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Original Article

Effects of various penetration enhancers on percutaneous absorption of piroxicam from emulgels

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Abstract

A suitable emulgel formulation of piroxicam was prepared and its percutaneous permeation was investigated using Wistar rat skin and diffusion cell technique. The concentrations of the drug in receptor phase of diffusion cells were measured using HPLC method. The effect of three types of penetration enhancers (Myrj 52, cineol and Transcutol P) with different concentrations on transdermal permeation of the drug was also evaluated. Flux, Kp and enhancement ratios (ERs) of piroxicam in the presence of enhancers was measured and compared with emulgel base alone and simple commercial gel. The results showed a significant enhancement in the flux from emulgel base compared to hydroalcoholic gel formulation (9.91 folds over simple gel). The highest enhancement ratio (ER=3.11) was observed for Myrj 52 at the concentration of 0.25%. Higher concentrations of Myrj 52did not show any enhancement in the drug flux due to micelle formation and solubilization of the drug by micelles. The increase in solubility, in turn, increases the saturated concentration and reduces the thermodynamic activity of the drug. Transcutol® P with concentrations higher than 0.25% w/w showed burst transportation of the drug through the skin. All concentrations of cineol and Transcutol did not show any enhancing effects over emulgel base alone (ER <1).

Keywords: Emulgel; Piroxicam; Penetration enhancer; Myrj 52

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in reducing inflammation and pain. However, NSAIDs are associated with gastrointestinal side effects and generally cause gastritis due to inhibition of cyclooxygenase-2 and in some cases cyclooxygenase-1 (1). These side effects can be overcome by topical administration of these drugs (2). The transdermal administration of these drugs has several advantages over other routes of administrations (3).

Human skin is a remarkably efficient barrier compared to other biological membranes. Hence, low permeability of the skin makes difficulties for the percutaneous delivery of therapeutic agents. In the last decade, several studies about NSAID formulations in lipid base (4) and Pluronic lecithin organogel (5, 6) have been reported. Gel formulations of piroxicam do not exhibit satisfying percutaneous absorption and hence, formulation of piroxicam in emulgel dosage forms would be more desirable. Emulgels are oil-in-water emulsions in which the external phase is in the gel form. Several studies have shown that the amount of drug absorbed from emulgel formulations was higher than that absorbed from simple hydroalcoholic gel formulations (7). Efforts have, therefore, been focused on developing methods and formulations to increase the permeability of human stratum corneum to these drugs. One promising approach to overcome barrier property of the skin is using skin penetration enhancers, which can increase the permeability of the stratum corneum (8) to drugs. Different groups of chemicals have been reported as transdermal penetration enhancers (9) which

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include surfactants, organic solvents, unsaturated fatty acids and also organic materials which are extracted from natural sources such as alkaloids and terpenes. Some of the studies have been carried out to predict the percutaneous absorption of piroxicam using different permeation enhancers (10-13).

In the present study, the penetration enhancing effect of emulgel formulations of piroxicam was compared to that of a simple gel formulation of this drug. The effects of some skin penetration enhancers on the skin permeation of piroxicam were also investigated. Penetration enhancers with different chemical structures, namely non ionic surfactants (Myrj 52), terpenes (cineol) and synthetic chemical penetration enhancers (Transcutol P) with different concentrations were studied. Myrj 52 (polyoxyethylene 40 stearate) is a nonionic surfactant with very low toxicity and irritancy which is widely used in pharmaceuticals and cosmetic formulations as emulsifier and stabilizer. Transcutol P is a wide range solvent which also has penetration enhancing ability for some drugs. Cineol is a terpene and has found applications as an adjuvant in the form of penetration enhancers for improving transdermal and transmucosal drug delivery.

MATERIALS AND METHODS

Materials

Piroxicam was generously provided by Zahravi Industrial Co. (Tabriz, Iran). Pluronic® F127 was purchased from Sigma-Aldrich Co. (USA), Carbopol® 940 from B.F. Goodrich Co. (USA), hydroxypropyl methylcellulose K4M from Colorcon Co. (UK), Transcutol P from GattefÖsse (France), and Myrj 52 from Croda Chemical Co. (Switzerland). Isopropyl Myristate, Methyl paraben, soya lecithin, propylene glycol, monobasic potassium phosphate, sodium hydroxide, methyl paraben, liquid silicone, silicon grease, cineol, triethanolamine, glacial acetic acid, triethanolamine, acetonitrile and sodium acetate were supplied by Merck (Darmstadt, Germany). Commercially available piroxicam gel was obtained from Razak Pharmaceutical Co. (Karaj, Iran) .

