similarly the film (of similar surface area) was glued to another holder of the same size. The skin was moistened with 25 µl of phosphate buffer pH 7.4. The two holders were put in contact with each other with uniform and constant pressure for 5 min (preload time). The tissue holder was allowed to hang on an iron stand with the help of a piece of aluminum wire. A pre-weighed polypropylene bag was attached to the hook on the backside of the film holder with a piece of aluminum wire. After a preload of 5 min, water was added to the polypropylene bag through an intravenous infusion set at a constant rate of one drop/sec until the film detached from fro the skin. The water collected in the measured and expressed as weight (g) required for detachment. Each experiment was repeated tree times.

3.2.3. In-Vitro Release Study:

The USP XXIII rotating paddle method was used to study drug release from the transdermal films; 200 ml of phosphate buffer pH 7.4 was used as the dissolution medium, at 37 ± 0.5° C, and a rotation speed of 50 rpm. One side of the film (5 cm^2) was attached to a glass plate with cyanoacrylate adhesive. The plate was put in the bottom of the dissolution vessel [10]. Samples (5 ml) were withdrawn at predetermined time intervals for up to 4h and replaced with fresh phosphate buffer pH 7.4. The samples were measured specrophotometrically at 321 nm. The experiments were performed in triplicate, and average values were reported.

3.2.4. In-Vitro Skin Permeation Study:

In-vitro skin permeation of KT through rat hairless skin was performed using in-vitro glass diffusion cell with diffusion surface area of 3.14 cm^2. Hairless rat skin was mounted between the donor and receptor compartments. The film was placed on the skin after being wetted with phosphate buffer pH 7.4, and the compartments were clamped together. The donor compartment was filled with 15 µl of phosphate buffer pH 7.4. The receiver compartment was filled with 15 ml of the same buffer. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead. At predetermined time intervals for up to 12 h, a 1 ml sample was withdrawn and replaced with fresh buffer, then assayed spectrophotometrically. The experiments were repeated three times and the average values were calculated.

The permeation parameters were calculated according to the following equations:

$$J = dQ/dt \cdot 1/A \quad (1)$$

$$P_{app} = dQ/dt \cdot 1/A \cdot 1/C \quad (2)$$

Where P_{app} is the apparent permeability coefficient, J is steady state flux, A is the effective diffusion area, C is the initial drug concentration and dQ/dt is the amount of drug permeated at time t.

Table I. Composition of the mixtures used for transdermal film preparation (% w/v)

	Film code											
Component	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
PVA	7.0	-	-	7.0	-	-	7.0	-	-	7.0	7.0	7.0
NaCMC	-	3.0	-	-	3.0	-	-	3.0	-	-	-	-
Chitosan	-	-	1.5	-	-	1.5	-	-	1.5	-	-	-
PVP	-	-	-	0.5	0.5	0.5	-	-	-	-	-	-
PL E35	-	-	-	-	-	-	10.0	10.0	10.0	10.0	10.0	10.0
Glycerin	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
KT	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
OA	-	-	-	-	-	-	-	-	-	5.0	-	-
PG	-	-	-	-	-	-	-	-	-	-	5.0	-
Na GC	-	-	-	-	-	-	-	-	-	-	-	5.0

PVA: Polyvinyl alcohol, NaCMC: Sodium carboxymethylcellulose
PVP: polyvinyl pyrroloidone, PL E35: Plastoid® E35 L
KT: Ketorolac tromethamine, OA: Oleyl alcohol
PG: Propylene glycol, Na GC: Sodium glycocholate

Table II. Physical parameters of ketorolac tromethamine transdermal films.

