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Transdermal Delivery of Diclofenac Using Microemulsions

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A transdermal preparation containing diclofenac diethylammonium (DDA) was developed using an O/W microemulsion system. Of the oils tested, lauryl alcohol was chosen as the oil phase of the microemulsion, as it showed a good solubilizing capacity and excellent skin permeation rate of the drug. Pseudoternary phase diagrams were constructed to obtain the concentration range of oil, surfactant and cosurfactant for microemulsion formation, and the effect of these additives on skin permeation of DDA was evaluated with excised rat skins. The optimum formulation of the microemulsion consisted of 1.16% of DDA, 5% of lauryl alcohol, 60% of water in combination with the 34.54% of Labrasol (surfactant)/ethanol (cosurfactant) (1:2). The efficiency of formulation in the percutaneous absorption of DDA was dependent upon the contents of water and lauryl alcohol as well as Labrasol:ethanol mixing ratio. It was concluded that the percutaneous absorption of DDA from microemulsions was enhanced with increasing the lauryl alcohol and water contents, and with decreasing the Labrasol:ethanol mixing ratio in the formulation.

Key words: Microemulsion, Diclofenac, Transdermal delivery, Topical application

INTRODUCTION

Percutaneous administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has been studied as a drug delivery route in order to increase therapeutic efficacy. Diclofenac, which belongs to the therapeutically important class of NSAIDs, is extensively metabolized in the liver. Because of its short biological half-life, the drug needs to be administered quite frequently (Menasse *et al.*, 1978). Transdermal delivery of diclofenac may provide better patient compliance over oral administration. However, diclofenac is not easily absorbed on transdermal application (Nishihata *et al.*, 1987).

Efforts have been made to increase the therapeutic efficacy of diclofenac after topical application. A popular technique is the use of penetration enhancers which reversibly reduce the permeability barrier of the stratum corneum (Barry, 1991). Many compounds, such as isopropyl myristate (Naito and Tominaga, 1985), *N,N*-diethyl-*m*-toluamide (Windheuser *et al.*, 1982), decylmethyl sulfoxide (Touitou and Fabin, 1988), ethanol (Nishihata *et al.*, 1988; Obata *et al.*, 1993), *n*-octanol and decanol (Takahashi *et al.*, 1991a, b), hydrogenated soya phospholipid (Nishihata *et al.*, 1987), and nonionic surfactants (Iwasa *et al.*, 1991) have been suggested to enhance the permeation of diclofenac through the skin.

The other approach is to modify the formulation of the vehicle which plays an important role in the percutaneous absorption (Nannipieri *et al.*, 1990; Loth, 1991). Recently, particulate systems such as liposomes and nanoparticles have been investigated as vehicles for the transdermal absorption of drugs (Knepp *et al.*, 1990; Cappel and Kreuter, 1991; Lasch *et al.*, 1991). Microemulsions, characterized as thermodynamically stable and clear isotropic systems, have also been proposed in pharmaceutical applications (Gallarate *et al.*, 1988; Iwamoto *et al.*, 1991). Currently, microemulsions are recognized as good vehicles for the percutaneous absorption of drugs (Fevrier *et al.*, 1991; Kemken *et al.*, 1991; Delgado-Charro *et al.*, 1997; Rhee *et al.*, 2001). Unlike liposomes, these systems are relatively stable at room temperature for a long period of time and solubilize considerable amounts of hydrophobic drugs in their lipophilic domain.

In this study, O/W microemulsions containing 1.16% diclofenac diethylammonium (DDA) have been developed

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after screening oils and obtaining optimum components and concentration ranges to provide maximal skin permeation rates of DDA.

MATERIALS AND METHODS

Materials

The following materials were kindly donated from Gattefossé (Saint Priest Cedex, France) and used as received: PEG-6 glyceryl linoleate (Labrafil M 2125), propylene glycol laurate (Lauroglycol FCC), caprylic/capric triglyceride (Labrafac lipo), diethylene glycol monoethyl ether (Transcutol), and PEG-8 glycol caprylate (Labrasol).

Soybean oil, corn oil, isopropyl myristate and mineral oil were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Olive oil was from Yakury Chemical Co. (Tokyo, Japan), lauryl alcohol and linoleic acid were from Fluka Chemical Co., (Switzerland), oleic acid, polysorbate 80 and polysorbate 85 were from Shinyo Chemical Co. (Tokyo, Japan), and 1,4-dioxane was from Junsei Chemical Co. (Tokyo, Japan). HPLC grade acetonitrile was obtained from Fisher Scientific (Fair Lawn, NJ, USA). Water was deionized and filtered in house. All other chemicals and solvents were of analytical reagent grade.

