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Effect of vehicles and pressure sensitive adhesives on the permeation of tacrine across hairless mouse skin

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Abstract

The purpose of this study was to investigate the feasibility of developing transdermal drug delivery (TDD) system for tacrine used for treating the symptoms of Alzheimer's disease. The effects of various vehicles on the percutaneous absorption of tacrine in solution formulation and in pressure sensitive adhesive (PSA) matrix across the hairless mouse skin were evaluated using flow-through diffusion cell system at 37°C. The permeation profiles of tacrine from solutions were different depending on vehicles used. The flux of tacrine increased significantly as its concentration in the solutions increased. The permeation rate of tacrine was higher in acrylic adhesives with hydroxyl functional group and without functional group than in polyisobutylene adhesive matrix. Incorporation of vehicles into the acrylic adhesive matrix significantly enhanced the permeation rate and shortened the lag time of tacrine. The maximum flux obtained from pressure sensitive adhesive matrix seemed to be high enough to obtain therapeutic effect.

Keywords: Transdermal; Tacrine; Vehicle effect; Pressure sensitive adhesive; Matrix

1. Introduction

Tacrine (9-amino-1, 2, 3, 4-tetrahydrochloride), a centrally acting acetylcholinesterase inhibitor, has been documented to be effective for the treatment of Alzheimer's disease resulting from the increase of the amount of acetylcholine in combination with the muscarine receptor (Sathan et al., 1995). However, peroral administration is known to exhibit extensive dose-dependent and reversible hepatotoxicity, extensive first-pass metabolism, short elimination half-life (1.38–3.6 h), low peroral bioavailability (5.5–36%), and peripheral cholinergic side effects (Sathan et al., 1995). Transdermal drug delivery system can: avoid first-pass metabolism, reduce side effects due to reduction of the peaks in plasma levels, and improve therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms (Ghosh et al., 1997a). In spite of many advantages of transdermal delivery system over oral delivery, only a limited number of drugs can be administered percutaneously due to low

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permeability of most drugs through the skin (Franz et al., 1992). Currently, the most widely utilized approach to enhance percutaneous absorption of a drug involves the use of chemical permeation enhancers. They generally partition into the skin, and interact with different skin constituents to elicit temporary and, ideally, reversible reduction of barrier properties (Ghosh et al., 1997b). Extensive studies have been conducted regarding the effect of various vehicles on the percutaneous absorption of a compound; however, most of studies were conducted using solution formulations other than adhesive matrix. The effects of an enhancer in solution formulations can be different from those in the pressure sensitive adhesive matrix. In transdermal drug delivery system, the pressure sensitive adhesive (PSA) fulfills the adhesion-to-skin function and serves as the formulation foundation, containing the drug and all excipients (Wilking et al., 1994). Commonly, three types of PSA are used in transdermal drug delivery systems: polyisobutylenes (PIB), silicones, and acrylics. The permeation rate of a drug, the compatibility with enhancers, and the skin adhesion must be considered before the selection of PSA.

In the present study, we investigated the effects of various vehicles on the percutaneous absorption of tacrine from solution formulations as well as from pressure sensitive adhesive matrix across hairless mouse skin. Furthermore, the influences of both the natures of pressure sensitive adhesive and the functional groups in acrylic adhesives on the permeation rate of tacrine were evaluated.

2. Materials and methods

2.1. Materials

Tacrine HCI was a gift from Jeil Pharm. (Seoul, South Korea). Diethylene glycol monoethyl ether (Transcutol®), PEG-8 glyceryl caprylate/caprate (Labrasol®), PEG-6 glyceryl mono oleate (Labrafil® 1944), and PEG-8 glyceryl linoleate (Labrafil® 2609) were obtained from Gatteposse Korea (Seoul, South Korea). Mineral oil was purchased from Sigma Chemical (St. Louis, MO). Fractionated coconut oil (Miglyol® 812) and propylene glycol dicaprylate/dicaprate (Miglyol® 840) were obtained from Huls America (Somerset, NJ). Peanut oil was obtained from Croda (Parsippany, NJ). Propylene glycol monolaurate (PGML) was obtained from Jeil Pharm. Acrylic pressure sensitive adhesive solutions in organic solvents were obtained from National Starch and Chemical Company (Bridgewater, NJ). Polyisobutylene (Vistanex LM-MH, Vistanex MML-100) were purchased from Exxon Chemical (Houston, TX). Silicone pressure sensitive adhesive was obtained from Dow Corning (Midland, MI). All other chemicals were reagent grade or above and were used without further purification.

