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RESEARCH ARTICLE

Effects of vehicles on the percutaneous absorption of donepezil hydrochloride across the excised hairless mouse skin

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Abstract

Objectives: This study aimed to examine the feasibility of developing donepezil transdermal delivery systems (TDSs).

Methods: Solution and pressure-sensitive adhesive (PSA) TDS were formulated using various vehicles and fatty acids, and the *in vitro* permeation study was conducted using the hairless mouse skin.

Key findings: Permeation fluxes (μg/cm^2/h) from solution formulations were generally low (0.05–3.40), except for formulations including isopropyl alcohol (IPA, 51.19), ethyl alcohol (27.32) and water (24.07). Dose-dependent permeation fluxes were obtained ($r^2 = 0.9754$). Even though the addition of fatty acids to IPA failed to increase donepezil permeation rates, it shortened lag times. Compared to those from solution formulations, permeation profiles from PSA TDS were totally different, and penetration rates were considerably low. PSA TDS comprising diethylene glycol monoethyl ether (DGME)-propylene glycol monolaurate (PGML) co-solvents (40:60) showed the highest permeation flux (0.10 ± 0.0024 μg/cm^2/h).

Conclusions: IPA-containing solution formulations and DGME-PGML (40: 60)-containing PSA TDS were found to be favorable candidates for donepezil transdermal delivery.

Keywords: Donepezil hydrochloride, solution formulations, pressure-sensitive adhesive transdermal delivery systems, vehicles, fatty acids

Introduction

Donepezil hydrochloride, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl] -1*H*-inden-1-one hydrochloride, is a piperidine-based, reversible inhibitor of acetylcholine esterase (AChE)[1]. It has been reported that donepezil hydrochloride is effective in the treatment of cognitive impairment and memory loss in patients with Alzheimer's disease[2].

Alzheimer's disease is a progressive neurodegenerative disorder characterized by the depletion of high-affinity nicotinic acetylcholine receptors[3] and marked loss of cholinergic neurons[4]. Donepezil hydrochloride is postulated to exert its therapeutic effects by enhancing the cholinergic function via the increment of the concentration of acetylcholine through the reversible inhibition of its hydrolysis by AChE.

Reviews of long-term cholinesterase inhibitor trials have concluded that the benefits of continued treatment could be maintained for 3–4 years[5,6]. However, although good adherence is required to slow disease progression and improve quality of life[7], non-compliance with oral agents has been a common problem, with the duration of Alzheimer's disease treatment rarely exceeding even 1 year[8]. To overcome the non-compliance problems, transdermal delivery systems (TDSs) could be an alternative dosage regimen[8,9]. In addition, the advantages of transdermal delivery are as follows: the avoidance of metabolism by oral administration and the constant maintenance of plasma drug concentrations. Among cholinesterase inhibitors, rivastigmine is the only drug to be studied for transdermal delivery[7]. No study has been carried out for the transdermal delivery of donepezil.

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Many studies have reported that pure vehicles including alcohol-, ester-, and ether-type solvents and co-solvents, with or without permeation enhancers, increased skin penetration of many drugs[10–12]. The hypothesis of this study is that those vehicles could enhance donepezil transdermal delivery.

The objective of this study was, therefore, to provide preliminary data for the transdermal delivery of donepezil by examining effects of vehicles and fatty acids on the permeation of donepezil hydrochloride from solution formulations and pressure-sensitive adhesive (PSA) TDS using the hairless mouse skin.

Materials and methods

Animals

Male hairless mice aged 6–8 weeks were purchased from Orient Bio Inc. (Sungnam, Korea). The animal studies were carried out according to the Principles for Biomedical Research Involving Animals developed by the Council for International Organizations of Medical Sciences.