Methods

Preparation of piroxicam emulgels

Emulgels are oil-in-water emulsions which are converted to gel by mixing with a gel forming agent (14). To develop a stable emulgel formulation, selection of proper gel forming agent, emulsifier and organic phase are of importance. For preparation of piroxicam emulgel, three types of gelling agents including Pluronic F127, hydroxypropylmethyl cellulose (HPMC) and Carbopol 934 were used. To achieve an emulgel with desirable characteristics, several formulations were prepared using different types and amounts of gel forming agents, emulsifiers, organic phase composition, and drug solvent.

Formulations were prepared at laboratory scale at room temperature by dissolving piroxicam in propylene glycol as a moisturizer and solubilizer. A fixed concentration of the drug was used in all cases to allow the comparison of the effect of vehicles on the percutaneous absorption of piroxicam. The pH of all prepared emulgels was adjusted to 6-6.5 using citric acid or triethanolamine. The enhancers were added to the organic phase (containing lecithin and isopropyl myristate in the ratio of 4:1) before the addition of the gel phase into the organic phase. The compositions of the prepared formulations are shown in Table 1.

Formulations containing HPMC 1% w/w (F1-F5) did not exhibit appropriate consistency. Therefore, to obtain desirable gel with suitable thickness, 2% w/w HPMC was used which resulted in formulations F6-F10. Though the amount of HPMC was increased, these formulations did not show desirable physical stability. HPMC with a concentration of 3% w/w produced (F11-F15) very thick gels whose incorporation with other ingredients of the formulation was difficult.

Emulgels containing Carbopol 940 as a gel forming agent did not result in a uniform and homogeneous gel (F21-F25). Therefore, these formulations were not considered for further experiments. Formulations prepared using Pluronic F127 (F16-F20) showed desirable characteristics and appearance. These formulations were kept at 40°C for a period of

Table 1. Composition (% w/w) of the formulations containing $HPMC_{K4M}$, Pluronic® F127, and Carbopol® 940. All formulations contained 0.5% (w/w) piroxicam and 10% (w/w) propylene glycol

Formulation	Organic phase	HPMC K4M 1%	HPMC K4M 2%	HPMC K4M 3%	Pluronic® F127	Carbopol® 940
F1	18	71.5	-	-	-	-
F2	20	69.5	-	-	-	-
F3	22	67.5	-	-	-	-
F4	22	62.5	-	-	-	-
F5	30	59.5	-	-	-	-
F6	18	-	71.5	-	-	-
F7	20	-	69.5	-	-	-
F8	22	-	67.5	-	-	-
F9	22	-	62.5	-	-	-
F10	30		59.5	-	-	-
F11	18	-	-	71.5	-	-
F12	20	-	-	69.5	-	-
F13	22	-	-	67.5	-	-
F14	22	-	-	62.5	-	-
F15	30	-	-	59.5	-	-
F16	18	-	-	-	71.5	-
F17	20	-	-	-	69.5	-
F18	22	-	-	-	67.5	-
F19	22	-	-	-	62.5	-
F20	30	-	-	-	59.5	-
F21	18	-	-	-	-	71.5
F22	20	-	-	-	-	69.5
F23	22	-	-	-	-	67.5
F24	22	-	-	-	-	62.5
F25	30	-	-	-	-	59.5

Table 2. Composition (% w/w) of selected formulations containing penetration enhancers (all formulations contained 0.5% piroxicam, 18 ml organic phase and 10 ml propylene glycol).

Formulation name	Pluronic F127	Myrj 52	Transcutol P	Cineol
F26	71.25	0.25	-	-
F27	71	0.5	-	-
F28	70.25	1	-	-
F29	69.25	2	-	-
F30	71.25	-	0.25	-
F31	71	-	0.5	-
F32	70.25	-	1	-
F33	69.25	-	2	-
F34	71.25	-	-	0.25
F35	71	-	-	0.5
F36	70.25	-	-	1
F37	69.25	-	-	2

two months in order to assess their physical stability based on their appearance in terms of microbial contamination and phase separation.

