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Effects of propylene glycol diesters of caprylic and capric acids (Miglyol® 840) and ethanol binary systems on in vitro skin permeation of drugs

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Summary

Miglyol® 840, propylene glycol diesters of caprylic and capric acids, in binary systems with ethanol markedly improved the in vitro skin permeation rate of several transdermal drug candidates such as tetrahydroaminoacridine (THA), diltiazem, atenolol, tazifylline and hydrocortisone, as compared to ethanol or Miglyol® 840 alone across human and hairless mouse skin. The addition of ethanol to Miglyol® 840 improved the drugs' skin permeation rates primarily as a result of increasing the drugs' solubility. The addition of ethanol to Miglyol® 840 also improved the relative permeation rate (permeation rate/initial concentration) of ethanol. No local irritation (erythema or edema) was noted over a 24 h period among four human volunteers wearing patches containing the binary vehicle, ethanol : Miglyol® 840 (20 : 80) or ethanol : Miglyol® 840 (40 : 60).

Introduction

The transdermal delivery of drugs usually requires the use of a safe and effective skin penetration enhancer to circumvent the low permeability of the skin. Several chemical agents have been reported to improve the skin permeation of drugs. These include alkanols (Friend et al., 1988; Tsuzuki et al., 1988), dimethylsulfoxides (Scheuplein, 1971), urea (Feldman and Maibach, 1974), Azone® (Stoughton, 1982), fatty acids (Cooper, 1984; Mahjour et al., 1989), alkyl esters (Friend et al., 1988), *N,N*-dialkyl-substituted amino acetates (Wong et al., 1989), soaps (Bettley, 1961), detergents and surfactants (Bettley, 1965), lecithins (Kato et al., 1987; Mahjour et al., 1990), polyethylene glycol monolaurates (Iyer et al., 1985), glycerol monolaurates (Cheng et al., 1988), pyrrolidone derivatives (Sasaki et al., 1991), and terpenes (Williams and Barry, 1991). Because of the safety issues such as toxicity, irritation, and sensitization, only a few of the above chemicals have been used in marketed transdermal products; and search for a safe and effective skin permeation enhancer continues.

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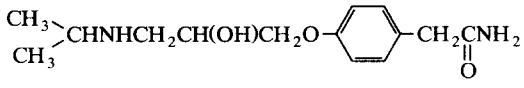
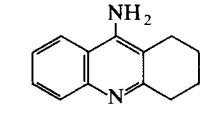
In the present study we evaluated the effects of propylene glycol diesters of caprylic and capric acids, Miglyol® 840, a non-irritating skin emollient (technical information provided by Dynamit Nobel of America), alone and in binary solvent systems with ethanol on the in vitro skin permeation of tetrahydroaminoacridine (THA, Tacrine®) and several other transdermal drug candidates of various chemical groups: diltiazem (vasodilator), atenolol (antihypertensive), tazifylline (antihistamine) and hydrocortisone (anti-inflammatory). The chemical structure and properties of the tested compounds are presented in Table 1. THA is a cholinergic agent that may be beneficial in the treatment of some of the amnesia characteristics associated with Alzheimer's Disease (Summers et al., 1981, 1986). Developing a transdermal system for THA may improve patient compliance especially in patients with impaired memory. The oral bioavailability of THA

TABLE 1

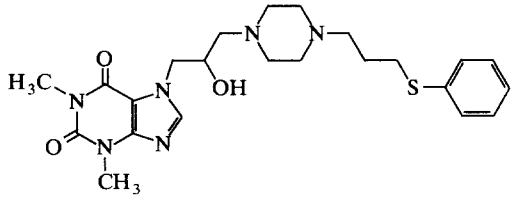
Chemical structure of the compounds tested



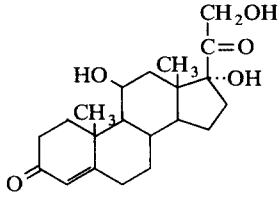
Atenolol
MW = 266.3
m.p. = 146–148°C
pK_a = 9.6
log PC (oct/water) = 0.23