2.2. Solubility test

Excess amount of tacrine base (obtained from its HC1 salt) was added to various solvents in screw-capped vials. The contents were stirred by an externally driven teflon-coated magnetic bar at room temperature until equilibrated. The saturated solution was then filtered through 0.45 μm millipore filter (Millipore, Bedfore, MA). The concentration of tacrine was measured by HPLC after appropriate dilution.

2.3. Preparation of test solution

To determine the effects of various vehicles on the permeation of tacrine, appropriate amount of tacrine was dissolved in each test vehicle. The saturated solutions were prepared by adding excess amount of tacrine in each test vehicle and mixing the solution in a shaker bath at room temperature for 24 h.

2.4. Preparation of adhesive matrices

Acrylic adhesive solution comprising tacrine was prepared by mixing tacrine solution in EtOH with acrylic adhesive solution in mixed solvents. Polyisobutylene (PIB) solution comprising tacrine was prepared by dissolving tacrine, PIB cut into small pieces, and other necessary components in chloroform/hexane mixture. Pressure sensitive adhesive matrix was prepared by casting the above

solutions on polyester release liner coated with silicone using a casting knife. It was set at room temperature for 10 min and were subsequently oven-dried at 90°C for about 20 min to remove the residual organic solvents. The dried film was laminated onto a backing film.

2.5. Diffusion cell system

A flow-through diffusion cell system consisting of a multichannel peristaltic pump (205S, Watson Marlow, UK), a fraction collector (Retriever IV, ISCO, NE), a circulating water bath (RB-10, Jeio-Tech, Korea), and flow-through diffusion cells was used. The flow-through cell consists of two side arms, which enabled conduction of receiver cell media from a peristaltic pump to a fraction collector. The temperature was maintained at 37°C by circulating constant temperature water through the outer jacket of the receiver cell. The surface area of the receiver cell opening was 2 cm^2, and the cell volume was 5.5 ml.

2.6. Procedure

Full-thickness hairless mouse skin was excised from the fresh carcass of animals that were humanely sacrificed with diethyl ether. Subcutaneous fat was removed carefully with scissors and scalpel. Each of the flow-through diffusion cell components was connected via silicone rubber tubing with an internal diameter of 0.015 inches. The receiver cell was filled with a pH 7.4 isotonic phosphate buffer solution and the media were stirred by an externally driven, teflon-coated magnetic bar to keep them well mixed. The hairless mouse skin was mounted onto each receiver cell, and O-ring and cell top were placed on the top of each skin. These components were then clamped securely in place. The system was first equilibrated for 30 min, then any air bubbles that remained in the receiver cells were removed. When solution formulations were tested, 300 μl of tacrine solution or suspension in various vehicles was placed in the donor compartment. When matrix formulations were tested, a disc with the surface area of 2 cm^2, was cut by a punch. The discs were applied to the epidermal side of the skin with slight pressure before mounting on the receiver cell. The samples were collected every 3 h for 24 or 30 h.

2.7. Data reduction

The permeation data were analyzed by the method developed for flow-through diffusion cell system (Choi and Angello, 1994).

2.8. Assay

Tacrine was analyzed by an HPLC system (Shimadzu Scientific Instruments, MD), consisting of a W detector (SPD-1OA), a pump (LC-1 OAD), and an automatic injector (SIL-1OA). The wavelength of the UV detector was 240 nm and the retention time of tacrine was 2.8 min. A reversed-phase column (Alltima C8, Alltech Associates, IL) was used. The column temperature was maintained at 30°C by a thin foil temperature controller (CH 1445, SYSTEC, MN). The flow rate was 1 ml/min The mobile phase consisted of methanol/acetonitrile/water/triethylamine (25/20/55/1). The pH ofthe mobile phase was adjusted to 6.4 by phosphoric acid.