For the sake of comparison, formulation F16 (with no penetration enhancer) was selected as the "base emulgel formulation" due to its

better stability and physicochemical properties over other formulations containing no enhancer. This formulation was used as the base for evaluation of the efficiency of some penetration enhancers on percutaneous absorption of piroxicam through the rat skin. To this end, three types of skin penetration enhancers including Transcutol P, Myrj 52 and cineol were examined at different concentrations (0.25, 0.5, 1 and 2% w/w). Percutaneous absorption of the drug through the rat skin in the presence of these penetration enhancers were assessed using a Franz diffusion cell. Details of prepared formulations are reported in Table 2.

In vitro permeation studies

The abdominal hair of Wistar male rats, weighing 180-200 g, was shaved using an electric razor after scarifying animals using excess ether anesthesia 24 h before the treatment. The experiments were performed in accordance with ethical committee of the Tabriz University of Medical Sciences. The abdominal skin was surgically removed and adhering subcutaneous fat was carefully cleaned. To remove extraneous debris and leachable enzymes, the dermal side of the skin was kept in contact with a normal saline solution up to one h before starting the diffusion experiment. The skins were mounted on the Franz-type diffusion cells (Erweka HDT6, Germany) with an available diffusion area of 5.1 cm^2 with the stratum corneum facing the donor compartment. All six Franz cells were placed on the skin penetration study apparatus. Each set of experiments was performed with minimum 3 diffusion cells ($n \geq 3$) and repeated 3 times in different days. 28.5 ml of phosphate buffer solution (pH=7.4) was used as the receptor medium and 0.5 g of the emulgel was placed on the skin surface in the donor compartment. The temperature of the receptor medium was maintained at 37°C by circulating of warm water between two layers of the diffusion cells and contents of receptor medium were stirred magnetically at 600 rpm. Samples of 1 ml were withdrawn from the receptor compartment at 15, 30, 60, 120 and 240 min and replaced with the same volume of phosphate buffer solution at 37°C to maintain the volume constant. The amount of piroxicam in the receptor phase was assayed with HPLC apparatus.

Analytical procedure

The HPLC apparatus (Shimadzu VP-Japan) equipped with UV detector (Shimadzu SPD-10A VP) and an ODS C18 (250×5 mm, 5 µm) (Shimadzu, Japan) HPLC column were used to perform the analysis. The mobile phase consisted of sodium acetate- acetonitrile (61:39) mixture which was adjusted at pH 4.0 by glacial acetic acid and eluted at the flow rate of 1.5 ml/min and the effluent was monitored at 330 nm using a UV detector (15). 20 µl of sample was injected into the HPLC column. The retention time of piroxicam at this HPLC condition was 11 min. Calibration curve with standard concentrations ranging from 0.125 to 2 µg/ml of piroxicam in phosphate buffer was constructed to measure the drug concentration in the samples.

Data treatment

According to Fick's second law of diffusion, the total amount of drug (Q_t) appearing in the receptor solution in time t is expressed as:

$$Q_t = AKLC_0 \left[\left(\frac{Dt}{L^2}\right) - \left(\frac{1}{6}\right) - \left(\frac{2}{\pi^2}\right)\sum \frac{(-1)^n}{n^2}\right] \times \exp\left(\frac{D^n 2\pi^2 t}{L^2}\right)$$

where, A is the effective diffusion area, C_0, represents the drug concentration which remains constant in the vehicle, D is the diffusion coefficient; L denotes the thickness of the membrane and K is the partition coefficient of the drug between membrane and vehicle. At steady-state is expressed as follows:

$$\frac{Q_t}{A} = KLC_0 \left[\left(\frac{Dt}{L^2}\right) - \left(\frac{1}{6}\right)\right]$$

The flux, J, was determined from the slope of the steady-state portion of the amount of the drug permeated divided by A versus time. The lag time values were determined from the x-intercept of the slope at steady-state. The flux is expressed as:

$$J = \frac{C_0 KD}{L} = C_0 K_p$$

where, K_p is the permeability coefficient.

