Drug Development and Industrial Pharmacy, 35:329–336, 2009

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802360494

informa
healthcare

Transdermal Delivery of Tadalafil. I. Effect of Vehicles on Skin Permeation

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Transdermal delivery that avoids the presystemic disposition can provide an alternative to oral administration of tadalafil. Accordingly, the aim of this study was to select the best vehicle as the first step in optimization of tadalafil transdermal delivery. The vehicles were used neat or in selected binary combinations and were evaluated for drug solubilization and transdermal delivery. The drug solubility in pure vehicles were ranked as polyethylene glycol (PEG) 400 > propylene glycol (PG) > ethanol > ethyl oleate (EO) > isopropyl myristate (IPM) > water. The solubility in binary systems containing ethanol at 2:1 ratios with EO or IPM was greater than that obtained with pure ethanol, EO, or IPM. This effect could be due to the cosolvency effect. The transdermal drug delivery from pure vehicles was ranked as IPM > EO > ethanol > PG > PEG > water. The delivery from binary mixtures of ethanol with either IPM or EO was higher than that obtained from pure solvents with the delivery increasing with increasing ethanol concentration in the mixtures. The delivery from binary mixtures was synergistic rather than additive. The study thus demonstrated a potential of tadalafil transdermal delivery. Binary combinations of ethanol with either IPM or EO provided the first step forward toward the development of transdermal delivery system for tadalafil.

Keywords tadalafil; tadalafil transdermal; solvents and skin; ethanol/isopropyl myristate binary systems; ethanol/ethyl oleate binary systems

INTRODUCTION

Tadalafil is a selective inhibitor of phosphodiesterase type 5 (PDE5), the predominant isoenzyme responsible for the metabolism of cyclic guanosine monophosphate (cGMP). During sexual stimulation, the cavernous nerves release nitric oxide, which induces cGMP formation and smooth muscle relaxation in the corpus cavernosum. Tadalafil inhibition of the PDE5 mediates a sequence of events starting with elevation in the cGMP, which causes corpus cavernosum smooth muscle relaxation, leading to increase in the blood flow and enhancement in the erectile function. The drug is approved as a therapeutic agent for the management of male erectile dysfunction (Buvat et al., 2006; Costa et al., 2006; Porst et al., 2003; Sussman, 2004).

Oral tadalafil is subjected to presystemic elimination which is mediated primarily by the cytochrome P450 isoenzyme CYP3A4 (Ring et al., 2005). This makes tadalafil susceptible to interaction with drugs or foods which affect the CYP3A4. Several drugs are known to inhibit CYP3A4, the principle isoenzyme responsible for the metabolism of tadalafil. These include cimetidine, ciprofloxacin, macrolide antibiotics such as erythromycin and clarithromycin, ciprofloxacin, antifungals such as ketoconazole and itraconazole, and protease inhibitors such as saquinavir and ritonavir. Inhibitors of CYP3A4 are expected to increase the plasma concentrations of the drug resulting in augmentation of the pharmacological and the adverse effects of tadalafil. It has been reported that co-administration of sildenafil (another PDE5 inhibitor which is a substrate for CYP3A4) with cimetidine, erythromycin, clarithromycin, ciprofloxacin, protease inhibitors, and grapefruit juice significantly increased the plasma concentrations of sildenafil in healthy male volunteers (Hedaya, El-Afify, & El Maghraby, 2006; Jetter et al., 2002; Muirhead, Faulken, Harness, & Taubel, 2002; Muirhead, Wulff, Fielding, Kleinermans, & Buss, 2000; Wilner, Laboy, & LeBel, 2002). These interactions require careful dose adjustment for

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patients receiving the CYP3A4 substrates such as tadalafil. The problem becomes even greater if the interacting material is food or drink such as grape fruit or other citrus juices. Accordingly, the development of alternative delivery system for tadalafil could provide a safer option for drug administration.