3. Results and discussion

3.1. Effect of vehicles in solution formulation

One of the approaches to improve the topical bioavailability of a drug is to incorporate vehicles that may enhance the permeation rate of the drug across the skin. Those vehicles may act as permeation enhancers by increasing the thermodynamic activity of the drug and/or changing the barrier property of the skin (Møllgaard and Hoelgaard, 1983). The relationship between the solubility of a drug in the vehicle and the thermodynamic activity of the drug in the vehicle was described in our previous paper (Cho and Choi, 1998). When a fixed concentration is used in all vehicles to be tested, the activity of a drug will vary depending on the solubility of the drug in the selected vehicle. An inverse relationship is expected between the solubility of the drug and its permeation rate across the skin in the absence of solvent-induced

skin damage (Twist and Zatz, 1990) and/or interaction between the vehicle and the drug. To investigate the relationship between the solubility of tacrine and its permeation rate across the skin and to identify suitable enhancers for the transdermal delivery of tacrine, the effect of various vehicles on the percutaneous absorption of the drug across the hairless mouse skin was measured. Table 1 shows the permeability coeffficient of tacrine across hairless mouse skin obtained from 5, 10, 20 and 40 mg/ml solutions in various vehicles for 30 h and the solubility in the same vehicles. The permeability coefficient was obtained from the points with the highest slope since permeation profiles of tacrine were quite different from each other depending on the vehicles used. In some of the vehicles tested, it was not possible to observe steady state due to the change in driving force and/or the change in the barrier property of the skin with time, which have resulted in various permeation profiles. In most of the cases, the shape of permeation plot obtained from various vehicles were similar to those of ketoprofen reported previously (Cho and Choi, 1998), even though their solubilities in various vehicles were different. It indicates that the difference in the permeation rate depending on the vehicles used may come mainly from their effect on the barrier property of the skin. Theoretically, the higher the solubility, the lower the flux of a compound when undersaturated solution is used. When the fluxes of tacrine in various vehicles with the solubility of

Table 1
Permeability coefficients (mean ± S.D.) of tacrine from 5, 10, 20 and 40 mg/ml solutions in various vehicles across hairless mouse skin ($n = 3$)

Vehicle	Permeability coefficient ($\times 10^3$ cm/h)				Solubility (mg/ml)
	5 mg/ml	10 mg/ml	20 mg/ml	40 mg/ml	
Oleyl alcohol	3.58 ± 1.55	3.27 ± 0.61	2.90 ± 0.11	2.58 ± 0.33	32.4 ± 4.72
PG[b]:OA[c] (2:8)	6.79 ± 1.84				130 ± 36.8
PG:OA (5:5)	10.8 ± 2.09				252 ± 14.3
PG:OA (8:2)	9.29 ± 1.24				300 ± 4.38
PG	0.38 ± 0.12				253 ± 20[a]
PG:EtOH[d] (5:5)	4.71 ± 0.50				250 ± 13[a]
Water	41.7 ± 1.26				0.28 ± 0.02[a]
Ethanol	9.47 ± 0.96				137 ± 16[a]
Octanol	12.2 ± 3.37	11.6 ± 0.23	7.85 ± 2.05	3.25 ± 0.29	34.5 ± 6.55
Transcutol®	0.08 ± 0.03				34.4 ± 4.12
Oleic acid	0.05 ± 0.00				24.8 ± 4.18
PGML[e]	2.75 ± 0.62	1.96 ± 0.09	2.91 ± 1.16	2.79 ± 0.05	27.5 ± 3.51
Miglyol 812®	2.40 ± 0.23				8.52 ± 0.41
Miglyol 840®	2.69 ± 0.35				8.67 ± 0.52
IPM[f]	10.3 ± 0.78	19.8 ± 1.43	24.5 ± 0.0	29.0 ± 0.38	3.99 ± 0.61
Mineral oil	23.2 ± 0.00				0.074 ± 0.00
Peanut oil	3.9 ± 2.10				2.15 ± 0.35
Labrasol®	0.14 ± 0.09				23.1 ± 4.72
Labrafil 1944®	1.00 ± 0.27				17.7 ± 4.29
Labrafil 2609®	2.20 ± 0.55				20.9 ± 0.2
Tween 20	0.07 ± 0.02				4.71 ± 0.86
Tween 80	0.25 ± 0.01				3.41 ± 2.85

[a] From Sathan et al. (1995).
[b] Propylene glycol.
[c] Oleyl alcohol.
[d] Ethanol.
[e] Propylene glycol monolaurate.
[f] Isopropyl myristate.