Film	Drug content (µg/ cm^2)	Thickness (mm)	Mass (mg)	Folding endurance	Bioadhesive Strength (g)
F1	985 ± 11.11	0.053 ± 0.04	72 ± 1	212 ± 10	6.6 ± 1.4
F2	977 ± 13.42	0.032 ± 0.05	26 ± 2	200 ± 12	8.5 ± 1.2
F3	989 ± 11.22	0.049 ± 0.07	53 ± 1	188 ± 14	5.8 ± 2.0
F4	982 ± 13.34	0.062 ± 0.07	76 ± 1	202 ± 10	10.6 ± 0.9
F5	991 ± 9.46	0.036 ± 0.05	29 ± 1	191 ± 14	11.1 ± 1.2
F6	987 ± 12.11	0.053 ± 0.09	55 ± 1	180 ± 17	10.5 ± 1.3
F7	1019 ± 10.35	0.065 ± 0.05	80 ± 1	197 ± 12	26.7 ± 0.7
F8	988 ± 11.56	0.039 ± 0.05	32 ± 2	188 ± 14	23.1 ± 0.9
F9	981 ± 13.36	0.057 ± 0.04	59 ± 2	174 ± 10	20.5 ± 1.4
F10	985 ± 11.41	0.066 ± 0.04	82 ± 2	198 ± 12	26.5 ± 1.3
F11	992 ± 9.55	0.067 ± 0.06	82 ± 1	198 ± 14	26.5 ± 0.6
F12	1002 ± 9.41	0.066 ± 0.07	80 ± 1	196 ± 10	26.1 ± 0.9

4. Results and Discussion:

4.1. Film Characterization:

Polymeric film formulations loaded with 1 mg/cm^2 KT using different polymers, were prepared. Table I reports the composition of the mixtures used for transdermal polymeric film preparation. The physical properties such as uniformity of drug content, mass, thickness, folding endurance and in-vitro bioadhesion were examined (Table II). Estimation of drug content at different places on each film indicated that KT was distributed uniformly throughout the films. The prepared films were smooth in appearance, uniform in thickness and mass and showed no visible cracks. The films exhibited good folding endurance (more than 150). Incorporation of PVP & PL E35, two typical adhesives for transdermal drug delivery, markedly improved the bioadhesive strength (Table II); especially PL E35 which showed a very good effect on increasing the adhesive character (the bioadhesive force increased by almost 3 to 4 folds). Films containing PL E35 (F7-F12) were completely self-adhesive when applied to skin after wetting. PVP and Plastoid® have been previously used as adhesives in PVA transdermal films [11-13]; however the bioadhesive force was not determined in those studies.

4.2. In-Vitro Release Study:

In-vitro drug release from different polymeric films was studied. Effect of adhesive on the in-vitro drug release is illustrated in Figure 1. PVP increased drug release especially from chitosan film (F6), while PL E35 had almost no effect on drug release. The weak aqueous solubility of the cationic polymer, chitosan resulted in retarded drug release from chitosan film (F3) where 40.87% of initial drug content was released after 4 h compared to 60.82% and 78.56% in case of NaCMC (F2) and PVA (F1), respectively.The hydrophilic polymer, PVA increased the surface wettability and consequently water penetration within the matrix. More of the water-soluble drug, KT would dissolve inside the hydrated matrix, resulting in a higher diffusional driving force and faster drug release. So, addition of PVA to chitosan film formulation increased the drug release to 70.57% after 4h (Figure 1,c). Patel *et al.* reported similar effect of incorporating PVP into chitosan buccal patches [14]. However, the effect of the adhesive PVP on the drug release from hydrophilic polymeric films (PVA and NaCMC films) was less evident, but still clear, the drug released increased from 78.56% (F1) to 85.66% (F4) and from 60.82% (F2) to 69.66% (F5) after 4 h (Figure 1,a and 1,b, respectively). Adding PVP increased water-soluble polymer content in these films resulting in faster swelling and higher release. Korsmeyer *et al.* investigated the influence of the addition of a second water-soluble polymer (PVP and PEG) to hydrophilic porous discs prepared from PVA on the drug release profile, and explained the role of dynamic swelling and dissolution of the polymer matrix on the release [15]. On the other hand, addition of the adhesive PL E35 (which is also a hydrophilic polymer) did not affect the drug release except for a slight increase in case of chitosan film (F9), (Figure 1,c). This effect was also related to increasing hydrophilicity of the hydrophobic film. However, this hydrophilic polymer (PL E35) obviously did not significantly affect the swelling behavior of the two hydrophilic polymeric films (Figure 1,a and 1,b). Therefore, these films should be applied to wet or hydrated skin not only to be self-adhesive, but also to facilitate the drug release.