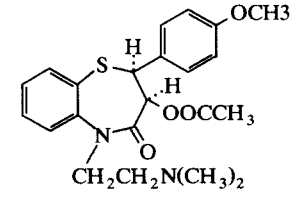
Tetrahydroaminoacridine (THA)
MW = 198.3
m.p. = 183–184°C
pK_a = 9.84
log PC (oct/buffer pH 7.4) = −0.5



Tazifylline
MW = 472.6
m.p. = 112°C
pK_a = 3.01, 7.52
log PC (oct/buffer pH 7) = 1.67



Hydrocortisone
MW = 362.5
m.p. = 214°C
log PC (oct/water) = 1.55



Diltiazem
MW = 414.52
m.p. = 187–188°C
pK_a = 7.7
log PC (oct/buffer pH 7.5) = 2.2

is reported to be low and variable ranging between 5.5 and 36% (Hartvig et al., 1990). Prolonged oral use of this agent may cause transaminase to build up in the liver among the geriatric patients (Summers et al., 1980). A transdermal product for this drug may reduce such an adverse effect.

Experimental

Materials

Miglyol® 840 (MIG) (lot 86125C) was obtained from Dynamit Nobel of America Inc. (Stony Point, NJ). Miglyol® 840 is the propylene glycol diester of saturated vegetable fatty acids of chain-length C_8–C_{10} and contains 65–80% caprylic acid and 15–30% capric acid. Tetrahydroaminoacridine was obtained from Warner-Lambert (Ann Arbor, MI) and tazifylline hydrochloride from Syntex Laboratories, Inc. (Palo Alto, CA). Tazifylline base was prepared from its hydrochloride salt by extraction from an alkalized salt solution with methylene chloride. Atenolol was obtained from Erregiere Industria Chemica (San Paolo D'Argon [BG], Italy), diltiazem from Fermion (Orion Corporation Ltd, Espoo, Finland), hydrocortisone from Berlichem (Wayne, NJ) and 95% ethanol (ET) USP grade from Quantum Chemical Co. (Cincinnati, OH). All other chemicals were of analytical grade. Standard static Franz® diffusion cells, FDC-100 (8 ml volume and 1.76 cm^2 surface area), were purchased from Crown Glass Co. (Somerville, NJ). The cells were equipped with a teflon O-ring and a magnetic stir bar to provide 600 rpm stirring. Hairless mice (SKH : hr-1, 8–10 weeks old) were purchased from the Skin Cancer Hospital, Temple University (Philadelphia, PA). The mice were killed by spinal cord dislocation at the neck, and the abdominal and dorsal sections of the skin were excised from the animals with surgical scissors. The adhering fat and other debris were removed carefully from the skin undersurface with tweezers. Human cadaver skin of a 69 year old male, leg portion (this skin was used for THA studies) and a 72 year old female, abdominal portion (this skin was used for diltiazem studies), was obtained from a local hospital and was frozen and stored at −20°C for about 3 months and 2 weeks, respectively, before use. After thawing, the skin was dermatomed (Padgett Co., Kansas City, MO) at a thickness of approx. 50 μm and cut into sections of about 4 cm^2 surface area. Some of these skin sections were then tape stripped 50 times with 3M Scotch cellophane tape (3M Co., St. Paul, MN) to remove the stratum corneum layer.