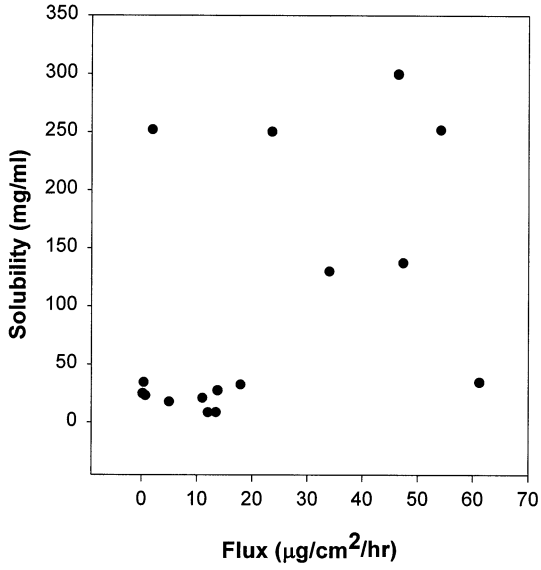

Fig. 1. Relationship between the solubility of tacrine in various vehicles and the flux from the vehicle.

higher than 5 mg/ml were plotted against the solubility, the above mentioned trend was not observed. As can be seen in Fig. 1, reverse relationship to the theory was observed, if there is a trend.

The permeation rate trends of tacrine from PG/OA mixtures were slightly different from those of ketoprofen (Cho and Choi, 1998). The highest permeation rate was obtained when the ratio was 5/5 and their trends were maintained up to the end of diffusion experiment. The permeation rate of tacrine from Transcutol® solution was extremely low. It was an order of magnitude slower than the permeation rate from aqueous solution. This result confirms our argument in the previous study that Transcutol® may not have profound effect on the structural integrity of the skin and may just ease the partition of some compounds by increasing the solubility in the skin. It is interesting to note that the permeation rate of tacrine in oleic acid was the lowest among tested vehicles. Oleic acid is a well known permeation enhancer and increased the permeation rate of ketoprofen significantly (Cho and Choi, 1998).

To investigate the effect of drug concentration on the permeation rate of tacrine, isopropyl myristate (IPM), oleyl alcohol (OA), propylene glycol monolaurate (PGML), and oleic acid were selected and tested using 5, 10, 20 and 40 mg/ml solutions of tacrine. The permeability coeffcient (cm/h) was defined as the flux normalized to the concentration of drug in the vehicle. In all cases tested with the exception of 40 mg/ml solution of octanol, the flux of tacrine increased significantly. However, the extent of change in the permeability coefficient was different depending on the vehicles used. The results indicate that the diffusion coefficient is a function of concentration, assuming partition coefficient is independent of concentration. In case of IPM, permeability coefficient increased as the amount of tacrine increased, even though the solutions are already saturated at 5 mg/ml. It should be noted, however, that the solubility was measured at room temperature and the percutaneous absorption study was conducted at 37°C. This may have caused further increase in the permeability at concentrations higher than 5 mg/ml. In addition, if the permeation process is dissolution rate controlled, higher flux can be expected when more solid particles are available. In case of PGML and OA, permeability coefficient did not change significantly with drug loading. In case of octanol, permeability coefficient decreased as the drug loading increased. Overall, the shape of permeation profile was similar within a same vehicle regardless of concentration used. When 40 mg/ml solutions were used, octanol showed the best enhancing effect in terms of flux followed by IPM and PGML. The rank order of flux obtained with 5 mg/ml solution was almost similar to that obtained with higher concentration. Theoretically, the effect of vehicles on the absorption process could in part be predicted from the knowledge of solute solubility (thermodynamic activity) in the vehicle (Hilton et al., 1994). When the permeation rates of tacrine in saturated solutions were compared, the flux of tacrine should be same in all cases, unless the vehicles affect the barrier properties of the skin. Even though the results obtained using four different saturated solutions showed similar fluxes, it is very likely that these vehicles changed the barrier properties of the skin based on results using subsaturated concentration and the results obtained previously with ketoprofen.