Tadalafil is (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-[(3,4-(methylenedioxy) phenyl]pyrazino[1′,2′:1,6]pyrido[3,4-b] indole-1,4-dione (Figure 1) (Cheng & Chou, 2005). It is a crystalline solid that is practically insoluble in water and slightly soluble in ethanol. It has a molecular weight of 389.404. The maximum plasma concentration (C_{max}) after oral administration of a 20 mg tablet is 378 μg/L. The efficacy of tadalafil has been maintained for 36 h, when the plasma concentrations drop to three-fold less than the C_{max}. This suggested a very low minimum effective concentration with a possibility of using lower doses (Shabsigh et al., 2006). Moreover, Cialis® (tadalafil) has been recently approved by the FDA for once daily use of 2.5 or 5 mg tablets for the treatment of erectile dysfunction (http://www.cialis.com/index2.jsp). Having these physicochemical and pharmacotherapeutic information of tadalafil, it is reasonable to suggest transdermal drug delivery as a possible alternative for tadalafil.

Development of transdermal delivery system for tadalafil will provide the benefit of avoiding the presystemic disposition of the drug. This will avoid the drug–drug and drug–food interactions based on presystemic metabolism. It can provide a promising alternative to the low dose once a day therapy. In addition, such a system can allow for dose reduction which will reduce the incidence of side effects. The latter is important for such a new drug even though the reported side effects are limited (Porst et al., 2003), as we never know what the periodic safety update data may reveal in the future. However, the barrier nature of the skin made it difficult for many drugs to permeate through it (Barry, 1983). Alternative strategies have been used to improve transdermal drug delivery. These include the use of chemical penetration enhancers (Williams & Barry, 2004), electrically driving molecules into or through the tissue employing iontophoresis (Miller, Kolaskie, Smith, & Rivier, 1990), physically disrupting the skin structure, for example, by electroporation or sonophoresis (Banga, Bose, & Ghosh, 1999; Kost et al., 1996), developing supersaturated drug delivery systems (Leichtnam, Roland, Wuthrich, & Guy, 2006), or incorporating the drug in colloidal drug delivery systems such as liposomes, niosomes, and microemulsions (El Maghraby, 2008; El Maghraby, Williams, & Barry, 1999, 2006; Mezei and Gulasekharam, 1980; Schreier & Bouwstra, 1994). However, the first step in optimizing transdermal drug delivery is to select a suitable solvent system (Mollgaard & Hoelgaard, 1983; Thomas & Panchagnula, 2003).

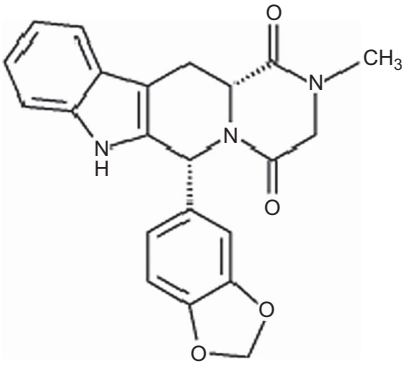

FIGURE 1. Chemical structure of tadalafil.

Alternative vehicles have been employed for transdermal drug delivery. These include both hydrophilic and lipophilic vehicles such as water, ethanol, propylene glycol (PG), polyethylene glycol (PEG), isopropyl myristate (IPM), ethyl oleate (EO), etc. Vehicles may act as penetration enhancers by increasing the thermodynamic activity of the drug and/or changing the barrier property of the skin (Aungst, Blake, & Hussain, 1990; Mollgaard & Hoelgaard, 1983; Panchagnula, Salve, Thomas, Jain, & Ramarao, 2001). These vehicles were used neat or in binary combinations with different solvent systems being suitable for different drugs, suggesting the need for optimization of the vehicle system for individual drug (Gorukanti, Li, & Kim, 1999; Kikwai, Kanikkannan, Babu, & Singh, 2002; Panchagnula et al., 2001).