Screening of oils for microemulsion

To find out appropriate oils that have good solubilizing capacity of the drug and thus can be used as the oil phase in microemulsion, the solubility of DDA in various oils was measured. Oils employed were listed in Table I. An excess amount of DDA was added to 5 mL of each oil and shaken with an isothermal shaker (KWSK-400, Ki Woo Trading Co., Korea) at 20±1°C for 48 h. The suspension was filtered through a membrane filter (Nylon Acrodisc®, 0.45 μm I.D., 13 mm, Gelman, U.S.A.), and the drug concentration in the filtrate was determined by HPLC (Nishihata *et al.*, 1987) after appropriate dilution with the mobile phase. Oils that showed high solubility of DDA were used in the preparation of the vehicles for the skin permeation study.

The vehicles were prepared by dissolving appropriate amounts of the drug and the oils directly in propylene glycol (PG). The concentrations of DDA and oil in PG were fixed to 1.16% and 5%, respectively. A control PG vehicle contained 1.16% DDA and no oil was used. The effect of oils on the skin permeation of DDA from the prepared vehicles was evaluated using Franz diffusion cells fitted with excised rat skins. After 2 mL of the vehicle was applied on the epidermal surface of the skin, 200 μL of the receptor medium were withdrawn at predetermined time intervals, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 12 h. The oil showing the highest skin permeation rate of the drug was chosen and used in the preparation of microemulsion.

Construction of phase diagram and formulation of DDA microemulsions

Pseudoternary phase diagrams were constructed to obtain the components and concentration ranges that resulted in a large existence area of microemulsion containing 1.16% DDA. The boundaries of the microemulsion domains in the triangular diagrams were determined by progressive titration of the four component mixtures for a series of surfactant (S)/cosurfactant (CoS) mixing ratios. At the ratio of S to CoS of 1/2, a desired amount of DDA was weighed out and dissolved in the surfactant mixture to make 1.16% DDA solution. Separately, the aqueous mixture of water and oil containing 1.16% DDA was also prepared. Then, the S/CoS mixture was added drop by drop, under gentle agitation, to each aqueous mixture of water and oil. Concentrations of the S/CoS mixture at which turbidity-to-transparency and transparency-to-turbidity transitions occurred were determined. By repeating this experiment at different S/CoS (2 and 5) ratios, boundaries of the microemulsion domain corresponding to a chosen value of S/CoS were determined. Eighteen different formulations with various values of oil of 5 and 10%, water of 30, 45, and 60% and S/CoS of 0.5, 2, and 5 were prepared for the *in vitro* skin permeation study (Table II). Effects of the contents of the oil and the mixture of S/CoS on the permeation of DDA through excised rat skins were evaluated.

Measurement of skin permeation rate of DDA

After hair was removed carefully with an electric clipper (Daito Electric, Japan, Model 900), a 4 cm × 4 cm patch of skin was excised from the dorsal region from each sacrificed rat and the subcutaneous fat and other extraneous tissues were trimmed. The excised skins were stored at -20°C and used within one week after the skin harvest.

The extent and rate of skin permeation of DDA from prepared microemulsions were determined using Franz diffusion cells fitted with excised rat skins. The receptor phase was an isotonic phosphate buffer (pH 7.4, 0.02 M) with a volume of 10 mL and its temperature was maintained at 37°C using a thermostatic water pump (Fine Scientific Instrument, Model FT-101). The receptor phase was continuously stirred at a constant rate of 600 rpm throughout the experiment. The skin surface area available for the permeation was 1.77 cm^2. The donor chamber was closed to the atmosphere with parafilm. After 2 mL of the microemulsion was applied on the epidermal surface of the skin, 200 μL of the receptor medium were withdrawn at 2, 4, 6, 8, 10, and 12 h, with the withdrawn volume being immediately replaced with fresh buffer. Concentrations of DDA in each sample was quantitated using an HPLC method.

HPLC analysis of DDA

DDA was analyzed with a slight modification of the HPLC method reported previously (Nishihata *et al.*, 1987). The HPLC system consisted of an isocratic pump (Hitachi L-6000, Ibraki-ken, Japan), an injector (Rheodyne 7125, Berkeley, CA, USA), and a UV/Vis detector (Hitachi L-4000, Ibraki-ken, Japan) at a wavelength of 280 nm interfaced with an integrator (Hitachi D-2500, Ibraki-ken, Japan). The column used was a C_{18} column (Cosmosil® C_{18}, 4.6 mm × 150 mm, 5 μm particle size, Nacalai Tesque, Japan). The mobile phase was a mixture of 0.02 M citrate buffer and acetonitrile in volume ratio of 1:1 and the flow rate was 1.0 mL/min.