Materials

Donepezil hydrochloride monohydrate was kindly provided by CJ Cheiljedang Co. (Seoul, Korea). Propylene glycol monolaurate (PGML), propylene glycol laurate (PGL), propylene glycol monocaprylate (PGMC), diethylene glycol monoethyl ether (DGME), oleoyl macrogol-6 glycerides (LBF 1944) linoleoyl macrogol-6 glycerides (LBF 2125), and polyethylene glycol-8 glyceryl linoleate (LBF 2609) were obtained from Gattefossé (Gennevilliers Cedex, France). Oleyl alcohol (OAl), polyethylene glycol 400 (PEG 400), propylene glycol (PG), isopropyl alcohol (IPA), ethanol, and *n*-octanol were purchased from Duksan Pure Chemicals Co., Ltd. (Ansan, Korea). Isopropyl myristate (IPM), caprylic acid, capric acid, lauric acid, oleic acid, and linoleic acid were purchased from Sigma Chemical Co. (St. Louis, MO). Acetonitrile and methanol used were of high-performance liquid chromatography (HPLC) grade (J.T. Baker Inc., Phillipsburg, NJ). Acrylic PSA solutions in organic solvents which were Duro-Tak® 87–2196 (copolymer: acrylatevinylacetate, functional group: -COOH, 45% solution of self-crosslinking acrylic copolymer, 3000 cps, solubility parameter 16) and Duro-Tak® 87–2510 (copolymer: acrylate, functional group: -OH, 40.5% solution of non-crosslinking acrylic copolymer, 4500 cps, solubility parameter 16) were obtained from National Starch and Chemical Company (Bridgewater, NJ). Other reagents were of analytical grade.

Analysis

Samples were analyzed through the HPLC method[13]. The HPLC system consisted of a pump (G1311A), with a detector (G1315A) set at 270 nm and an integrator (G1313A, Agilent Technologies, Inc., Santa Clara, CA). A Luna 5 μ C18 column (150 × 4.6 mm, Phenomenex, Torrance, CA) was used. The mobile phase consisted of phosphate buffer (0.02 M), percholoric acid (6 M), and acetonitrile (59.5:0.5:40, v/v) and was delivered at a flow rate of 1.0 mL/min at 40°C[14]. The injection volume was 40 μL. The internal standard used was naproxen sodium (20 μg/mL in methanol). A calibration curve was constructed based on peak area measurements.

Solubility determination

An excess amount of donepezil hydrochloride was added to various pure solvents or IPA with various enhancers and shaken at 37°C for more than 48 h. The solutions were then filtered by a Polyvinyledene Difluoride syringe filter (0.45 μm; Whatman International Ltd, Maidstone, Kent, UK), and the supernatant was assayed by HPLC after appropriate dilution.

Partition coefficient determination

n-Octanol and water were saturated in each other before the experiment. Donepezil hydrochloride solution (50 μg/mL) was prepared with water saturated with *n*-octanol. Two milliliter of this solution was then transferred to a 15 mL centrifuge tube containing 2 mL of *n*-octanol saturated with water. The tube was vortexed for 10 min and centrifuged at 4500 rpm for 10 min. After centrifugation, 40 μL was withdrawn from the water phase and *n*-octanol phase, respectively, and the intrinsic P_c was determined by HPLC.

Preparation of donepezil TDSs

Acrylic adhesive solutions were prepared by mixing 0.5 mL of 20 mg/mL donepezil hydrochloride solutions in various vehicles with 2.5 g of acrylic solution. PSA TDSs were prepared by casting the solutions above onto polyester release liner coated with silicone (Gelroflex ALU-PET 100 μ-2S DR, 3M, St. Paul, MN) using a casting knife. The area and thickness of the cast solution were 5 × 8 cm and 0.6 mm per 3 g solution, respectively. They were set at room temperature for 10 min to evaporate the solvents and then were oven-dried at 90°C for 20 min to remove the residual organic solvents. The dried film was transferred onto a backing film (Scotchpak 1109, 3M, St. Paul, MN).