The ER was calculated from the following equation (16). The values reported are mean ratios from a minimum of three replicates.

$$ER = \left(\frac{K_p \ with \ pretreatment}{K_p \ without \ pretreatment} \right)$$

RESULTS

Fig. 1(a) shows the permeation profiles of the drug from commercially available piroxicam hydroalcoholic simple gel and emulgel base formulation (F16). As shown in this figure, the permeation rate of the drug from emulgel base is significantly higher than that of hydroalcoholic gel. The flux of piroxicam from emulgel base (F16) was found to be 1.428 $\mu gcm^{-2}h^{-1}$ which is 9.92 folds higher than that of the commercial simple gel formulation (0.144 $\mu gcm^{-2}h^{-1}$). These results showed that the type of base could greatly influence the transdermal flux of the drug. Emulgel bases are also more compatible with the skin compared with alcoholic or hydroalcoholic gels (17).

Fig. 1(b) shows the transdermal permeation of the drug from different emulgel formulations containing various concentrations (0.25, 0.5, 1 and 2% w/w) of Myrj 52. As shown in this figure, the highest ERs (Table 3) were observed in the presence of Myrj 52 at 0.25% w/w concentrations (ERs=3.11). Enhancement of the drug transport rate may relate to the ability of the surfactant molecules to penetrate the skin and increase its permeability. The ER values reduced when the higher amount of Myrj 52 was used (ER was 0.289 and 0.046 for 1% and 2% w/w respectively).

Piroxicam permeation profiles from formulations contained different percent of Transcutol P are shown in Fig. 2(a) and their corresponding parameters including fluxes and ERs are reported in Table 3. As seen in Fig. 2(a), all the concentrations of Transcutol P except 0.25% w/w could permeate their drug content into the skin as the burst transportation (18, 19). In these cases, two stages are seen in the profile of the amounts of the drug permeated per unit area of the skin versus time where the first stage is due to the burst transportation and the second stage is related to the steady state condition of the drug permeation. A direct relationship was observed between the amounts of piroxicam penetrated into the skin and the concentrations of the enhancers at the initial sampling times. Burst transportation of the drug in the presence of Transcutol P at 1% and especially 2% (F32 and F33) concentration was initiated immediately whereas in the case of the formulation containing 0.5% Transcutol P (F31),

Table 3. Flux values, Permeablity coefficients (Kp) and enhancement ratios of evaluated formulations

Enhancer concentration (%w/w)	Steady- state flux ($\mu gcm^{-2}h^{-1}$)	*Kp* ($\times 10^3$; cm h^{-1})	E.R.
Commercial gel (Razak)	0.144±0.053	0.0288±0.011	0.101
Emulgel base without enhancer	1.428±0.703	0.2856±0.141	1.000
	Myrj 52		
0.25	4.440±1.807	0.8880±0.036	3.110
0.50	3.978±1.504	0.7956±0.301	2.785
1.00	0.414±0.008	0.0828±0.002	0.289
2.00	0.066±0.014	0.0132±0.003	0.046
	Transcutol P		
0.25	1.194±0.891	0.2388±0.178	0.836
0.50	0.228±0.071	0.0456±0.014	0.117
1.00	0.366±0.118	0.0732±0.024	0.256
2.00	0.387±0.038	0.0774±0.008	0.277
	Cineol		
0.25	0.186±0.069	0.0372±0.014	0.130
0.50	0.702±0.302	0.1404±0.060	0.491
1.00	0.144±0.078	0.0288±0.016	0.101
2.00	0.588±0.198	0.1176±0.040	0.412

the burst transportation started 30 min after contacting with the skin. The burst transportation was not observed when the concentration of Transcutol P in the formulation was reduced from 0.5% to 0.25% w/w (F30).

Drug permeation profiles of emulgel base formulations containing different concentrations of cineol as penetration enhancer are shown in Fig. 2(b). Cineol did not show a significant improvement in the flux of piroxicam through the rat skin (P>0.05). The results showed that none of the used concentrations of cineol could improve the flux of piroxicam compared to emulgel base alone (Table 3).