3.2. Effect of adhesive matrix

The effect of pressure sensitive adhesive (PSA) matrix on the permeation of tacrine was investigated using polyisobutylene (PIB), silicone and acrylic adhesive matrix. The maximum flux of tacrine saturated in polymer (J_{max}) can be expressed:

$$J_{max} = \frac{D \cdot K}{h} \cdot C_{PSA}$$

where D is diffusion coefficient, K is partition coefficient between the skin and the PSA, h is thickness of hairless mouse skin, and C_{PSA} is the solubility of tacrine in PSA. Since $K \cdot C_{PSA}$ is C_m (solubility of tacrine in the skin), $K \cdot C_{PSA}/h$ can be considered as constant and the same flux can be expected regardless of chemical nature of PSA based on Fick's law. However, glass transition temperature of PSA, interaction between drug and functional group of PSA, characteristics of surface, adhesive force, and many other factors can influence flux of a drug from PSA (Kokubo et al., 1991, 1994) across the skin. As a result, selection of appropriate PSA matrix is very important in designing transdermal drug delivery system. Table 2 shows the flux of tacrine saturated in PIB, silicone and acrylic PSA. These results show that the flux of tacrine across hairless mouse skin was affected significantly by the chemical nature of PSA and acrylic PSA may be the choice of matrix in developing transdermal delivery system for tacrine.

The effect of drug loading in PIB matrix on the amount of tacrine permeated across hairless mouse skin as a function of time is shown in Fig. 2. The flux of tacrine increased as the drug loading in PIB matrix increased from 1.7 to 9.7%. It is interesting to note that sigmoidal permeation profile was obtained especially when the drug loading was 6.6 and 9.7%. The first inflection point may be attributable to the lag time. The gradual decrease in the later phase of the permeation profile may be attributable to dissolution controlled permeation. The concentration of solubilized drug in the PIB matrix decreases in the later phase, and the rate of dissolution of undissolved drug particles is slower than the permeation rate of the drug, resulting in the decrease in the driving force. Fig. 3 shows the effect of adding mineral oil in PIB matrix on the permeation of tacrine across the skin. Mineral oil acts as a plasticizer and eases the movement of the drug molecule within the PIB matrix. Overall, the addition of mineral oil into PIB matrix increased the permeation rate of tacrine except 9.7% drug loading. It also changed the sigmoidal permeation profile into pseudo-steady state profile possibly by increasing the rate of drug movement and facilitating the dissolution process of tacrine within the PIB matrix. When mineral oil was incorporated, there was no significant difference in permeation rate between 6.6 and 9.7% drug loading.

Table 2
Effect of various pressure sensitive adhesives on the flux of tacrine saturated in the adhesive matrix

Pressure sensitive adhesive	Concentration (% w/w)	Flux (μg/cm²/h)
Polyisobutylene	9.7	8.7
Silicone	2.4	2.4
Acrylic	21.0	55.4

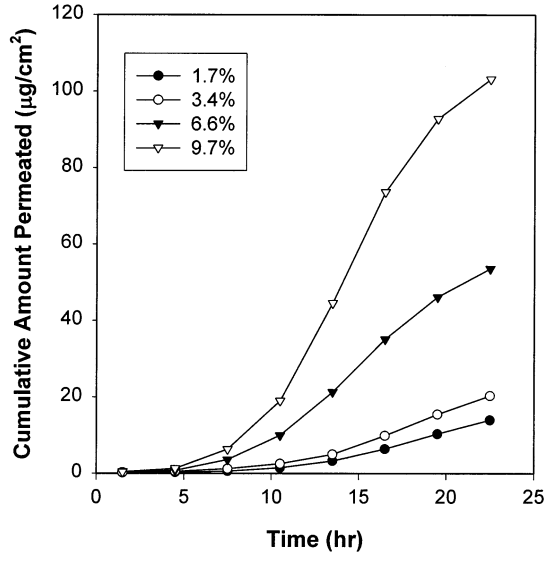

Fig. 2. Effect of drug loading on the permeation of tacrine across hairless mouse skin from polyisobutylene adhesive matrix. The percentage in the legend represents amount of tacrine loaded in polyisobutylene adhesive polymer (% w/w). Each point represents average of four measurements.

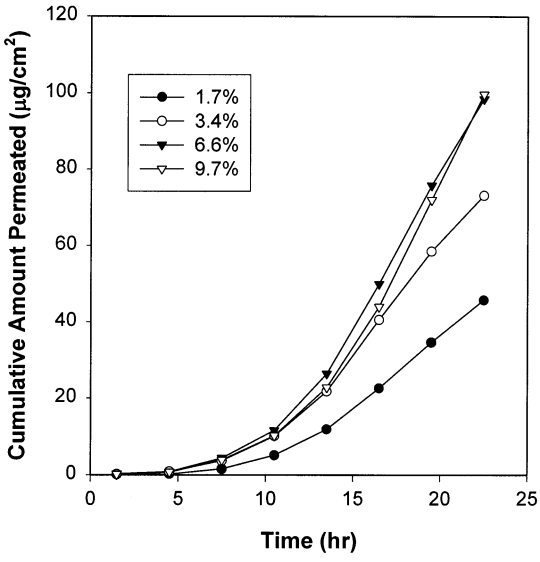

Fig. 3. Effect of adding mineral oil on the permeation of tacrine across hairless mouse skin from polyisobutylene adhesive matrix. The percentage in the legend represents amount of tacrine loaded in polyisobutylene adhesive polymer (% w/w). Each point represents average of four measurements.