Procedure for skin permeation from solution formulations and PSA TDSs

After sacrificing, the skin of each hairless mouse was excised. For the permeation of donepezil from solution formulations using various vehicles, donepezil hydrochloride solution at a concentration of 1 mg/mL was used. For dose-dependency experiments, various concentrations of donepezil hydrochloride in IPA (1, 5, 10, 15 mg/mL) were employed. One milliliter of donepezil solution and PSA TDS of 2 × 2 cm size were separately applied to the epidermal side of the skin and mounted on a Franz Cell Permeation System (Diffusion Cell Drive System, Labfine, Anyang, Korea); the dermal side was in contact with the receptor compartment. The surface area of the

receiver cell opening was 2 cm², and the cell volume was 12.5 mL. The receiver cells were filled with pH 7.4 isotonic phosphate buffer solution, and the media were stirred by a Teflon-coated magnetic bar to keep them well mixed. The skin permeation studies were performed at 37°C. At predetermined time intervals (3, 6, 9, 12, 24, 36 h), 1 mL of receptor solutions was withdrawn and replaced simultaneously, and the amount of donepezil permeated was determined by HPLC.

Data analysis

As described by Barry[15], the steady-state flux (J_s), lag time (T_L), diffusion coefficient (D), skin/vehicle partition coefficient (K), and apparent permeability coefficient (P_{app}) are defined by Equations (1–3).

$$J_s = \left(\frac{dQ}{dt}\right)_{ss}\frac{1}{A} = \frac{DKC}{h} \quad (1)$$

$$D = \frac{h^2}{6T_L} \quad (2)$$

$$P_{app} = \frac{dQ}{dt}\frac{1}{A}\frac{1}{C_s} \quad (3)$$

where, A is the effective diffusion area; h, the thickness of skin; C, the constant concentration of the donor solution; C_s, the drug concentration in the saturated solution; $(dQ/dt)_{ss}$ the steady-state slope.

Results and discussion

In the transdermal drug delivery, penetration of the lipid layer of stratum corneum is known to be a rate-limiting step. To evaluate partitioning to the lipid layer, the partition coefficient between water and *n*-octanol, which is known to have similar polarity with skin lipid[16], was measured. A low partition coefficient of 0.075 (±0.001, $n = 3$) was obtained with donepezil hydrochloride.

Kasting et al.[17] presented that the permeability coefficient for the transcellular route ($k_{p,lipid}$) can be calculated by Equation 4, and Potts and Guy[18] suggested that the permeability coefficient for the paracellular route (k_p) can be estimated by Equation 5, using the partition coefficient between water and *n*-octanol (K_{oct}) and the molecular weight (MW) of a drug.

$$\log k_{p,lipid} = \log K_{oct} - 0.0078\,MW - 2.87 \quad (4)$$

$$\log k_p = 0.17 \log K_{oct} - 0.0061\,MW - 2.72 \quad (5)$$

With a molecular weight of 415.96 and a K_{oct} of 0.075, the $k_{p,lipid}$ and k_p of donepezil hydrochloride were calculated to be 5.7×10^{-8} cm/h and 3.5×10^{-6} cm/h, respectively. Because the k_p was more than 50 times greater than the $k_{p,lipid}$, donepezil hydrochloride was thought to permeate the skin through the paracellular route rather than the transcellular route.

Various vehicles were selected to examine the effects on the skin permeation of donepezil. Four mechanisms have been suggested to enhance transdermal delivery of drugs—the reduction of skin resistance as a permeability barrier by disrupting tightly packed lipid regions of stratum corneum, an increase in the skin/vehicle partitioning of a drug, an increased solvent transport into or across the skin, and an increase of drug solubility in the vehicle[16,19,20].

The permeation profiles of donepezil hydrochloride through the excised hairless mouse skin from various vehicles are presented in Table 1. This result indicates that the permeation fluxes (μg/cm²/h) of donepezil hydrochloride from 1 mg/mL solutions in various vehicles are generally low, except for in IPA (51.19), EA (27.32) and water (24.07).

As shown in Table 1, the high permeation fluxes in IPA, EA and water were attributable to high skin/vehicle partition coefficient (K) values, compared to other vehicles. In contrast to cases in water and EA, donepezil in IPA showed the highest apparent permeability coefficient (P_{app}), possibly because of increased thermodynamic activity due to its low solubility in IPA.