4.3. In-Vitro Skin Permeation Study:

In-vitro skin permeation studies were performed to evaluate transdermal absorption of KT from these film preparations. Table III shows the permeation parameters of KT in all the film formulations. It can be seen that, PVA film (F1) showed the highest permeation parameters followed by NaCMC (F2) then chitosan (F3). In-vitro skin permeation was slightly enhanced by PVP (F4, F5 and F6); however the films containing PL E35 (F7, F8 and F9) showed a markedly increased permeation Table III and Figure 2). The PVA films containing adhesives still showed the highest permeation compared to the other two polymeric films with the same adhesive, i.e. the rank was F4 > F5 > F6 and F7 > F8 > F9.

PL E35 is a hydrophilic copolymer of dimethylaminoethyl methacrylate (Eudragit® E100) 34 % w/w with lauric acid 8.4 % w/w and adipic acid 1.7 % w/w. It is well known that lauric acid can act as a penetration enhancer for transdermal drug delivery, because it is able to penetrate into the stratum corneum and alter its lamellar structure, decreasing the overall lipid order [16-20]. The difference observed between the effects PL E35 and PVP on the in-vitro skin permeation was also reported by Padula *et al.* for transdermal films containing lidocaine [13]. Their work revealed that Plastoid ® acts on the partitioning parameter, increasing it, while the diffusive parameter is not affected. However, the use of PVP produced a decrease of lidocaine permeation across artificial silicone membrane, which resulted from a considerable reduction of the diffusive parameter. Artusi *et al.* [20] also have shown that lauric acid (which is contained in PL E35); at 4% w/v increased the partitioning parameter of the hydrophilic molecule thiocolchicoside across rabbit ear skin.

Then, the adhesive seems to play an important role in drug release and permeation.

PVA film containing PL E35 (F7) showed the highest release, permeation and bioadhesion, so it was selected for studying the effect of permeation enhancers.