Based on the data reported in Table 3, ERs of all concentrations of cineol with emulgel

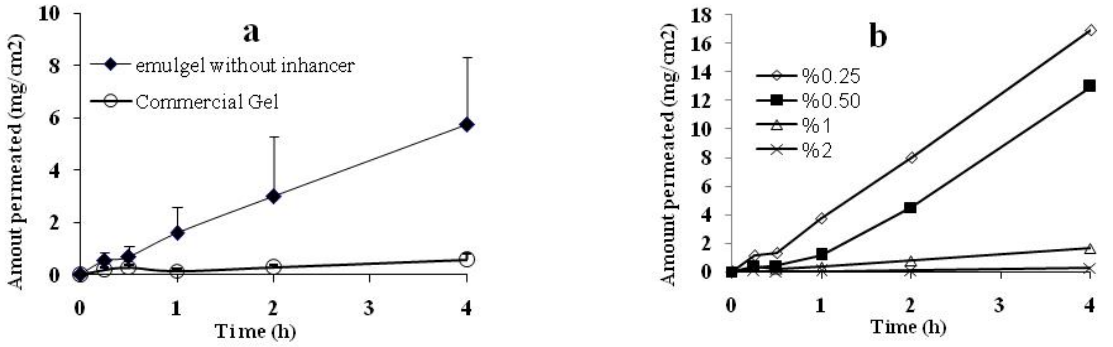

Fig. 1. Piroxicam skin permeation from **(a),** emulgel base alone (F16) and commercial gel formulations and **(b),** the emulgel formulations containing different concentration of Myrj 52 as penetration enhancer (F26-F29).

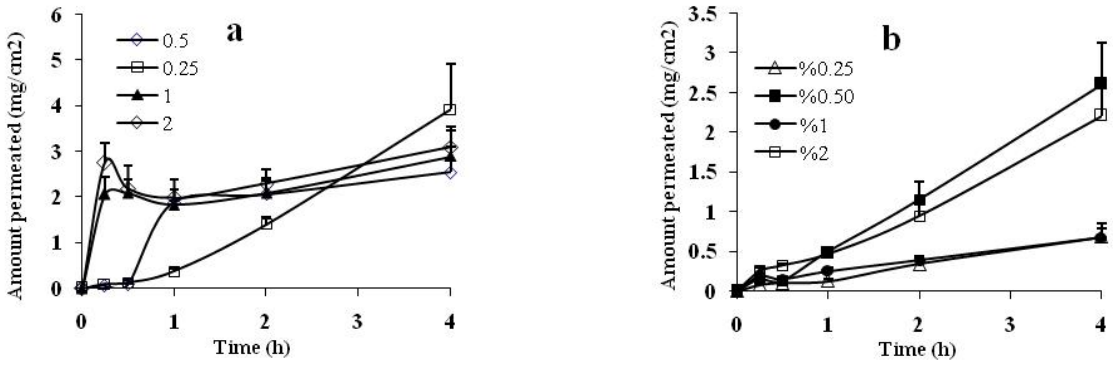

Fig. 2. Transdermal permeation profiles of piroxicam from emulgel formulations containing different concentration of **(a)**, Transcutol P **(b)**, Cineol as penetration enhancer.

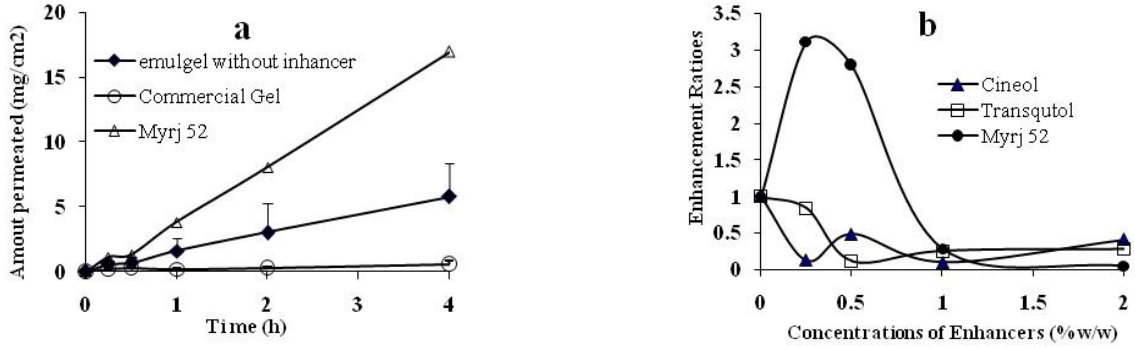

Fig. 3. Permeation profiles of the drug from **(a)**, commercial gel, emulgel base alone and emulgel base plus Myrj 52 with 0.25% w/w concentration (F26) **(b)**, Enhancement ratios of different concentrations of various penetration enhancers.

base were below 1 which indicates that all concentrations of cineol have decreased permeation rate of piroxicam compared to emulgel base alone.