Accordingly, the primary objective of this study was to select the best vehicle system as the first step in the optimization of transdermal delivery of tadalafil. The study used six of the commonly used vehicles in pure form. These were evaluated for solubilizing capacity and transdermal delivering efficiency. Binary systems of selected vehicles were also evaluated. The binary systems were prepared by mixing the vehicle producing the highest transdermal drug flux with another miscible vehicle dissolving the greatest amount of the drug.

MATERIALS AND METHODS

Materials

Tadalafil was kindly provided by Saudi Pharmaceutical Industries & Medical Appliances Corporation (SPIMACO), Al-Qassim, Saudi Arabia. IPM, PEG 400, and EO were obtained from Fluka AG, Buchs, Switzerland. Ethanol (96%), PG, methylparaben, acetonitrile (high-performance liquid chromatography [HPLC] grade), methanol (HPLC grade), and sodium dihydrogen phosphate were purchased from BDH, Poole, UK.

Solubility Studies

The saturation solubility of the drug in different vehicles was determined at 32°C. Excess drug was added to known volumes of solvents, and the mixtures were equilibrated by continuous mixing in a shaking water bath maintained at 32°C for 72 h. The excess drug was removed by centrifugation at $4753 \times g$ for 15 min. The supernatant was analyzed by HPLC after appropriate dilution.

Preparation of Skin Samples

Due to the difficulty of obtaining human skin samples, the rabbit ear model was used. This model was adopted to monitor the skin delivery of a variety of drugs from various vehicles and formulations (Corbo, Liu, & Chien, 1990; El Maghraby, 2008; Touitou, Dayan, Bergelson, Godin, & Eliaz, 2000). Full thickness skin obtained from the inner side of freshly excised ears of male rabbits, weighing 2–3 kg, was used. The skin was peeled from the underlying cartilage after cutting along the tips of the ears. The skin samples were mounted immediately on the diffusion cells (see below). The study was conducted using 12 rabbits in six permeation experiments.

Skin Permeation Studies

The FDC-6 Transdermal Diffusion Cell Drive Console (Logan Instrument Corp., Somerset, NJ, USA) was employed. The skin was mounted with the stratum corneal side uppermost on the vertical glass diffusion cells. These cells provided a diffusional area of 1.7 cm^2 and the receptor compartment was 12 mL. To ensure sink conditions, 30% (vol/vol) ethanol in water was used as a receptor. Ethanolic receptor with up to 50% (vol/vol) ethanol was employed to monitor skin delivery of lipophilic drugs (El Maghraby et al., 1999; El Maghraby, Williams, & Barry, 2000). The system was adjusted to ensure that the skin surface was maintained at 32 ± 1°C to mimic in vivo conditions. The mounted skin was equilibrated overnight. The saturated drug solutions with excess drug crystals in each vehicle (2 mL) were applied to skin surface before occluding the donor compartments with parafilm. The excess crystals were included to maintain saturation throughout the permeation experiments, thus ensuring equal thermodynamic activity of the drug in all vehicles. Receptor samples were taken at predetermined time intervals (2, 4, 6, 8, 10, 24, and 27 h) after application and replaced with equal volumes of fresh receptor fluid. The sample volume taken was 2 mL for all time points except for those taken after 10 and 24 h for which we collected 5 mL samples. This was conducted to ensure adequate dilution of the receptor and thus maintaining the sink condition during the long time intervals. These samples were analyzed for the drug content by HPLC.

Chromatography

The drug concentrations in all samples were determined using HPLC analysis. This employed a high-pressure liquid chromatograph using Waters™ 600 controller (Waters Inc., Bedford, MA, USA) equipped with a variable wavelength UV-Vis detector (SPD-10 AV, Shimadzu, Kyoto, Japan) and an automatic sampling system (Waters™ 717). The mobile phase consisted of acetonitrile and 20 mM phosphate buffer (pH 7) (38:62), and the flow rate was 1 mL/min. Separation was achieved using a 15 cm × 3.9 mm (i.d.) C_{18}, μ Bondapak™, Waters, reversed phase column with an average particle size of 10 μm, and the column was kept at ambient temperature. The column effluent was monitored at 290 nm, and the chromatographic data analysis was performed with the Millinium™ Program (Waters). Methylparaben was used as the internal standard.