Preparation of prototype patch

Prototype patches of 2.5 and 2 cm^2 surface area were prepared similar to that reported previously (Rashidbaigi and Mahjour, 1989) for irritation and permeation studies, respectively. The patch for irritation study (placebo patch) was fabricated from six layers: a 3M acrylic adhesive foam pad (3M Co., St. Paul, MN); a 3M impervious backing aluminum disc with an EVA lining; a drug-absorbing non-woven fabric pad (70% rayon and 30% polyester from Du Pont, Inc.); a 3M polyethylene microporous membrane (gurly number of 24 s/50 ml); a 3M release liner ring siliconized on one side and polyethylene coated on the other side; and a protective cover, lined with a heat-sealable coating called Surlyn® (James River Co., San Leandro, CA). 50 $\mu l/cm^2$ of solvent system was absorbed to the non-woven pad which was situated over the slightly larger impervious aluminum disc. The microporous membrane was then placed on the pad, and its periphery was heat sealed to the backing membrane. The sealed component was placed on the center of the adhesive foam (the backing membrane toward the foam), and the release liner ring was placed around the sealed component on the adhesive foam. The aluminum protective cover was placed on the sealed component and was heat sealed to the rim of the backing membrane to prevent the loss of the solvent. The active patch of 2 cm^2 surface area was prepared for diffusion study, without adhesive pad, similar to the placebo patch using 50 $\mu l/cm^2$ of saturated drug solution in the binary solvent systems ET : MIG (40 : 60) or ET : MIG (20 : 80).

Permeation studies

Excised full-thickness human or hairless mouse skin and standard static Franz® diffusion cells

were used in all experiments. The skin was sandwiched between the two diffusion half-cells, with stratum corneum facing the donor compartment. To remove extraneous debris and leachable enzymes, the lower compartment, the receiver side, was filled with warm (37°C) normal saline and stirred for 2 h. The receiver fluid was replaced with fresh, warm receiver solution before beginning the permeation studies. 1 ml of saturated drug solution or of drug suspension (saturated drug solution with a few drug crystals) or an active patch was placed on the stratum corneum in the donor compartment ($n = 2$–4). The donor compartment was covered with cellophane and Parafilm® (American Can Co., New York, NY) to minimize the evaporation of alcohol and to prevent the loss of vehicle during refilling of the receiver compartment (to eliminate air bubbles which were usually trapped under the skin, the diffusion cells have to be tilted during refilling). Normal saline solution was used as the receiver solution for THA, atenolol, diltiazem, and hydrocortisone. Isotonic citrate phosphate buffer pH 4.6 was used for tazifylline. The buffer was chosen to improve the solubility of tazifylline so as to provide sufficient sink conditions. To maintain the concentration of drug in the receiver solution as low as possible, the entire receptor fluid was removed and replaced with fresh receiver solution at predetermined time intervals (every 1.5 or 2 h except for overnight samples). The concentrations of drug and ethanol in the receiver samples were determined by HPLC and GC, respectively. A brief description of the analytical HPLC methods is provided in Table 2. A Hewlett-Packard (HP) 5890 GC equipped with a flame ionization detector attached to an HP 7673A automatic sampler, an HP 3393A integrator, an HP 7673A controller, and an HP 9122 dual disc drive was used for analysis of alcohol in the receiver samples. The GC operation conditions were as follows: column, Glass column 6 ft × 2 mm i.d. packed with 100/120 Porapack® QS; flow rate, 50 ml/min (helium); column temperature, 170°C; injection temperature, 220°C; detection temperature, 250°C; retention time, about 1.2 min.

Preliminary skin irritation test

In a limited skin irritation test, three human volunteers, two females and one male, were tested

TABLE 2

Reverse phase HPLC assay methods for analysis of the drugs tested in skin diffusion samples

Compound	λ_{max} (nm)	HPLC column	Mobile phase	Flow rate (ml/min)	RT (min)
THA	240	Supelco LC-18-DB 150 × 4.6 mm 5 μm	85 : 15 0.05 M TEA pH 3: ACN	2	3.2
AT	225	Altex ODS 250 × 4.6 mm 5 μm	85 : 15 0.1% H_3PO_4 pH 3: ACN	1.5	5.4
DI	236	Supelco CN 33 × 4.6 mm 3 μm	35 : 35 : 30 0.05 M $NH_4H_2PO_4$ pH 3 : water : ACN	1.5	2.0
HC	248	Supelco LC-18-DB 33 × 4.6 mm 3 μm	47 : 35 : 18 0.05 M KH_2PO_4: methanol : ACN	1.0	1.5
TZ	257	Zorbax CN 250 × 4.6 mm 5 μm	30 : 70 ACN : 0.05 M $NH_4H_2PO_4$	1.5	4.0