Fig. 3(a) shows the skin permeation profiles of the drug from commercial gel, emulgel base formulation and emulgel base in the presence of 0.25% Myrj 52 as the penetration enhancer (F26) which indicated the highest enhancement ratio between various concen-trations of the three types of the used penetration enhancers (ER=3.11). As shown in this figure, F26 showed significantly greater permeation rate in comparison with emulgel base alone.

The plot of ERs versus various concentrations of the penetration enhancers is shown in Fig. 3(b). As it is clear from this figure among three penetration enhancers used in the present study, only Myrj 52 with concentrations below 0.5% w/w showed ERs greater than emulgel base alone. On the other hand, all concentrations of Transcutol P and cineol showed lower flux than emulgel base alone (ERs <1). This diagram also clearly shows that in order to achieve the highest ER value, an optimum level of the enhancer is needed. This figure also demonstrates that the nature and physicochemical properties of the drug molecule and the enhancers are very important factors in enhancing the skin permeation of the drugs.

DISCUSSION

Piroxicam exhibits a weakly acidic 4-hydroxy proton (pKa, 5.1) and weakly basic pyridyl nitrogen (pKa, 1.8); thus, the pH of medium can play an important role in its solubility in aqueous solutions. Topical preparations of this drug are usually formulated in the pH range of 6-6.5 to increase the skin compatibility and to reduce skin irritancy. In a simple aqueous or hydroalcoholic gel with pH of 6, about 87% of piroxicam is in the ionized form. Intrinsic logP octanol/water of piroxicam is 3.06 (20) which indicates that the solubility of non-ionized form of the drug in octanol is much greater than that of the aqueous solutions (more than 1000 times). In the emulgel formulations, the non-ionized portion of the drug mainly enters the organic phase which is isolated from the aqueous phase of the emulgel. In this situation, a given amount of ionized drug in aqueous phase converts to non-ionized form to maintain the equilibrium between two forms of the drug in aqueous phase of the emulgel formulation. This process is continued until the majority of the drug dissolves in the oily phase in the form of non-ionized which has ability to penetrate into the skin. This causes a significant increase in the drug concentration and the thermodynamic activity of non-ionized form of the drug which is considered as effective form of the drug in transdermal absorption. Hence, the great enhancement in penetration of the drug into the skin was observed. Another advantage of emulgels over hydroalcoholic gels is related to physiological and structural characteristics of the skin. Emulgels are alcohol free formulations. Alcohol can cause the irritation of the skin especially dry skins due to its ability to dissolve and remove natural lipids of stratum corneum.

Myrj 52 or polyoxyethylene 40 stearate are nonionic surfactants. Several studies have reported the enhancing effects of nonionic surfactants on transdermal and transmucosal permeation of the drugs (19-22). There are two possible mechanisms involved in the enhancement of drug transport by nonionic surfactants (23, 24). Initially, the surfactants may penetrate into the intercellular regions of the stratum corneum, increase the fluidity of lipids and eventually solubilize and extract the lipid components. Secondly, penetration of the surfactant into the intracellular matrix followed by interaction with and binding to keratin filaments may result in a disruption within the corneocytes. Myrj 52 is thought to enhance the permeation of the drug by disruption of lipid arrangement in the stratum corneum and to increase water content of the proteins in the barrier. Oxyethylene units and long hydrocarbon chain in the structure of Myrj 52, allow partitioning between lipophilic mortar substance and the hydrophilic protein domains. It can also interact with polar head groups of the skin lipids and the modification of H-bonding and ionic forces may occur. The other possible mechanism is related to keratin

fibrils and their associated water molecules as targets of enhancers. The disruption caused by the enhancer makes this area more aqueous. With high enough volumes, an increase in solubilizing ability of the aqueous layer could result in the operational partition coefficient of this region of the skin (25). This would then allow the drug transport through the corneocytes.