Data analysis

Cumulative amounts of DDA permeated through excised rat skins were plotted as a function of time. The slope and intercept of the linear portion of the plot was derived by regression. The permeation rate at steady-state (J_s, μg/cm^2/h) was calculated as the slope divided by the skin surface area. The intercept on the X-axis was taken as the lag time (T_L, h)

Statistics

All the skin permeation experiments were repeated three times and their mean values with standard deviation were presented. Two-way ANOVA was used to elucidate the influence of different vehicle systems on the percutaneous absorption of DDA.

Determination of droplet size in microemulsion

The size of oil droplets in microemulsion was determined using a dynamic light scattering method employing He-Ne laser (Lexer Laser Inc., U.S.A., Model 127).

RESULTS AND DISCUSSION

Screening of oils for microemulsion

The solubility of DDA determined in various oils is shown in Table I. The drug solubility was the highest in lauryl alcohol (73.5±6.0 μg/mL), followed by linoleic acid (30.1±0.2 μg/mL) and oleic acid (19.1±1.4 μg/mL). To study the effect of oils on the skin permeation of DDA, the oils showing high drug solubility profiles (lauryl alcohol, linoleic acid and oleic acid) were incorporated into 1.16% DDA-PG vehicle, and the skin permeation of the drug was measured using excised rat skins. Permeation profiles of DDA from these vehicles containing 5% of individual oils are shown in Fig. 1. The permeation rate of DDA for the control PG vehicle was increased significantly with the addition of oils. Lauryl alcohol showed the highest permeation rate (64.65±3.93 μg/cm^2/h) followed by linoleic acid (15.03±1.88 μg/cm^2/h) and oleic acid (5.39±1.08 μg/cm^2/h). These permeation rates were increased by approximately 100-1300-folds over the control vehicle. Generally, the skin permeation is inhibited as the affinity to vehicle becomes greater due to a slow release of the drug and/or a poor transfer from the vehicle to the skin (Takahashi *et al.*, 1991a). In this study, however, lauryl alcohol resulted in the highest skin permeation enhancing effect even though it showed the highest solubilizing capacity among oils employed. The enhancing mechanism of lauryl alcohol may be explained by the solvent drag effect, which may be caused due to its high solubilizing capacity and lipophilic properties, making more drug partition to the stratum corneum. Lauryl alcohol was subsequently used

Table I. Solubility of diclofenac diethylammonium (DDA) in various oils at 20°C

Group	Oils	Solubility (μg/mL)
Natural oils	Squalene	1.9 ± 0.1[a]
	Soybean oil	1.4 ± 0.1
	Olive oil	0.8 ± 0.1
Polyglycolyzed glycerides	Labrafil M 2125	12.5 ± 0.7
	Lauroglycol FCC	11.5 ± 0.5
Glycerides	Triacetin	1.5 ± 0.1
	Labrafac lipophile	1.2 ± 0.1
	Myvacet	3.4 ± 0.2
Fatty acids and alcohols	Lauryl alcohol	73.5 ± 6.0
	Oleic acid	19.1 ± 1.4
	Linoleic acid	30.1 ± 0.2
Others	Mineral oil	0.4 ± 0.1
	IPM	1.1 ± 0.1

Mean±S.D.(n=3)

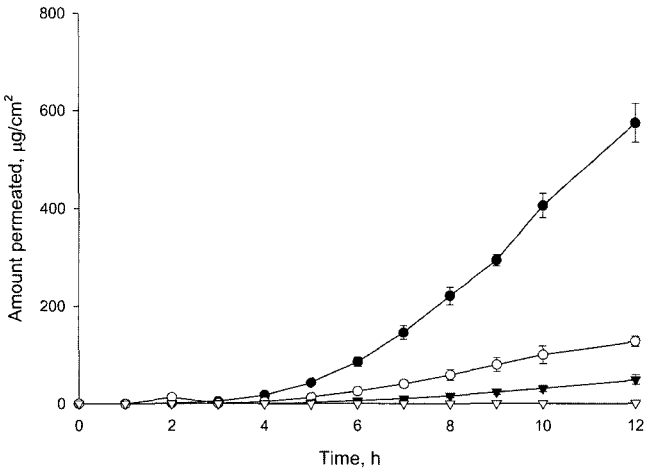

Fig. 1. Effect of oils in PG vehicle containing 1.16% diclofenac diethylammonium on the drug permeation through excised rat skins (Mean±S.D., n=3). Key: ▽; control, ●; lauryl alcohol, ○; linoleic acid, ▼; oleic acid.

as the oil phase for the formulation of microemulsions.