RT, retention time; THA, tetrahydroaminoacridine; AT, atenolol; DI, diltiazem; HC, hydrocortisone; TZ, tazifylline; ACN, acetonitrile; TEA, triethylamine.

with four patches (2.5 cm^2 surface area) containing 50 $\mu l/cm^2$ of the 95% ethanol: Miglyol® 840 (ET: MIG, 20:80) binary solvent system. These patches were applied to the lower dorsal section of the female volunteers' left forearms and both arms of the male volunteer. The patches remained in contact with the skin for a period of 24 h. Similarly, one human male was tested with four patches (2.5 cm^2 surface area) containing 50 $\mu l/cm^2$ of 95% ethanol: Miglyol® 840 (40:60). At the conclusion of the test and at 24 h afterwards, the skin was examined for gross signs of irritation, erythema or edema, over the contact surfaces.

Solubility measurement

The solubility at room temperature or 32°C was estimated by adding excess drug to the solvent systems, followed by several minutes of sonication. After shaking for about 3 h at room temperature or 32° C, the solutions were filtered through nylon filters (0.45 μm) and assayed by HPLC.

Data analysis

Due to the permeation of ethanol from the donor solution (see Table 5) and, as a result, a continuous change in drug solubility, steady state permeation rates could not be established. Given this condition, the average permeation rate (24 h average, APR) was calculated by dividing the total amount of drug that permeated into the receiver solution in 24 h by 24 and by the surface area of the skin.

Results and Discussion

Fig. 1 and Table 3 show the in vitro permeation of THA across human skin from ET: MIG (40:60 w/w), ethanol and Miglyol® 840. The solubility of THA in alcohol is about 18-times more than that in Miglyol® 840, but the average permeation rate from the drug saturated solution (suspension) in alcohol is only about 1.5-times more than the average permeation rate from the saturated solution (suspension) of THA in Miglyol® 840. The addition of ethanol to Miglyol® 840 resulted in a greater than 20-fold increase in THA solubility and a 2-fold increase in its average permeation rate as compared to the saturated solution (suspension) in Miglyol® 840 alone (Fig. 1). Stripping the skin further improved the drug's permeation indicating that the stratum

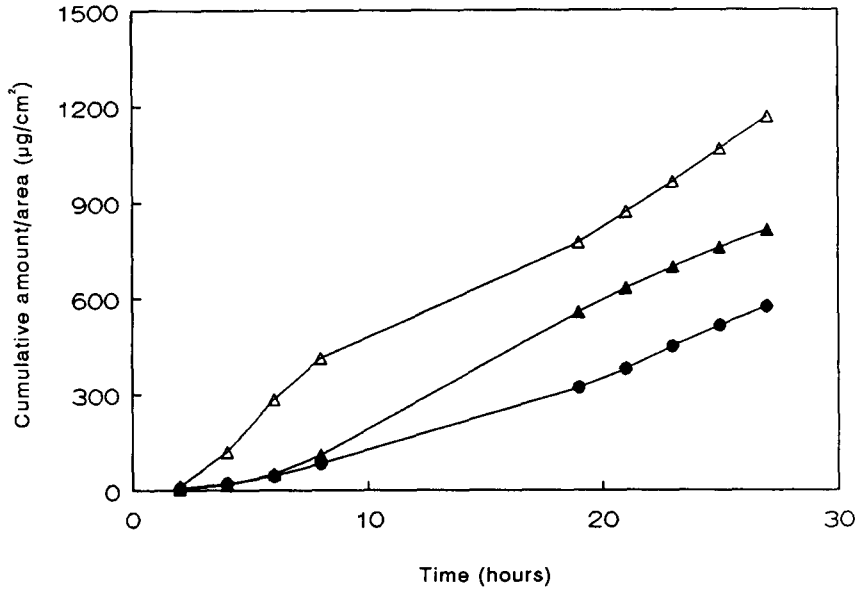


Fig. 1. Permeation of tetrahydroaminoacridine from ET: MIG (40:60), ethanol, and Miglyol® 840 solutions across human skin ($n = 2$). (△) 95% ethanol: Miglyol® 840 (40:60), (▲) 95% ethanol, (●) Miglyol® 840.