The samples were suitably diluted with a mobile phase before addition to test tubes spiked with the internal standard in an amount sufficient to produce a concentration of 5 μg/mL. The tubes were vortex mixed for 2 min before loading into the HPLC vials and injecting 30 μL into the HPLC. The retention time of the internal standard was 3.4 min with tadalafil being eluted after a retention time of 7.2 min.

Data Analysis

The cumulative amounts of the drug permeated with time produced the permeation profiles. These were typical steady-state profiles that are expected after occlusive application of saturated systems (Figure 2). These profiles were used to calculate the transdermal drug flux, which was obtained from the slope of the regression line fitted to the linear portion of the profile. Extrapolation of this line will intercept with the *x*-axis at a time equal to the lag time. The permeability coefficient K_p was calculated according to the following equation (Barry, 1983):

$$J = K_p C$$

where J is the steady-state flux and C is the drug concentration in the donor.

Data were expressed as a mean of three experiments ± the standard deviation. Data were analyzed by one-way analysis of variance using SPSS® statistical package (version 10, 1999, SPSS Inc., Chicago, IL, USA). Statistical differences yielding $p \leq .05$ were considered significant. Tukey's multiple-comparison post hoc tests were applied.

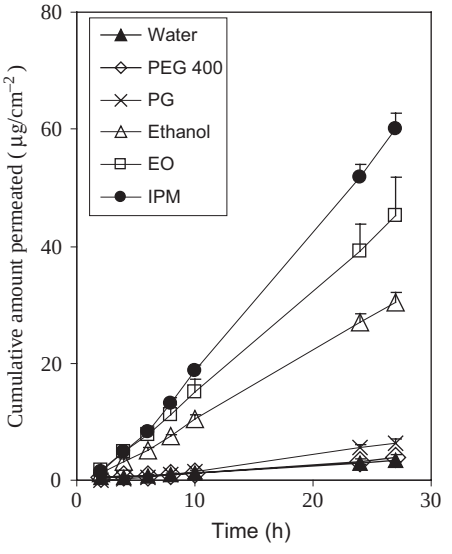

FIGURE 2. The transdermal permeation profiles obtained after application of tadalafil saturated solutions in different vehicles.

RESULTS AND DISCUSSION

Solubility of Tadalafil

The saturation solubility of tadalafil in pure vehicles and in the binary combinations was determined at 32°C to mimic the skin permeation experimental conditions. This will allow correlation between the solubility and transdermal permeability. The solubility data together with the transdermal permeation parameters are presented in Tables 1–3. Considering the pure vehicles, PEG 400 produced the greatest solubility which was significantly higher than that obtained in the other tested vehicles with water producing the lowest solubilization capacity for the drug (Table 1). PG and ethanol showed statistically similar solubilization power that was higher than that obtained with

TABLE 1
The Solubility of Tadalafil in Pure Vehicles and the Transdermal Permeation Parameters Obtained After Occlusive Application of Saturated Solutions of Tadalafil in These Vehicles to Full Thickness Rabbit Skin In Vitro

Vehicle	Solubility (mg/mL)	Flux ($\mu g/cm^2$ h)	Lag time (h)	$K_p \times 10^3$ (cm/h)
Water	0.0182 (0.0007)	0.131 (0.024)	1.15 (0.217)	7.18 (1.3)
PG	2.89 (0.082)	0.289 (0.034)	4.13 (0.400)	0.10 (0.012)
PEG 400	20.18 (0.95)	0.155 (0.028)	2.08 (0.68)	0.0078 (0.0012)
Ethanol	2.75 (0.009)	1.18 (0.14)	1.20 (0.39)	0.429 (0.005)
Ethyl oleate	0.515 (0.06)	1.79 (0.41)	1.65 (0.29)	3.48 (0.80)
IPM	0.132 (0.007)	2.45 (0.12)	2.03 (0.52)	18.6 (0.94)

Values between brackets are *SD*.