Optimization of microemulsion formulation

Phase diagrams were constructed to show the influence of the S/CoS on the area of existence of stable O/W microemulsion consisting of DDA, lauryl alcohol, Labrasol, ethanol and water (Fig. 2). Labrasol and ethanol were used as the surfactant and the cosurfactant, respectively, based on the preliminary results (data not shown). At S/CoS ratios of 1/2, 2 and 5, no significant difference in microemulsion existence area was observed. Among formulations tested, seventeen formulations (except for Formula 4) existed inside the area of the O/W microemulsion formation in the pseudoternary phase diagram and formed a clear microemulsion at the additive concentrations examined. Using these seventeen microemulsion formulations (Table II), effects of the contents of oil, water and S/CoS mixture on the skin permeation of DDA were evaluated with excised rat skins.

The contents of oil and water were varied from 5 to 10% and from 30 to 45 and 60%, respectively, while the content of S/CoS mixture was varied at 30, 40, 45, 60 and 65%. The skin permeation rates of the drug calculated from the permeation profiles of each formula are shown in Table III. Among the formulations tested, Formula 1 which was composed of 1.16% DDA, 5% lauryl alcohol, 60% water and 34.54% Labrasol/ethanol (1/2) mixture showed

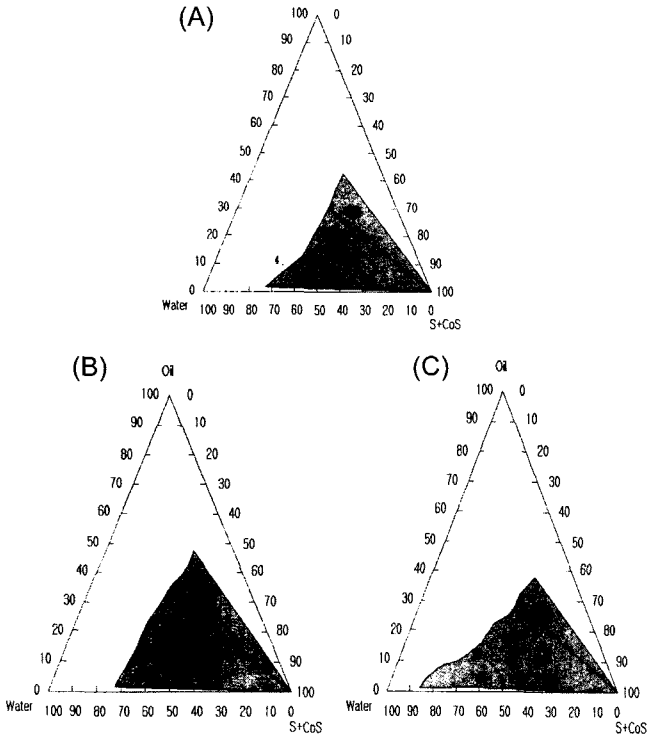

Fig. 2. Pseudoternary phase diagrams of microemulsion composed of diclofenac diethylammonium, lauryl alcohol (oil), Labrasol (surfactant, S), ethanol (cosurfactant, CoS) and water. Key : A; S/CoS=1/2, B; S/CoS=2, C; S/CoS=5.

Table II. Diclofenac diethylammonium (DDA) microemulsion of *different compositions used for optimization*

Formulation #	DDA	S/CoS	Oil (w/w %)	Water (w/w %)
1	1.16	0.5	5	60
2	1.16	0.5	5	45
3	1.16	0.5	5	30
4	1.16	0.5	10	60
5	1.16	0.5	10	45
6	1.16	0.5	10	30
7	1.16	2	5	60
8	1.16	2	5	45
9	1.16	2	5	30
10	1.16	2	10	60
11	1.16	2	10	45
12	1.16	2	10	30
13	1.16	5	5	60
14	1.16	5	5	45
15	1.16	5	5	30
16	1.16	5	10	60
17	1.16	5	10	45
18	1.16	5	10	30

Table III. Permeation parameters of diclofenac diethylammonium (DDA) through excised rat skins from 1.16% DDA microemulsions having different compositions