TABLE 3

In vitro permeation of THA (n = 2) from ET:MIG, ethanol and Miglyol® 840 saturated solutions [a] across human skin

Solvent system	APR [b] (μg/cm^2 per h)	Sol_0 [d] (mg/ml)	APR/Sol_0 ($\times 10^5$) (cm/h)
ET:MIG 40:60	42.2	270.60	15.6
ET:MIG 40:60	92.5 [c]	270.60	34.2
ET	29.9	218.30	13.7
MIG	19.8	12.01	164.9

MIG, Miglyol® 840; ET, 95% ethanol.
[a] The solutions contained some drug crystals.
[b] Average permeation rate over 24 h; individual values were within 25% of the average.
[c] Skin was tape stripped 50 times with 3M Scotch cellophane tape to remove the stratum corneum layers.
[d] Solubility at 32°C.

corneum is the rate limiting barrier for THA permeation (Table 3). An average permeation rate of about 42 μg cm^{-2} h^{-1} ($\sim$ 1 mg cm^{-2} 24 h^{-1}) was obtained for THA across human skin using the MIG : ET (60 : 40) binary solvent system.

Table 4 shows the in vitro skin permeation data for other compounds studied using hairless mouse skin and saturated donor solutions. The APRs for atenolol, diltiazem, hydrocortisone and tazifylline increased upon the addition of ethanol to Miglyol® 840. No correlation between improvement in average permeation rate and melting point (range 112–214°C), molecular weight (range 198–472), pK_a (range 7.5–9.8 and higher) or partition coefficient (log PC -0.5 to $+2.2$)

TABLE 4

In vitro permeation of atenolol, diltiazem, hydrocortisone and tazifylline (n = 2–4) from ET:MIG, ethanol, and Miglyol® 840 saturated solutions across hairless mouse skin

Compound	Solvent system	APR [a] (μg/cm^2 per h)	Sol_0 [b] (mg/ml)	APR/Sol_0 ($\times 10^4$) (cm/h)
AT	ET:MIG (20:80)	233.4	11.0	212.2
	ET	62.8	100.0	6.3
	MIG	59.9	9.0	66.5
DI	ET:MIG (20:80)	49.3	142.8	3.5
	ET	16.3	250.1	0.6
	MIG	35.8	32.0	11.2
HC	ET:MIG (20:80)	7.8	7.9	9.8
	ET	0.7	22.7	0.33
	MIG	1.4	0.6	23.7
THA	ET:MIG (20:80)	1632.1	146.3	111.6
	ET	677.0	197.3	34.3
	MIG	234.5	10.7	219.2
TZ	ET:MIG (20:80)	238.9	52.1	45.9
	ET	6.6	57.2	1.2
	MIG	36.5	3.1	117.7

AT, atenolol; DI, diltiazem; HC, hydrocortisone; TZ, tazifylline; MIG, Miglyol® 840; ET, 95% ethanol.
[a] Average permeation rate over 24 h; individual values were within 20% of the average.
[b] Solubility at room temperature.