Permeation profiles through the excised hairless mouse skin from IPA containing various concentrations of donepezil hydrochloride are presented in Figure 1 and Table 2. Since the solubility of donepezil hydrochloride in IPA was 1.15 ± 0.069 mg/mL, solutions containing 5–15 mg of donepezil hydrochloride in 1 mL of IPA were thought to have the same thermodynamic activity. However, the J_s of donepezil hydrochloride dramatically increased as the amount of drug in the solution increased; permeation flux increased dose-dependently ($r^2 = 0.9754$). Considering that lag times were almost the same in solutions containing 5–15 mg of donepezil hydrochloride, the increment of K seemed to be responsible for the increase of the permeation flux.

Fatty acids are known to have permeation enhancing effects by increasing partitioning rates or disrupting tightly packed lipid regions of stratum corneum[21]. To investigate the effects of various fatty acids on the donepezil hydrochloride permeation, five fatty acids were added to IPA, which showed the highest J_s among vehicles used: two were unsaturated fatty acids-C_{18} with one double bond (oleic acid) and C_{18} with two double bond (linoleic acid) and three were saturated fatty acids-C_8 (caprylic acid), C_{10} (capric acid), and C_{12} (lauric acid). The permeation profiles of donepezil hydrochloride through the excised hairless mouse skin from IPA containing fatty acids as enhancers are shown in Table 3.

Even though the addition of fatty acids to IPA failed to increase donepezil permeation rates, it shortened lag times. Especially, the addition of unsaturated fatty acids dramatically decreased lag times. Donepezil permeation fluxes decreased in a fatty acid concentration-dependent manner. Compared to cases with unsaturated fatty acids, donepezil with saturated fatty acids showed higher J_s. Among saturated fatty acids, shorter chain acids revealed

Table 1. Permeation parameters of donepezil hydrochloride through the excised hairless mouse skin from various pure vehicles.

Vehicles	J_s (μg/cm²/h)	T_L (h)	D (×10⁻⁹, cm²/h)	K	P_{app} (×10⁻⁵, cm/h)	Solubility (mg/mL)
Water	24.07 ± 10.81	8.72 ± 1.83	4.95 ± 1.18	2637.24 ± 1560.24	10.96 ± 4.92	219.68 ± 3.78
IPA	51.19 ± 9.43	13.31 ± 0.28	3.13 ± 0.07	8158.52 ± 1350.30	4447.07 ± 818.87	1.15 ± 0.07
EA	27.32 ± 19.77	22.21 ± 0.40	1.88 ± 0.03	7279.04 ± 5212.24	85.01 ± 61.52	32.14 ± 1.57
PEG 400	0.05 ± 0.02	6.69 ± 2.55	6.86 ± 2.53	3.83 ± 1.87	1.31 ± 0.44	3.57 ± 0.19
PG	0.22 ± 0.08	8.86 ± 2.34	4.98 ± 1.55	24.19 ± 13.36	0.63 ± 0.24	35.06 ± 1.25
OAl	1.94 ± 0.11	0.44 ± 0.38	1432.01 ± 2368.29	10.42 ± 8.92	178.96 ± 10.47	1.08 ± 0.04
DGME	0.10 ± 0.04	Immediate	NA	NA	3.00 ± 1.22	3.49 ± 0.00
PGML	0.40 ± 0.04	Immediate	NA	NA	6.36 ± 0.63	6.22 ± 0.10
PGMC	0.99 ± 0.28	0.51 ± 0.88	2786.94 ± 0.00	7.94 ± 0.00	35.24 ± 9.94	2.81 ± 0.10
IPM	3.40 ± 1.03	4.67 ± 1.68	9.88 ± 4.06	188.84 ± 81.27	118.70 ± 36.03	2.86 ± 0.00
LBF 1944	1.67 ± 0.18	4.18 ± 0.81	10.19 ± 1.80	84.93 ± 23.67	172.04 ± 18.06	0.97 ± 0.10
LBF 2125	1.46 ± 0.20	3.16 ± 1.52	15.32 ± 6.86	53.69 ± 22.30	278.68 ± 38.84	0.52 ± 0.01
LBF 2609	2.22 ± 0.28	9.52 ± 0.44	4.39 ± 0.20	253.57 ± 29.00	163.19 ± 20.69	1.36 ± 0.05
PGL	1.38 ± 0.03	0.15 ± 0.27	2807.77 ± 0.00	2.73 ± 0.00	97.86 ± 2.24	1.41 ± 0.00