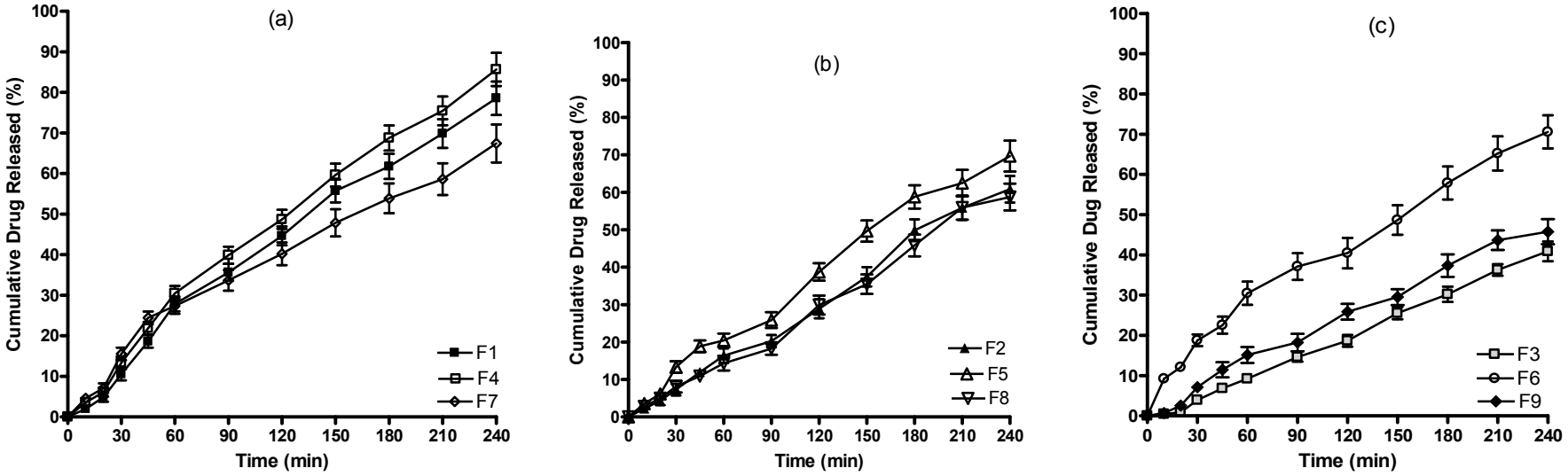

Fig. 1. Effect of adhesive on the in-vitro release of KT from: (a) PVA film, (b) NaCMC film and (c) chitosan film.
F1, F2 and F3: films without adhesive, F4, F5 and F6: films containing PVP as adhesive, F7, F8 and F9: films containing PL E35 as adhesive.

Table III. In-vitro skin permeation parameters of ketorolac tromethamine incorporated in different polymeric films.

Film	P_{app} x 10^2 (cm/h)	J (µg/cm^2/h)	Drug permeated after 12 h (%)
F1	1.61 ± 0.05	15.86 ± 1.21	23.74 ± 2.23
F2	1.26 ± 0.03	12.31 ± 1.11	18.29 ± 2.08
F3	0.47 ± 0.02	4.65 ± 0.29	10.27 ± 1.28
F4	1.90 ± 0.07	18.66 ± 1.43	27.67 ± 1.75
F5	1.36 ± 0.04	13.48 ± 0.94	20.56 ± 1.09
F6	0.82 ± 0.04	8.09 ± 0.91	13.26 ± 1.26
F7	2.29 ± 0.07	23.33 ± 1.51	32.36 ± 1.59
F8	1.93 ± 0.05	19.07 ± 1.33	25.00 ± 1.07
F9	1.04 ± 0.01	10.20 ± 0.87	16.29 ±1.29
F10	3.23 ± 0.04	31.81 ± 2.15	46.37 ± 1.74
F11	2.61 ± 0.04	25.89 ± 1.88	38.01 ± 2.49
F12	4.13 ± 0.05	41.38 ± 2.46	60.76 ± 2.77