TABLE 5

In vitro permeation of diltiazem and ethanol from ET:MIG solvent systems across human skin (n = 2–4)

ET:MIG (w/w)	Diltiazem			Ethanol		
	APR [a] (μg/cm^2 per h)	Sol [b] (mg/ml)	APR/Sol_0 ($\times 10^5$) (cm/h)	APR [a] (mg/cm^2 per h)	C_0 [c] (mg/ml)	APR/C_0 [d] ($\times 10^3$) (cm/h)
00:100	3.1	26.1	11.9	0.0	0.0	0.0
10:90	11.3	85.9	13.2	1.4	90.0	15.0
20:80	10.7	136.3	7.9	2.2	174.8	12.4
40:60	12.4	195.5	6.3	3.8	348.0	10.8
80:20	3.7	254.9	1.4	2.1	666.6	3.1
100:00	2.0	227.0	0.9	2.0	816.0	2.4

[a] Average permeation rate over 24 h; individual values were within 20% (within 25% for ethanol) of the average.
[b] Solubility at room temperature.
[c] Calculated concentration of 95% ethanol.
[d] Average permeation rate of ethanol divided by initial ethanol concentration.

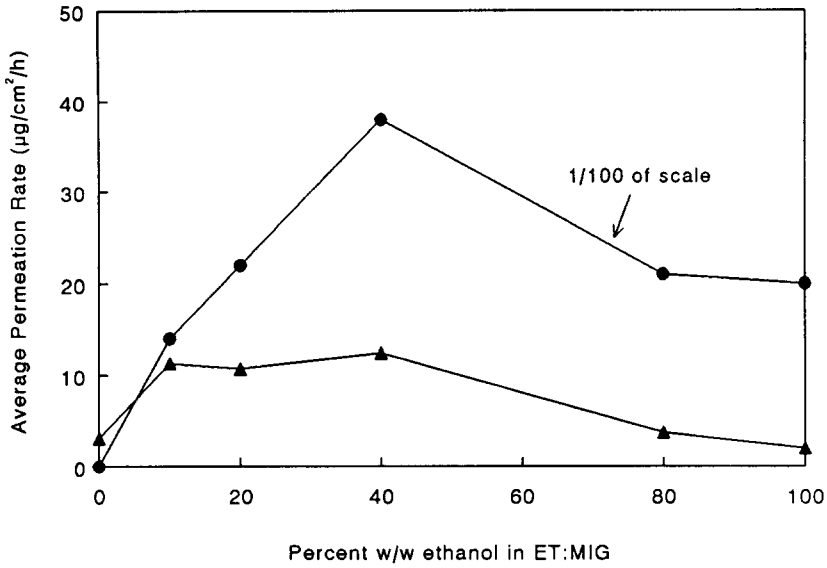


Fig. 2. Effects of increasing ethanol concentration in ET:MIG on the diltiazem and ethanol average permeation rates across human skin ($n = 2$–4). (▲) Diltiazem, (●) ethanol.

was found for the tested compounds. These findings may indicate a non-discriminative enhancement effect as a result of a reduction in the stratum corneum diffusional resistance. The reduction in the stratum corneum diffusional resistance may be caused by an increase in the stratum corneum lipid fluidity or the extraction of the stratum corneum's lipids by Miglyol® 840 and the ET:MIG vehicles. At present, the exact mechanisms are not known, and further experi-