Data were expressed as the mean ± S.D. (n = 3).
NA, not available; J_s, permeation flux; T_L, lag time; D, diffusion coefficient; K, skin/vehicle partition coefficient; P_{app}, apparent permeability coefficient; IPA, isopropyl alcohol; EA, ethyl alcohol; PEG 400, polyethylene glycol 400; PG, propylene glycol; OAl, oleyl alcohol; DGME, diethylene glycol monoethyl ether; PGML, propylene glycol monolaurate; PGMC, propylene glycol monocaprylate; IPM, isopropyl myristate; LBF 1944, oleoyl macrogol-6-glycerides; LBF 2125, linoleoyl macrogol-6 glycerides; LBF 2609, polyethylene glycol-8 glyceryl linoleate; PGL, propylene glycol laurate.

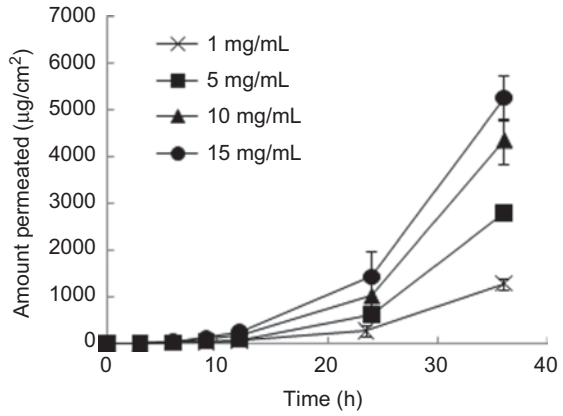

Figure 1. Effects of drug concentrations on the permeation of donepezil hydrochloride through the hairless mouse skin as a function of time (mean ± S.D., n = 3). The donor vehicle was isopropyl alcohol.

higher permeation rates. Considering that lag times were shortened with the increase in fatty acid concentrations, the decreased J_s values were attributable to the decreased K by Equations 1 and 2.

In designing a transdermal drug delivery system, it is essential to determine an appropriate vehicle that solubilizes the target drug, mixes adequately with PSA, and/or enhances the permeation rate. To evaluate the effects of PSAs, two kinds of acrylic adhesives were employed: Duro-Tak® 87–2196 and Duro-Tak® 87–2510.

The functional groups of Duro-Tak® 87–2196 and 87–2510 are carboxylate and hydroxyl, respectively. It's known that the chemical property of the adhesive can affect drug permeation rate due to the drug release change by the interaction between a drug and adhesive[22]. However, in this study, the functional group of the adhesives did not influence the permeation rate, and permeation profiles of donepezil from the two adhesives were almost the same; the permeation fluxes (×10⁻², μg/cm²/h) with Duro-Tak® 87–2196 and 87–2510 were 2.94 ± 0.44 and 3.18 ± 0.23, respectively. The onset of the permeation was instant with both adhesives.

Table 2. Permeation parameters of donepezil hydrochloride through the excised hairless mouse skin from isopropyl alcohol with various concentrations of drug.

Concentration	J_s (μg/cm²/h)	T_L (h)
1 mg/mL	51.19 ± 9.43	13.31 ± 0.28
5 mg/mL	112.73 ± 6.70	13.70 ± 0.22
10 mg/mL	172.93 ± 32.66	13.32 ± 0.24
15 mg/mL	208.54 ± 40.70	12.96 ± 0.29

Data were expressed as the mean ± S.D. (n = 3).
J_s, permeation flux; T_L, lag time.