As it is clear from Fig. 1(b), the ER values reduced when higher amount of Myrj 52 was used (ER was 0.289 and 0.046 for 1% and 2% w/w respectively). This could be explained by the fact that surfactants are able to produce micelles in concentrations higher than their critical micelle concentration (CMC) in the related medium or base. Although the CMC concentration of non ionic surfactants in pure water is relatively low (lower than 0.1% w/w), it has been shown that the presence of other water miscible cosolvents such as propylene glycol increases their CMC up to ten-fold compared to pure water (26). Surfactant micelles can interact with drug molecules and increase their solubility. Solubilization of the drug by surfactant micelles decreases the thermodynamic activity of the drug and, hence, decreases the driving force of the drug absorption. These results are in agreement with our previous works (19, 20).

Transcutol P is soluble both in water and oil and can form an intracutaneous depot for drugs used in topical formulations. Piroxicam permeation profiles in Fig. 2(a) indicate that the enhancer can penetrate into the skin rapidly and depot in the skin due to its physicochemical properties and high solvency effects to aqueous and oily medium. The drug can co-transport with the enhancer which led to a high drug permeation rate in a short period of time. Afterward, the transportation of piroxicam reaches to an equilibrium or steady state and permeation of the drug across the skin is performed by a constant rate. At low concentrations (0.25% w/w), Transcutol P cannot transport the drug across the skin immediately after contacting with the skin and hence, burst transportation was not seen. As shown in Table 3, all tested concentrations of Transcutol P showed lower ERs in comparison with emulgel base alone. The saturated concentration of the non-ionized drug in organic phase of the emulgel increases in the presence of Transcutol P whereas the total amount of the drug in the formulation is constant. This resulted in the reduction of the relative solubility of the non-ionized form of the drug and consequently a reduction in the thermodynamic activity of the drug in the skin permeation process.

Cineol or eucalyptol is a terpene ether which is naturally obtained from eucalyptus extract. Terpenes like menthol, cineole, and limonene have been used to enhance permeation of both hydrophilic and lipophilic drugs (27). Cineole is reported to be the most efficient penetration enhancer for propranolol hydrochloride across the rat skin, compared with menthol and propylene glycol (28). In a separate study, Nokhodchi and coworkers investigated the effect of different terpens on the penetration of diclofenac sodium from the rat skin and they concluded that the most outstanding penetration enhancer was nerolidol, providing an almost 198-fold increase in the permeability coefficient of diclofenac sodium, followed by farnesol with a 78-fold increase in skin permeability (29). Cineol like other terpenes exerts its enhancing effect by interacting with intercellular stratum corneum lipids to increase the diffusivity, but its acceleratory effects are not the result of partitioning (9). Neither partition coefficient nor thermodynamic activity was altered by the terpenes. It is suggested that the possible mechanism of permeation enhancement of the drugs by terpenes is the result of the modification of skin barrier properties It has been shown that terpenes with minimal degree of unsaturation like menthol and cineol are good sorption promoters for polar and water soluble drugs (28,30).

Despite several reports regarding the enhancing effect of cineol on transdermal flux of some drugs such as propranolol and zidovudine (31), cineol did not show a significant improvement in the flux of piroxicam through the rat skin in the current study (P>0.05). This could be due to the high lipophilicity of piroxicam (water solubility of piroxicam is 23 mg/L (32). It has been reported that the optimum permeation enhancing effect of cineol observed in the case

of polar and water soluble drugs (27,30). Apart from this, it seems that cineol can interfere with skin permeation of piroxicam with other mechanisms. Experimental Log P oct/water of cineol is reported to be 2.74 (33), which is close to the log P of piroxicam (3.05). This indicates that cineol may compete with the non-ionized form of the drug in entering the oily phase of the emulgel and switch the ionization equilibrium of the drug toward the production of ionized form in the aqueous phase due to the low volume of oily phase of the formulation (about 3.5% w/w) and its limited capacity of dissolving lipophilic substances. The authors called this phenomenon as *cineoling out*.

CONCLUSION

Piroxicam is more efficiently transported across the skin from emulgels compared to hydroalcoholic gels. Penetration enhancers can markedly increase the transdermal absorption of piroxicam if the type and concentration of the enhancer in formulation is optimized. The results revealed that Myrj 52 resulted in the greatest enhancing activity at concentrations lower than 0.5% w/w for emulgel formulations containing piroxicam. The results of this study show that the type and concentration of penetration enhancers and base of the formulation are very important variables and should be optimized for achieving an efficient transdermal delivery of the drug from emulgel formulations.

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