Fig. 4 shows the effect of drug loading in acrylic adhesive matrix having carboxyl functional group on the permeation of tacrine across hairless mouse skin. When tacrine was added to acrylic adhesive matrix having carboxyl functional group, the tack of adhesive matrix reduced and the permeation rate of tacrine was generally low, which may be due to the interaction between amine group of tacrine and carboxyl group of acrylic adhesive. It is interesting to note that the amount of tacrine permeated was almost nothing at the drug loading of below 8% and increased significantly as the amount of drug loading increased from 12 to 15%. It seems that the amount of tacrine loaded is almost entrapped within the matrix and only a small portion of the drug is released very slowly due to the interaction until the drug loading of 8%. The increase of permeability between 12 and 15% drug loading may be attributable to the increase of drug that is not entrapped within the matrix. No further increase of the permeation rate at the drug loading of above 15% may be attributable to the saturation of tacrine within adhesive matrix.

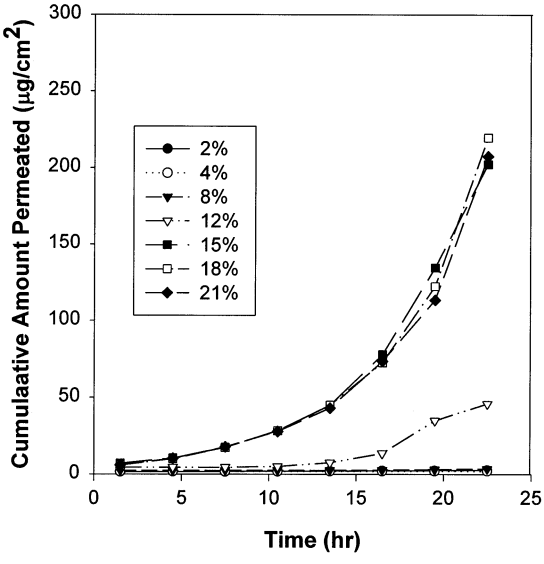

Fig. 4. Effect of drug loading on the permeation of tacrine across hairless mouse skin from acrylic adhesive matrix having carboxyl functional group. The percentage in the legend represents amount of tacrine loaded in acrylic adhesive polymer (% w/w). Each point represents average of four measurements.

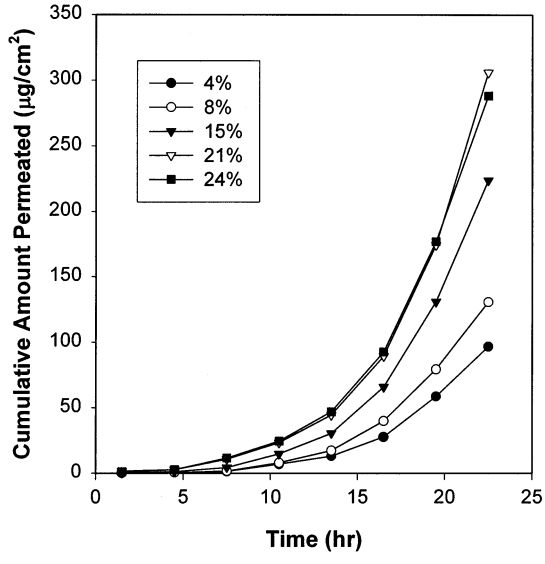

Fig. 5. Effect of drug loading on the permeation of tacrine across hairless mouse skin from acrylic adhesive matrix having hydroxyl functional group. The percentage in the legend represents amount of tacrine loaded in acrylic adhesive polymer (% w/w). Each point represents average of four measurements.