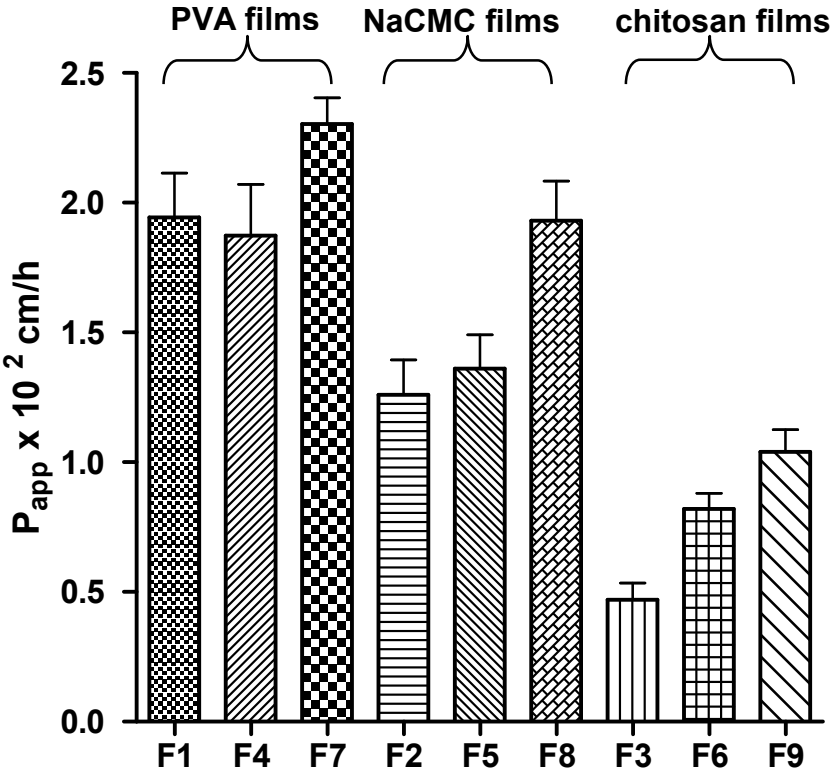

Fig. 2. Effect of adhesive on the in-vitro skin permeation of KT from different films. F1, F2 and F3: films without adhesive, F4, F5 and F6: films containing PVP as adhesive, F7, F8 and F9: films containing PL E35 as adhesive.

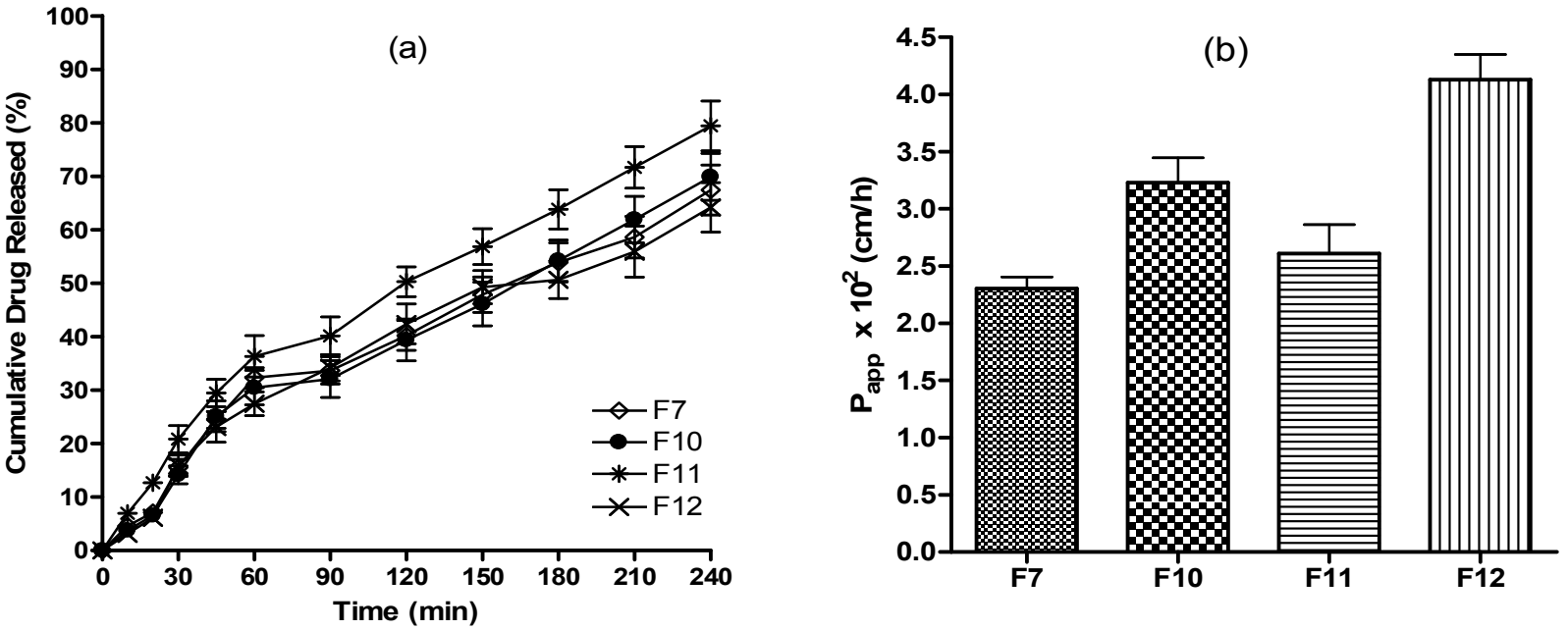

Fig. 3. Effect of permeation enhancers on (a) the in-vitro release and (b) in-vitro skin permeation of KT from PVA film. F7: PVA film containing PL E35 adhesive without enhancer, F10: PVA film containing PL E35 adhesive and OA as enhancers, F11: PVA film containing PL E35 adhesive and PG as enhancer, F12: PVA film containing PL E35 adhesive and NaGC as enhancer.