TABLE 2
The Solubility of Tadalafil in Ethanol/IPM Binary Mixtures and the Transdermal Permeation Parameters Obtained After Occlusive Application of Saturated Solutions of Tadalafil in These Vehicles to Full Thickness Rabbit Skin In Vitro

Ethanol/IPM	Solubility (mg/mL)	Flux ($\mu g/cm^2$ h)	Lag time (h)	$K_p \times 10^3$ (cm/h)
0:1	0.132 (0.007)	2.45 (0.12)	2.15 (0.32)	18.6 (0.94)
1:2	2.10 (0.27)	5.37 (0.99)	1.29 (0.18)	2.56 (0.47)
1:1	2.63 (0.28)	9.08 (1.6)	0.865 (0.52)	3.45 (0.60)
2:1	3.26 (0.10)	11.38 (2.1)	1.25 (0.64)	3.49 (0.63)
1:0	2.75 (0.009)	1.18 (0.14)	1.20 (0.39)	0.429 (0.005)

Values between brackets are *SD*.

TABLE 3
The Solubility of Tadalafil in Ethanol/Ethyl Oleate Binary Mixtures and the Transdermal Permeation Parameters Obtained After Occlusive Application of Saturated Solutions of Tadalafil in These Vehicles to Full Thickness Rabbit Skin In Vitro

Ethanol/ethyl oleate	Solubility (mg/mL)	Flux ($\mu g/cm^2$ h)	Lag time (h)	$K_p \times 10^3$ (cm/h)
0:1	0.515 (0.06)	1.79 (0.41)	1.65 (0.29)	3.48 (0.80)
1:2	2.56 (0.11)	7.92 (0.16)	1.36 (0.16)	3.09 (0.06)
1:1	2.76 (0.10)	8.04 (1.2)	1.31 (0.28)	2.91 (0.45)
2:1	3.43 (0.06)	10.95 (1.8)	1.33 (0.20)	3.19 (0.52)
1:0	2.75 (0.009)	1.18 (0.14)	1.20 (0.39)	0.429 (0.005)

Values between brackets are *SD*.

EO and IPM. EO solubilized greater amounts than IPM. The solubility of the drug in binary systems containing ethanol at 2:1 ratios with EO or IPM was greater than that obtained with pure ethanol, EO, or IPM. This effect could be due to the cosolvency effect.

Transdermal Delivery of Tadalafil from Pure Solvents

Higuchi (1960) reported that vehicles containing a drug at the same thermodynamic activity should provide similar transdermal drug flux values provided that these vehicles have no effect on the skin. Any variation in the fluxes could imply an effect for the vehicle. Accordingly, to ensure equal thermodynamic activities, this study employed saturated drug solutions in different vehicles with excess crystals included to maintain saturation throughout the permeation experiments. This design will ensure that the variation in drug flux will be due to the effect of the vehicle. The transdermal permeation profiles of tadalafil from different vehicles are shown in Figure 2 with the calculated permeation parameters being presented in Table 1.