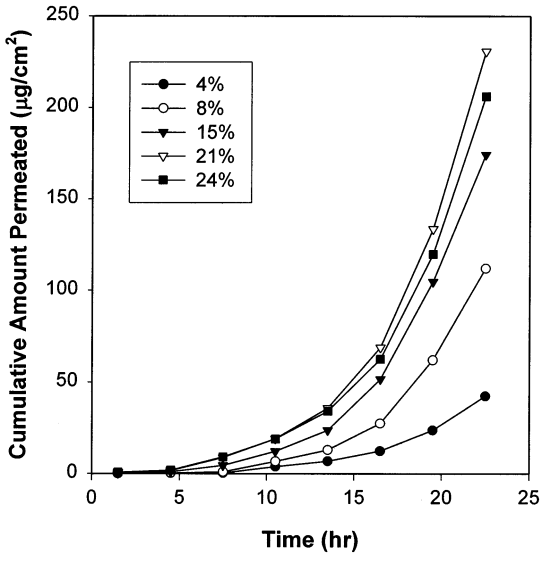

Fig. 6. Effect of drug loading on the permeation of tacrine across hairless mouse skin from acrylic adhesive matrix having no functional group. The percentage in the legend represents amount of tacrine loaded in acrylic adhesive polymer (% w/w). Each point represents average of four measurements.

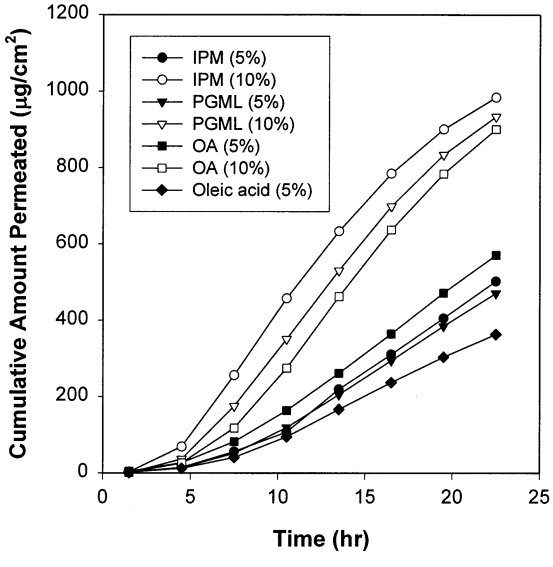

Fig. 7. Effect of various vehicles on the permeation of tacrine across hairless mouse skin from acrylic adhesive matrix. The percentage in the legend represents amount of vehicle loaded in acrylic adhesive polymer (% w/w). Each point represents average of four measurements.

Fig. 5 shows the effect of drug loading in acrylic adhesive matrix having hydroxyl functional group on the permeation of tacrine across hairless mouse skin. The permeation rate from acrylic adhesive matrix having hydroxyl functional group was much higher than that from acrylic adhesive having carboxyl functional group due to the lack of interaction between the drug and the adhesive matrix. It increased significantly as the amount of drug loading increased from 4 to 21%. No further increase in the permeation rate was observed at the drug loading of above 21%, indicating saturation of tacrine was attained within the adhesive matrix. Fig. 6 shows the effect of drug loading in acrylic adhesive matrix having no functional group on the permeation of tacrine across hairless mouse skin. Similar permeation profiles with slightly lower permeation rate were observed when compared to that obtained with acrylic adhesive having hydroxyl functional group. These results suggest that the chemical nature of the adhesive must be considered before the selection of adhesive matrix (Roy et al., 1996), since the interaction between a drug and PSA can affect the release rate of the drug significantly (Kokubo et al., 1994). One disadvantage of two types of acrylic adhesives was extremely long lag time of >10 h.

To develop matrix-type transdermal delivery system for a drug, an appropriate vehicle is often required to enhance the permeation rate and/or to increase the solubility of the drug in the adhesive. A vehicle can also act as a plasticizer in the adhesive, increasing the mobility of the drug in the adhesive. To further increase the permeation rate of tacrine and to reduce the lag time, the effect of some vehicles on the permeation of tacrine from acrylic adhesive matrix was investigated. The effect of PGML, IPM, oleyl alcohol, and oleic acid on the permeation of tacrine across hairless mouse skin from acrylic adhesive with no functional group is given in Fig. 7. The amount of each vehicle tested was 5 and 10% of the weight of acrylic adhesive polymer, respectively. Since oleic acid caused significant loss of adhesive force, the permeation rate was not determined at 10% level. Incorporation of vehicles into the acrylic adhesive matrix significantly enhanced the permeation rate and shortened lag time. The permeation rate of