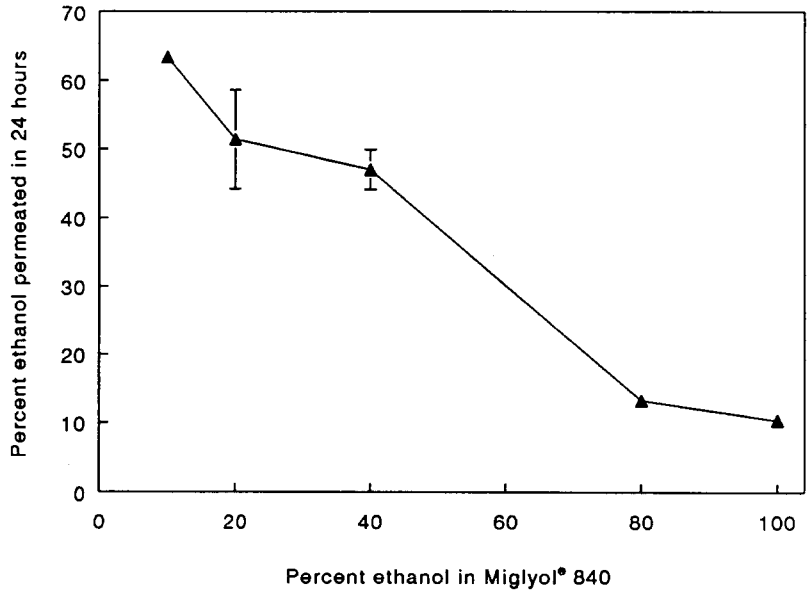


Fig. 3. Effect of increasing percentage of ethanol in ET:MIG on the percent dose of ethanol (±S.D., only for 20 and 40% ethanol) permeated in 24 h across human skin ($n = 2$–4).

ments are required to explain the mechanism of enhancement by Miglyol® 840 and the ET:MIG mixture.

Table 5 and Fig. 2 show the effects of increasing the percentage of ethanol in ET:MIG systems on the APRs of diltiazem and alcohol across human skin. The optimum ET:MIG ratio for the permeation of diltiazem was about 40:60 w/w. Fig. 3 shows the percent of ethanol permeated across human skin in 24 h from the ET:MIG donor solutions of diltiazem indicated in Table 5.

Although the quantity of drug in the donor compartment was high and for most of the tested compounds only a fraction of the total dose permeated the skin in 24 h, the steady state permeation rates were not achieved with the binary systems. This may be attributed to: (a) the depletion of ethanol from the donor compartment due to its permeation, (b) changes in drug solubility because of alcohol depletion from and back diffusion of water into the donor compartment, (c) changes in drug partitioning and as a result changes in drug permeability coefficient, and (d) time dependent enhancement effects of the enhancer systems. The higher permeation rates observed for diltiazem from the binary systems as compared to the Miglyol® 840 solution alone (Table 5) may be primarily due to an increase in diltiazem solubility. Table 5 shows that the addition of Miglyol® 840 to ethanol also increased the permeation rate of ethanol 2-fold at 60% Miglyol® 840. It is also apparent that the permeation rates of diltiazem and ethanol are dependent on the composition of the solvent system.

No local irritation (erythema or edema) was noted for the four volunteers wearing placebo patches (free of drug) containing binary vehicles, ET:MIG (20:80) or ET:MIG (40:60), for 24 h. The in vitro skin permeation results for ethanol and THA from similar patches but containing THA indicated that THA and ethanol were readily released from the patches and permeated the skin. The THA 24 h average permeation rate from the patch containing ET:MIG (20:80) was about 1600 $\mu g\ cm^{-2}\ h^{-1}$ across hairless mouse skin and about 40 $\mu g\ cm^{-2}\ h^{-1}$ from the patch containing ET:MIG (40:60) across human skin as compared to 42 $\mu g\ cm^{-2}\ h^{-1}$ from the ET:MIG (40:60) solution across human skin. These results indicate that the THA release from the patches is not the rate limiting step.

Conclusions

This study shows that Miglyol® 840 alone and in combination with ethanol is a good skin permeation enhancer with favorable skin irritation characteristics. The addition of ethanol to Miglyol® 840 improves the skin permeation rate of tetrahydroaminoacridine, diltiazem, atenolol, tazifylline, and hydrocortisone mainly by increasing the drugs' solubility. The ethanol:Miglyol® 840 binary systems effectively improve the permeation rate of drugs across human skin. In addition, the ethanol:Miglyol® 840 (20:80 or 40:60) binary systems show no evidence of skin irritancy in humans. Due to the loss of ethanol during the permeation process and the back diffusion of water into the donor compartment, the true steady-state permeation rates cannot be achieved with the binary systems. THA can be delivered at a rate of about 1 mg $cm^{-2}\ day^{-1}$ from an ethanol Miglyol® 840 binary system across human skin.

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