	Permeation parameters	
Formulation #	T_L (h)	J_s (μg/cm²/h)
1	2.87 ± 0.42[a]	18.89 ± 1.64
2	2.20 ± 0.91	10.72 ± 1.03
3	3.72 ± 0.06	6.10 ± 1.16
4	–	–
5	3.35 ± 0.30	14.24 ± 0.81
6	3.44 ± 0.06	11.27 ± 0.56
7	3.29 ± 0.67	2.67 ± 0.04
8	2.54 ± 0.69	1.75 ± 0.05
9	2.78 ± 0.50	0.78 ± 0.04
10	2.80 ± 0.78	8.22 ± 2.46
11	2.83 ± 0.72	4.82 ± 0.92
12	3.42 ± 0.13	1.13 ± 0.18
13	2.91 ± 0.47	1.82 ± 0.51
14	4.16 ± 0.05	1.30 ± 0.24
15	2.43 ± 0.85	0.93 ± 0.12
16	2.35 ± 0.38	6.05 ± 1.33
17	3.98 ± 0.06	0.61 ± 0.14
18	5.53 ± 0.07	0.41 ± 0.06

[a]Mean±S.D., n=3

the highest permeation rate (18.99±1.64 μg/cm²/h). The average size of oil droplets in microemulsion of Formula 1 was 32 nm, with the range of 7-112 nm.

The content of surfactant mixture (S/CoS) in microemulsion affected the skin permeation rate of DDA significantly. As the content of surfactant mixture was decreased from 65% to 35% at S/CoS = 0.5, the skin permeation rate of DDA increased by 3-folds. This may be due to an increased thermodynamic activity of the drug in the microemulsion at the lower content of surfactant, as DDA is poorly water-soluble and yet solublized in the surfactant mixture. On the other hand, as the content of water in microemulsions was decreased from 60% to 30%, the skin permeation of the drug was decreased for the same reason.

It was also found that skin permeation of the drug in microemulsion was significantly influenced by the content of ethanol (CoS) in S/CoS mixture. When the S/CoS was decreased from 5 to 1/2, the skin permeation rate of DDA was increased by 9.7-folds. The highest percutaneous DDA absorption was obtained with microemulsions containing 23% ethanol. It is possible that, with increasing the content of ethanol, the size of the internal phase was decreased making the surface area of the droplet increased significantly. The influence of ethanol in aqueous solutions upon the transport behavior of several permeants across the skin has been evaluated (Obata *et al.*, 1991; Takayama *et al.*, 1991). It has been reported that ethanol may alter or form additional pore/polar pathways in the stratum corneum as a result of a combination of changes in protein conformation, reorganization within the lipid polar head region or lipid extraction. The content of oil also showed similar effects on the skin permeation of DDA but its mechanism is different from that of the S/CoS. As the content of oil was increased, the number of the internal phase was increased, which increased the skin permeation rate of the drug.

A dermally applied microemulsion is expected to penetrate the stratum corneum and exist intact in the whole horny layer as previously suggested in the double-labelling studies (Hofland *et al.*, 1990) and the freeze-fracture electron microscopic studies (Weiner and Egbaria, 1990). Once it enters into the stratum corneum, microemulsions may simultaneously alter both the lipid and the polar pathways. The lipophilic domain of the microemulsion can interact with the stratum corneum in many ways. DDA dissolved in the lipid domain of a microemulsion can directly partition into the lipids of the stratum corneum or the lipid vesicles themselves can intercalate between the lipid chains of the stratum corneum, thereby destabilizing its bilayer structure. In effect, these interactions will lead to increase the permeability of the lipid pathway to DDA.

On the other hand, the hydrophilic domain of the microemulsion can hydrate the stratum corneum to a greater extent. There is a general experience that hydration of the skin plays an important role in the percutaneous uptake of DDA. When the aqueous fluid of the microemulsion enters the polar pathways, it will increase the interlamellar volume of stratum corneum lipid bilayers, resulting in a disruption of the interfacial structure. Since some lipid chains are covalently attached to corneocytes, hydration of these proteins will also lead to the disorder of lipid bilayers. Similarly, swelling of the intercellular proteins may also disturb the lipid bilayers; a lipophilic drug like DDA can then permeate more easily through the lipid pathway of the stratum corneum. The greater drug penetration enhancing activity of microemulsions may be attributed to the combined effects of both the lipophilic and hydrophilic domains of microemulsions.

The particle size of the microemulsion also affects the percutaneous absorption of drugs. When the particle size is very small, there is a chance that the number of vesicles that can interact on a fixed area of stratum corneum will be increased, thereby increasing its efficiency in the percutaneous uptake of drugs. This may be the reason why microemulsions of other formula whose particle sizes were larger than that of Formula 1 showed relatively lower DDA permeation.

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