4.4. Effect of Permeation Enhancers:

OA, PG or NaGC were incorporated into PVA film containing PL E35 at a concentration of 5 % w/v (F10, F11 and F12, respectively). The physical parameters of these films were evaluated and it can be seen from Table II that these films maintained the good quality and high bioadhesion as the PVA film (F7), and that the three enhancers had no effect on the physical parameters of the film.

The permeation enhancers had no effect on the in-vitro drug release except in case of film containing PG (F11) which showed increased drug release (Figure 3,a). Although the mechanism for this effect remains to be clarified, the greater amount of water absorbed into the film by an enhancer would contribute to the more rapid release of the drug from the films [21]. PG can absorb moisture into the film because of its humectant ability [22]. The other two enhancers however, showed no effect on drug release as it is known that chemical enhancers usually produce their effect on the skin rather than affecting the drug or the formulation. So, their effect would be more evident on the skin permeation rather than on drug release.

The effect of enhancers on the in-vitro skin permeation is shown in Figure 3, b and Table III. It can be seen that the permeation parameters were increased in the presence of enhancers and the rank of effectiveness was NaGC (F12) > OA (F10) > PG (F11) with enhancement ratios of 1.80, 1.41 and 1.14, respectively. The enhancing effect of PG was not so remarkable, although it was reported that PG enhanced the skin permeation of several drugs [23-25] without any alteration in the skin structure [26]. The increase in solubilizing ability of the aqueous site in the stratum corneum is considered to be a main mechanism for PG to improve the skin permeation of drugs [27]. However the enhancing activity of PG is controversial [28], because PG also has several characteristics that can decrease the skin permeation of drugs such as its humectant character [22] that causes dehydration of the skin, the higher affinity of drugs for PG may contribute to reduced permeation [29] and the solubilizing effect of PG may lead to decrease in the chemical potential of drugs in the stratum corneum [27]. However the slight increase in the skin permeation of the drug by PG in this study may be related to the increase in drug release from the film as mentioned earlier in the in-vitro release results.

In case of using OA as an enhancer, the steady state flux and P_{app} were increased 1.41 folds. OA belongs to lipid disrupting agents which have been shown to increase the fluidity of the stratum corneum lipids, reducing its barrier properties, thereby increasing drug transport [30]. The enhancer which resulted in the highest permeation was the trihydroxy bile salt, NaGC (1.80 fold increase in steady state flux and P_{app}). Bile salts are well known for their transdermal and transmucosal permeation enhancing properties. Enhancement of drug permeation in the presence of bile salts is believed to happen by a complex process. Some of the proposed modulation mechanisms of bile salts include solubilization and micellar entrapment of intercellular lipids, denaturation and extraction of proteins, enzyme inactivation, and tissue swelling [31-34]. The drug permeated after 12 h when NaGC was incorporated in film (F12) was fairly high (60.76 ± 2.77 %) indicating the possibility of using this formulation for transdermal delivery of KT.

5. Conclusion:

The formulated polymeric films had good appearance and physical characterestics (no cracks, uniform thickness, mass and drug conent) and were self-adhesive after wetting with water when plastoid® E35L and PVP were incorporated. They showed fairly high in-vitro release and skin permeation. The skin permeation sustained for at least 12 h. The PVA film containing plastoid® E35L showed the best bioadhesion, highest release and permeation especially with the use of permeation enhancers, suggesting that this formulation can be a promising therapeutic system for the transdermal delivery of kT to avoid the disadvantages of parenteral and oral routes.

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