The permeation profiles (Figure 2) reflected the dependence of tadalafil transdermal permeation on the type of vehicle with the transdermal drug delivery from different vehicles ranked as IPM > EO > ethanol > PG > PEG > water. The calculated transdermal steady-state flux values (Table 1) revealed no significant difference between the IPM and EO ($p > .05$) with the IPM producing significantly higher flux compared with the rest of the solvents ($p < .001$). For EO, the flux was statistically similar to that obtained from ethanol ($p > .05$) with both fluxes being significantly higher ($p < .001$) than that obtained from PG, PEG, or water. PG produced a flux value higher than that obtained from either PEG or water. The flux obtained from PEG was similar to that obtained from water, which produced the smallest flux values in this study. Correlating these results with the solubility (Table 1), it is interesting to note that PEG, which solubilized the greatest amount of drug, produced a flux value similar to that of water, which solubilized the smallest amount of the drug. In addition, ethanol and PG solubilized similar amounts of the drug but produced different flux values. Furthermore, IPM, which produced the greatest flux, solubilized smaller amount of drug compared with all solvents except water (Table 1). This poor correlation between the flux and solubility is expected as the permeation process is governed by many other factors. For the drug to permeate through the skin, it has to be released from the vehicle before partitioning into and diffusion through the skin. The lower flux value obtained from PEG, which incorporated the greatest amount of drug, can be due to the high affinity of drug to the solvent in addition to the weak enhancing effect of PEG on skin permeation. The permeability coefficient (K_p) is a parameter depending both on the flux and on the solubility of the drug in the vehicle. IPM produced the highest K_p value compared with other tested solvents. The rank order of K_p was IPM > EO > water > ethanol > PG > PEG. Generally speaking, the K_p is inversely proportional to the solubility unless the solvent has strong penetration-enhancing effect. This is clear if we compare the K_p values of either IPM or EO to that of water. Similar trends for the effect of solvents on transdermal drug permeation have been previously obtained (Kikwai et al., 2002; Krishnaiah, Satyanarayana, & Karthikeyan, 2002; Rhee et al., 2007). The lag time data (Table 1) revealed no significant difference between the lag time values in cases of IPM, EO, ethanol, PEG, and water. The lag time is a permeation parameter depending mainly on the diffusivity of the drug through the skin with the lag time being reduced with increasing diffusivity. However, for diffusion to take place the drug has to release from the applied formulation and partition into the upper layers of the skin. The lag time can thus indirectly depend on the drug release as well (El Maghraby, 2008). This may explain comparable lag time from solvents with different enhancing properties. The longest lag time was obtained from PG despite of producing higher flux compared with PEG and water. This may be explained taking into consideration that the enhancing effect of PG is exerted by increasing the drug partitioning into the skin. To do this, PG has to partition into the stratum corneum (SC), accumulating into the intercellular and protein regions of SC changing its solubilization power with subsequent increase in the drug partitioning into the SC (Barry, 1987). This may explain the extended lag time.

Vehicles can enhance drug permeation by many mechanisms. They can increase the thermodynamic activity, they can increase the skin/vehicle partition coefficient, they can increase the solubilizing power of the skin to the drug, or they can reduce the barrier nature of the skin (Barry, 1987; Twist & Zatz, 1988). IPM has been reported to intervene with the lipid components of the SC making them more permeable (Gorukanti et al., 1999). Fatty acid esters such as EO are known to increase the fluidity of the SC lipids, increasing the skin permeability to drugs (Golden, McKie, & Potts, 1987). This explains the enhancing effects of IPM and EO. For ethanol, alternative mechanisms have been reported to explain its skin penetration-enhancing effect. These included extracting the SC lipids (Bommannan, Potts, & Guy, 1991) and fluidizing the lipid bilayers of the SC (Panchagnula et al., 2001) and thus altering the barrier nature of the skin. Ethanol was also reported to function as a solvent-type enhancer, which permeates through the skin and increases the partition of a drug into skin (Knutson, Krill, & Zhang, 1990).

Transdermal Delivery of Tadalafil from Binary Mixtures

Takahashi et al. (1991) highlighted that the important factors of increasing transdermal drug delivery is to select an oily solvent that has low affinity to the drug and to add a cosolvent that increases the drug concentration. Accordingly, IPM and EO, which produced the greatest flux, were selected as the oily vehicles and ethanol was used as the cosolvent. The latter was selected taking into consideration the miscibility with the oils,

the relatively higher solubilizing capacity compared with the oils, and enhancing effect.