tacrine increased as the amount of vehicles added into the acrylic adhesive matrix increased. It is interesting to note that the remarkable enhancement effects obtained from the solution formulations were similarly observed from the acrylic adhesive matrix. The maximum flux obtained from matrix formulation was >60 μg/cm^2 per h. Based on oral daily dose of 40 mg/day and ca 20% of bioavailability, 8 mg/day of tacrine must be absorbed transdermally to achieve pharmacological effect. The area of transdermal delivery system required to provide required permeation rate is only 5.6 cm^2. The human skin is generally less permeable than the hairless mouse skin (Durrheim et al., 1980; Sherertz et al., 1990) and the actual size of the system must be determined after evaluating the permeation rate across the human skin.

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References

Cho, Y.J., Choi, H.K., 1998. Enhancement of percutaneous absorption of ketoprofen; effect of vehicles and adhesive matrix. Int. J. Pharm. 169, 95–104.

Choi, H.K., Angello, J.T., 1994. Mathematical analysis and optimization of flowthrough diffusion cell system. Pharm. Res. 11, 595–599.

Durrheim, H., Fkynn, G.L., Higuchi, W.I., Behl, C.R., 1980. Permeation of hairless mouse skin I: Experimental methods and comparisons with human epidermal permeation by alkanols. J. Pharm. Sci. 69, 781–786.

Franz, T.J., Tojo, K., Shah, K.R., Kydonieus, A., 1992. Transdermal Delivery. Marcel Dekker, New York.

Ghosh, T.K., Pfister, W.R., Yum, S.I., 1997. Transdermal and topical drug delivery systems. In: Pfister, W.R. (Ed.), Transdermal and Dermal Therapeutic Systems: Current Status. Interpharm Press, Illinois, pp. 38–59.

Ghosh, T.K., Pfister, W.R., Yum, S.I., 1997. Transdermal and topical drug delivery systems. In: Buyuktimkin, N., Buyuktimkin, S. (Ed.), Chemical Means of Transdermal Drug Permeation Enhancement. Interpharm Press, Illinois, pp. 357–371.

Hilton, J.B., Woollen, H., Scott, R.C., Auton, T.R., Trebilcock, K.L., Wilks, M.F., 1994. Vehicle effects on in vitro percutaneous absorption through rat and human skin. Pharm. Res. 11, 1396–1399.

Kokubo, T., Sugibayashi, K., Morimoto, Y., 1991. Diffusion of drug in acrylic 19 type pressure-sensitive adhesive matrices. I. Influence of physical property of the matrices on the drug diffusion. J. Contol. Rel. 17, 69–78.

Kokubo, T., Sugibayashi, K., Morimoto, Y., 1994. Interaction between drugs and pressure-sensitive adhesives in transdermal therapeutic systems. Pharm. Res. 11, 104–107.

Møllgaard, B., Hoelgaard, A., 1983. Vehicle effect in topical drug delivery I. influence of glycols and drug concentration on skin transport. Acta Pharm. Suec. 20, 433–442.

Roy, S.M., Gutierrez, M., Flynn, G.L., Cleary, G.W., 1996. Controlled transdermal delivery of fentanyl: characterization of pressure-sensitive adhesives for matrix patch design. J. Pharm. Sci. 85, 491–495.

Wilking, S.M., Husberg, M.L., Ko, C.U., Wick, S.M., 1994. The effect of excipients on the physical properties of selected acrylate, polyisobutylene, and silicone pressure-sensitive adhesives commonly utilized in transdermal 20 drug delivery systems. Pharm. Res. 11, S226.

Sherertz, E.F., Sloan, K.B., McTiernan, R.G., 1990. Transdermal delivery of 5-fluorouracil through skin of hairless mouse and humans in vitro: a comparison of the effect of formulations and a prodrug. Arch. Dermatol. Res. 282, 463–468.

Twist, J.N., Zatz, J.L., 1990. The effect of solvents on solute penetration through fuzzy rat skin in vitro. J. Soc. Cosmet. Chem. 40, 231–242.

Wilking, S.M., Husberg, M.L., Ko, C.U., Wick, S.M., 1994. The effect of excipients on the physical properties of selected acrylate, polyisobutylene, and silicone pressure-sensitive adhesives commonly utilized in transdermal 20 drug delivery systems. Pharm. Res. 11, S226.