To formulate TDS, 10 mg of donepezil hydrochloride was dissolved in 0.5 mL of various pure solvents and mixed with 2.5 g of Duro-Tak® 87–2196. Among the area of the cast solutions of 40 cm², 2 cm² was employed for each experiment. Therefore, the theoretical amount of donepezil hydrochloride was 1 mg for each experiment, which was the same as that of solution formulation. The permeation fluxes and apparent permeation coefficients are shown in Table 4.

Compared to those from solution formulations, permeation profiles from PSA TDSs were totally different, and penetration rates were considerably low, probably due to the change of solubility and/or diffusivity. Lag times were drastically shortened: no lag time except for DGME (4.36 ± 1.58 h) could be calculated because permeations were initiated immediately.

Table 3. Permeation parameters of donepezil hydrochloride through the excised hairless mouse skin from isopropyl alcohol in the presence and absence of fatty acids.

Enhancers	J_s (μg/cm²/h)	T_L (h)
None	51.19 ± 9.43	13.31 ± 0.28
Caprylic acid 3%	47.76 ± 4.70	10.32 ± 1.56
Caprylic acid 6%	35.34 ± 6.44	8.16 ± 3.47
Caprylic acid 10%	15.34 ± 4.52	1.71 ± 2.95
Capric acid 3%	37.47 ± 2.23	9.36 ± 2.07
Capric acid 6%	18.17 ± 2.98	1.90 ± 3.29
Capric acid 10%	11.24 ± 2.07	1.28 ± 2.21
Lauric acid 3%	20.52 ± 4.07	4.87 ± 4.22
Lauric acid 6%	11.10 ± 1.37	1.03 ± 1.78
Lauric acid 10%	4.42 ± 0.03	Immediate
Oleic acid 3%	12.03 ± 0.38	Immediate
Oleic acid 6%	5.26 ± 0.13	Immediate
Oleic acid 10%	3.03 ± 0.44	Immediate
Linoleic acid 3%	12.74 ± 1.39	1.83 ± 2.93
Linoleic acid 6%	5.89 ± 1.40	Immediate
Linoleic acid 10%	4.01 ± 0.55	Immediate

Data were expressed as the mean ± S.D. (n = 3).
J_s, permeation flux; T_L, lag time.

Table 4. Permeation parameters of donepezil hydrochloride through the excised hairless mouse skin from pressure-sensitive transdermal delivery systems containing various vehicles.

Vehicles	J_s (×10⁻², μg/cm²/h)	P_{app} (×10⁻⁵, cm/h)
IPA	2.82 ± 0.80	2.45 ± 0.70
EA	1.59 ± 0.66	0.05 ± 0.02
PG	1.60 ± 0.75	0.05 ± 0.02
DGME	4.45 ± 0.32	1.28 ± 0.09
PGML	7.03 ± 0.81	2.50 ± 0.29
PGMC	1.91 ± 0.38	0.31 ± 0.06
IPM	4.28 ± 0.93	1.50 ± 0.32
LBF 1944	4.39 ± 2.17	4.51 ± 2.23
LBF 2125	4.50 ± 1.45	8.60 ± 2.77
LBF 2609	9.20 ± 1.57	6.75 ± 1.15

Data were expressed as the mean ± S.D. (n = 3).
J_s, permeation flux; P_{app}, apparent permeability coefficient; IPA, isopropyl alcohol; EA, ethyl alcohol; PG, propylene glycol; OAl, oleyl alcohol; DGME, diethylene glycol monoethyl ether; PGML, propylene glycol monolaurate; PGMC, propylene glycol monocaprylate; IPM, isopropyl myristate; LBF 1944, oleoyl macrogol-6-glycerides; LBF 2125, linoleoyl macrogol-6 glycerides; LBF 2609, polyethylene glycol-8 glyceryl linoleate.