The transdermal permeation profiles of tadalafil from different mixtures of ethanol with IPM are shown in Figure 3A with the calculated permeation parameters being presented in Table 2. The permeation profiles revealed that the transdermal delivery of tadalafil from ethanol/IPM binary mixtures is higher than that obtained from ethanol or IPM in the pure state with the delivery increasing with increasing ethanol concentration in the mixtures. The permeation parameters (Table 2) revealed significantly higher flux values from different binary mixtures compared with the pure solvents. The lag time was shorter in case of binary mixtures compared with that of IPM. This indicates improved diffusivity or increased drug release. The K_p values obtained from the binary mixtures were significantly reduced compared with that obtained from IPM. This can be attributed to the significant increase in the drug solubility. Contrary to these, K_p values were significantly higher than that obtained from pure ethanol. Comparing different binary mixtures, they were statistically similar with respect to the lag time and K_p. For the steady-state flux, however, there was no significant difference between 1:1 and 2:1 ethanol/IPM binary mixture, but their fluxes were significantly higher than that of 1:2 ethanol/IPM binary mixture.

The transdermal permeation profiles of tadalafil from different mixtures of ethanol with EO are shown in Figure 3B. The calculated permeation parameters are presented in Table 3. As for ethanol/IPM mixtures, the permeation profiles revealed higher transdermal delivery of tadalafil from ethanol/EO binary mixtures compared with pure ethanol or EO with the delivery increasing with increasing ethanol concentration in the mixtures. The permeation parameters (Table 3) revealed significantly higher flux values from different binary mixtures compared with the pure solvents. There was only a trend of reduction in the lag time from the binary mixtures relative to pure EO. The K_p of the drug from binary mixture were significantly increased compared with pure ethanol. This was the case even with the binary mixture containing 2:1 ethanol/EO, which solubilized higher amounts of the drug compared with pure ethanol. This further reflects the augmented penetration-enhancing effect of the binary mixture. Comparing different binary mixtures the flux increased with increasing ethanol concentration with comparable lag time and K_p values.

As for pure IPM or EO, there were no significant differences between the transdermal permeation parameters of tadalafil from the binary mixtures of ethanol/IPM and those obtained from the corresponding ethanol/EO binary mixtures. The structure–activity relationship of amphiphilic skin penetration enhancers has been reviewed (Vávrová, Zbytovská, & Hrabálek, 2005). It was reported that branching near the polar head group can decrease the enhancing potency by reducing the membrane-disrupting ability of the enhancer (Chantasart et al., 2004; Hrabálek, Vávrová, Dolezal, & Machácek, 2005). Taking this into consideration, we should expect lower penetration-enhancing efficacy