Considering that the donepezil daily dose is 5–10 mg, and the drug is dissolved in 1 mL of vehicles, it is required to have vehicles whose solubility is at least 5 mg/mL. To ensure reasonable permeation fluxes and solubilities, DGME and PGML co-solvents were employed for further investigation. As shown in Figure 2, DGME at 40% showed the highest permeation flux (0.10 ± 0.0024 μg/cm²/h).

PGML is an ester-type vehicle in which a relatively considerable quantity of donepezil hydrochloride can be dissolved (solubility: 6.22 ± 0.10 mg/mL). It has been suggested that DGME itself may not have a profound

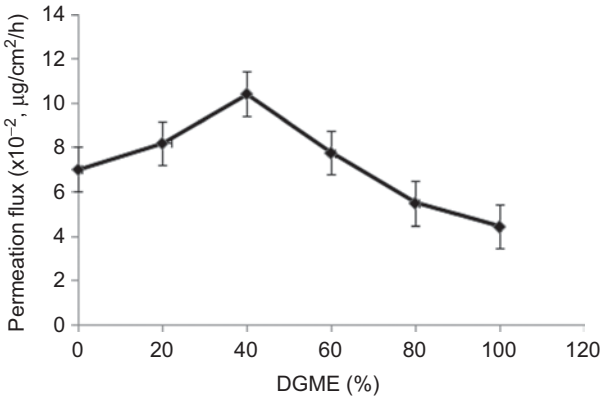

Figure 2. Effects of diethylene glycol monoethyl ether (DGME) concentrations in mixture solutions with propylene glycol monolaurate on donepezil permeation fluxes (mean ± S.D., n = 3).

effect on the structural integrity of the skin and that it just eases the partition of a compound by increasing the solubility of the compound in the skin[23]. Many studies have revealed that the addition of DGME at concentrations of 20–40% to the ester-type vehicles such as PGL, PGMC, and PGML considerably increased the permeation flux of many drugs including melatonin[24], ondansetron[25], and ketorolac[26].

In this study, K values were calculated to be 0.0084, 5.90, 7.34, 3.39, 1.94, and 2.26 at 0, 20, 40, 60, 80, and 100% DGME, respectively. The addition of DGME greatly increased the K, compared to the PGML only formulation. However, the increase in the K was not DGME concentration-dependent. At 20–40% of DGME, relatively high K values were obtained.

Results from our study provide evidence for the hypothesis that several vehicles could enhance the permeation of donepezil; IPA-containing solution formulations and DGME-PGML (40:60)-containing PSA TDS were found to be favorable candidates for the transdermal delivery of donepezil. It should be cautious, however, to conclude that the formulations could be used in humans because it is known that the hairless mouse skin showed increased permeability compared to the human skin[27]. Nevertheless, this study was considered to provide some preliminary data to develop donepezil TDSs.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

References

1. Sugimoto H, Iimura Y, Yamanishi Y, Yamatsu K. (1995). Synthesis and structure-activity relationships of acetylcholinestrase inhibitors: 1-benzil-4-[(5,6-dimethoxy-1-oxoindan-2yl)methyl] piperidine hydrochloride and related compounds. J Med Chem, 38:4821–4829.

2. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. (1998). A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology, 50:136–145.
3. Collerton D. (1986). Cholinergic function and intellectual decline in Alzheimer's disease. Neuroscience, 19:1–28.
4. Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, Delon MR. (1982). Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science, 215:1237–1239.
5. Machado JC, Caramelli P. (2006). Treatment of dementia: anything new? Curr Opin Psychiatry, 19:575–580.
6. Winblad B, Jelic V. (2004). Long-term treatment of Alzheimer disease: efficacy and safety of acetylcholinesterase inhibitors. Alzheimer Dis Assoc Disord, 18 Suppl 1:S2–S8.
7. Bassil N, Grossberg GT. (2009). Novel regimens and delivery systems in the pharmacological treatment of Alzheimer's disease. CNS Drugs, 23:293–307.
8. Small G, Dubois B. (2007). A review of compliance to treatment in Alzheimer's disease: potential benefits of a transdermal patch. Curr Med Res Opin, 23:2705–2713.
9. Cummings J, Winblad B. (2007). A rivastigmine patch for the treatment of Alzheimer's disease and Parkinson's disease dementia. Expert Rev Neurother, 7:1457–1463.
10. El Maghraby GM, Alanazi FK, Alsarra IA. (2009). Transdermal delivery of tadalafil. I. Effect of vehicles on skin permeation. Drug Dev Ind Pharm, 35:329–336.
11. Rastogi R, Anand S, Dinda AK, Koul V. (2010). Investigation on the synergistic effect of a combination of chemical enhancers and modulated iontophoresis for transdermal delivery of insulin. Drug Dev Ind Pharm, 36:993–1004.
12. Thakur RA, Michniak BB, Meidan VM. (2007). Transdermal and buccal delivery of methylxanthines through human tissue in vitro. Drug Dev Ind Pharm, 33:513–521.
13. Kafkala S, Matthaiou S, Alexaki P, Abatzis M, Bartzeliotis A, Katsiabani M. (2008). New gradient high-performance liquid chromatography method for determination of donepezil hydrochloride assay and impurities content in oral pharmaceutical formulation. J Chromatogr A, 1189:392–397.
14. Yasui-Furukori N, Furuya R, Takahata T, Tateishi T. (2002). Determination of donepezil, an acetylcholinesterase inhibitor, in human plasma by high-performance liquid chromatography with ultraviolet absorbance detection. J Chromatogr B Analyt Technol Biomed Life Sci, 768:261–265.
15. Barry BW. (1983). Dermatological Formulations. New York, USA: Marcel Dekker.
16. Aungst BJ, Blake JA, Hussain MA. (1990). Contributions of drug solubilization, partitioning, barrier distruption, and solvent permeation to the enhancement of skin permeation of various compounds with fatty acids and amines. Pharm Res, 7:712–718.
17. Kasting GB, Smith RL, Anderson BD. (1992). Prodrugs for dermal delivery: solubility, molecular size, and functional group effects. In: Sloan KB ed. Prodrugs. New York, USA: Marcel Dekker, pp. 117–161.
18. Potts RO, Guy RH. (1992). Predicting skin permeability. Pharm Res, 9:663–669.
19. Green PG, Guy RH, Hadgraft J. (1988). *In vitro* and *in vivo* enhancement of skin permeation with oleic acid and lauric acids. Int J Pharm, 48:103–111.
20. Yamada M, Uda Y, Tanigawara Y. (1987). Mechanism of enhancement of percutaneous absorption of molsidomine by oleic acid. Chem Pharm Bull, 35:3399–3406.
21. Nomura H, Kaiho F, Sugimoto Y, Miyashita Y, Dohi M, Kato Y. (1990). Percutaneous absorption of indomethacin from mixtures of fatty alcohol and propylene glycol (FAPG bases) through rat skin: effects of oleic acid added to FAPG base. Chem Pharm Bull, 38:1421–1424.
22. Kim J, Cho Y, Choi H. (2000). Effect of vehicles and pressure sensitive adhesives on the permeation of tacrine across hairless mouse skin. Int J Pharm, 196:105–113.
23. Cho YJ, Choi HK. (1998). Enhancement of percutaneous absorption of ketoprofen: effect of vehicles and adhesive matrix. Int J Pharm, 86:95–104.
24. Gwak HS, Kim SU, Chun IK. (2002). Effect of vehicles and enhancers on the *in vitro* permeation of melatonin through hairless mouse skin. Arch Pharm Res, 25:392–396.
25. Gwak HS, Oh IS, Chun IK. (2004). Transdermal delivery of ondansetron hydrochloride: effects of vehicles and penetration enhancers. Drug Dev Ind Pharm, 30:187–194.
26. Choi JS, Cho YA, Chun IK, Jung SY, Gwak HS. (2007). Formulation and evaluation of ketorolac transdermal systems. Drug Deliv, 14:69–74.
27. Bond JR, Barry BW. (1988). Hairless mouse skin is limited as a model for assessing the effects of penetration enhancers in human skin. J Invest Dermatol, 90:810–813.