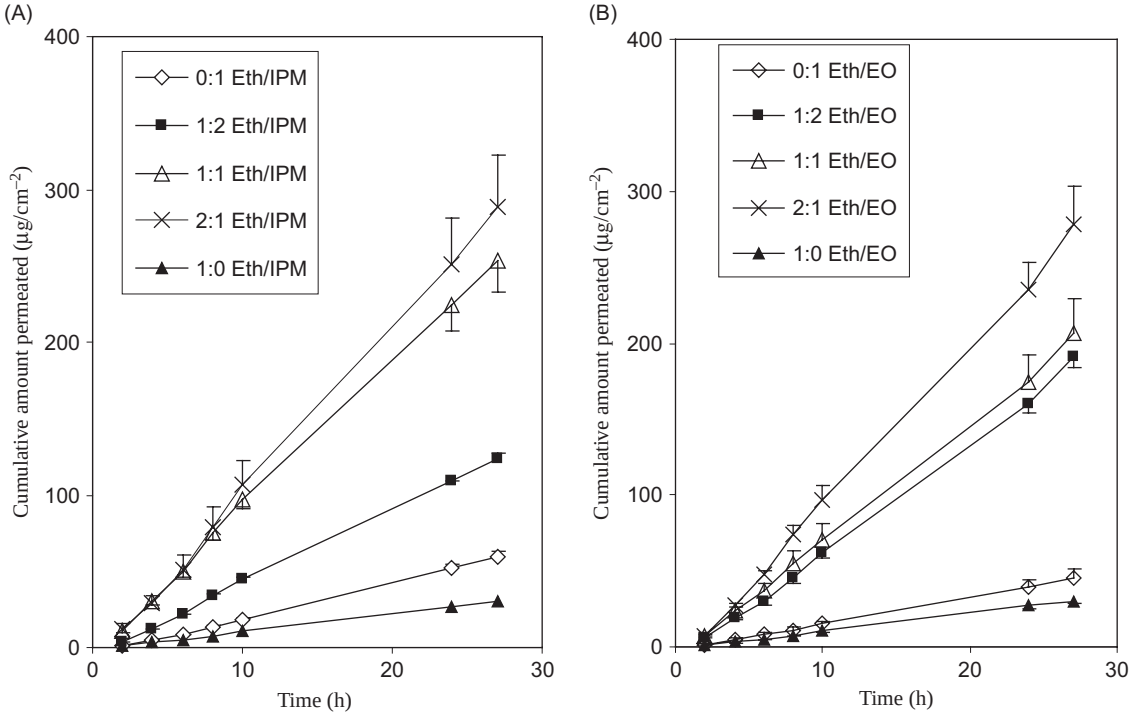

FIGURE 3. The transdermal permeation profiles obtained after application of tadalafil saturated solutions in different binary mixtures of ethanol with isopropyl myristate (A) or with ethyl oleate (B).

from IPM (with the branched isopropyl group) compared with EO. However, this was not the case in our study. This can be attributed to the fact that the overall transdermal delivery is a complex process depending not only on the penetration-enhancing potency of the vehicle but also on the release of the drug from the vehicle and its partitioning into the SC.

The marked enhancement in tadalafil transdermal delivery obtained from binary mixtures of ethanol with either IPM or EO compared with that obtained from the corresponding pure solvent demonstrated synergistic rather than the additive effect. Synergistic enhancement has been similarly reported in case of the IPM binary mixture with alkanols in the delivery of benztropine mesylate with the authors recording only additive effect in case of benztropine base (Gorukanti et al., 1999). The combination of lipophilic and hydrophilic vehicles is believed to improve the transdermal delivery (Panchagnula, Desu, Jain, & Khandavilli, 2005; Rhee et al., 2007). Ethanol/IPM binary systems increased the skin delivery of the lipophilic drug paclitaxil compared with the pure solvents. These systems were considered optimum as they combine the benefit of improved partitioning and diffusivity (Panchagnula et al., 2005). They concluded that one of the components of the binary systems must be miscible with both lipophilic and hydrophilic phases of the skin. Similar synergy was recorded between lipophilic and hydrophilic compounds with skin penetration enhancers being used at low concentrations rather than as solvents (Holas, Vávrová, Sima, Klimentová, & Hrabálek, 2006).

CONCLUSION

This study demonstrated a promising potential for transdermal delivery of tadalafil, but this requires further optimization. IPM and EO were the best pure vehicles for transdermal delivery of tadalafil. Their binary combinations with ethanol resulted in marked synergism. These binary mixtures provided the first step forward toward the development of pharmaceutically acceptable dosage form for transdermal delivery of tadalafil. The study added further emphasis on the feasibility of combining lipophilic vehicles with a cosolvent that combines the affinity to lipid and aqueous phases for transdermal drug delivery.

ACKNOWLEDGMENTS

The authors acknowledge the Research Center, College of Pharmacy, King Saud University for sponsoring this work.

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