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Transdermal delivery of ketoprofen using microemulsions

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Abstract

A transdermal preparation containing ketoprofen was developed using O/W microemulsion system. Of the oils tested, oleic acid 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 ketoprofen was evaluated with excised rat skins. The optimum formulation of the microemulsion consisted of 3% ketoprofen, 6% oleic acid, 30% Labrasol/Cremophor RH 40 (1:1) and water. Terpenes were added to the microemulsion at the level of 5% and their effect on the skin permeation of ketoprofen from the microemulsion was evaluated. Of the four terpenes used, only limonene resulted in a powerful enhancing activity (3-fold increase over control).

Keywords: Microemulsion; Ketoprofen; Enhancer; Transdermal delivery

1. Introduction

Ketoprofen, a potent non-steroidal anti-inflammatory drug (NSAID), has been widely used for the treatment of rheumatoid arthritis and related diseases (Kantor, 1986). However, it accompanies adverse side effects including gastrointestinal irritation when administered orally. Since ketoprofen is usually given to patients over an extended period, efforts to reduce its adverse side effects have been attempted. One promising method is to administer the drug via skin. Ketoprofen is an excellent candidate for transdermal delivery among various NSAIDs (Cordero et al., 1997; Vincent et al., 1999), as it has an appropriate partition coefficient and adequate aqueous solubility compared to other NSAIDs. Although ketoprofen has a short elimination half-life of 1.5–4 h after oral administration (Jamali and Brocks, 1990), its plasma levels were maintained relatively consistent for $\sim$24 h after transdermal application (Chi, 1989). Thus, transdermal delivery of ketoprofen may provide better patient compliance over oral administration. Various transdermal dosage forms containing ketoprofen have been reported, including patches (Yim et al., 1994; Valenta and Almasi-Szabo, 1995; Singh et al., 1996), gels (Noda et al., 1983; Chi and Jun, 1990), creams (Itoh et al., 1985) and ointments (Henmi et al., 1994; Gurol et al., 1996). In an attempt to

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improve the skin permeation of ketoprofen, several physicochemical methods have been evaluated. Those are the development of appropriate vehicles (Rhee et al., 1999; Valenta et al., 2000), iontophoresis (Panus et al., 1997; Tashiro et al., 2000), and use of permeation enhancers (Obata et al., 2000).

Microemulsion is defined as an O/W or W/O emulsion producing a transparent product that has a droplet size < 0.15 μm and does not have the tendency to coalesce. It consists of oil phase, surfactant, cosurfactant and aqueous phase. Microemulsions have received a great attention in recent years for various applications, including transdermal delivery of drugs (Delgado-Charro et al., 1997). Several mechanisms have been proposed to explain the advantages of microemulsion for the transdermal delivery of drugs. First, a large amount of drug can be incorporated in the formulation due to the high solubilizing capacity. Second, the permeation rate of the drug from microemulsion may be increased, since the affinity of a drug to the internal phase in microemulsion can be easily modified, to favor partitioning into stratum corneum, using different internal phase, changing its portion in microemulsion or adjusting its property. Third, the surfactant and cosurfactant in the microemulsions may reduce the diffusional barrier of the stratum corneum by acting as permeation enhancers. Although many drugs have been incorporated in microemulsions, ketoprofen has not been evaluated.

In this study, O/W microemulsions containing 3% ketoprofen have been developed after screening oils, obtaining the components and their concentration ranges for microemulsion formation, and optimizing them to achieve maximum skin permeation rate of ketoprofen. Also, terpenes were evaluated as potential permeation enhancers for ketoprofen in microemulsion.

2. Materials and methods

2.1. Materials

The following reagents were used as received without further purification: ketoprofen, triacetin, cotton seed oil, corn oil, sesame oil, olive oil, isopropyl myristate (IPM), light mineral oil and squalene (Sigma Chemical Co., USA), limonene, cineole, menthol and camphor (Wako Pure Chemical, Japan), oleic acid (Shinyo Chemical Co., Japan), and HPLC grade acetonitrile (Mallinckrodt Chemical Inc., USA).

PEG-8 glycol caprylate (Labrasol) was kindly donated by Gattefossé, France, polyoxyl 40 hydrogenated castor oil (Cremophor RH 40) by BASF, Germany, and acetylated monoglycerides (Myvacet) by ChoongWae Pharma Corp., Korea. Water was deionized and filtered in house. All other chemicals and solvents were of analytical reagent grade.

2.2. Screening of oils for microemulsion

To find out appropriate oils that have good solubilizing capacity of ketoprofen and, thus, can be used as the oil phase in microemulsion, the solubility of ketoprofen in various oils was measured. Oils employed were vegetable oils (cotton seed oil, corn oil, sesame oil and olive oil), mineral oil, squalene, oleic acid, Myvacet, IPM and triacetin. An excess amount of ketoprofen was added to 5 ml of each oil and shaken reciprocally at 20°C for 72 h. The suspension was filtered through a membrane filter (Nylon Acrodisc®, 0.45 μm, Gelman Sciences Inc., USA) and the drug concentration in the filtrate was determined using an HPLC method (Satterwhite and Boudinot, 1988) after the appropriate dilution with mobile phase.

The oils which showed high solubility of ketoprofen were used in the preparation of microemulsion containing 3% ketoprofen, and their effect on the skin permeation of ketoprofen from the prepared microemulsion was evaluated using excised rat skins.

2.3. Construction of phase diagrams and formulation of ketoprofen microemulsion

Pseudoternary phase diagrams were constructed to obtain the components and their concentration ranges that can result in large existence area of microemulsion without the drug or containing 3%

ketoprofen (Gattefossé, 1994). At the ratio of surfactant to cosurfactant (S/CoS) of 1/2, oily mixtures of oil, surfactant and cosurfactant were prepared. The ratio of oil to the mixture of surfactant and cosurfactant was varied as 3, 10, 20, 30, 40, 50 and 70%. Water was added drop by drop, under gentle agitation, to each oily mixture. Usually, after the clear mixture became turbid at a certain point (beginning of phase inversion area), the turbid mixture turned to be clear (beginning of O/W microemulsion area) and, then, finally turbid once again (end of O/W microemulsion area) with the continuous addition of water. The experiment was repeated at different S/CoS (1, 3, 5 and 7). Based on these results, appropriate oil, surfactant and cosurfactant were selected and used in the preparation of microemulsions containing ketoprofen. The effects of the contents of the oil and the mixture of surfactant and cosurfactant (surfactant mixture) on the permeation of ketoprofen through excised rat skins were evaluated.

To improve the skin permeation rate of ketoprofen, selected terpenes (limonene, menthol, cineole and camphor) were further added to the final microemulsion formulation at the concentration level of 5%w/w and the effect of these terpenes on the skin permeation of ketoprofen from microemulsion was also evaluated.

2.4. 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., USA, Model 127).

2.5. Measurement of skin permeation rate of ketoprofen

Skins were obtained from male Sprague-Dawley rats weighing 250 ± 20 g. After hair was removed carefully with an electric clipper (Daito Electric, Japan, Model 900), a 5×5 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 rat skins were stored at $-20°$ and used within one week after the skin harvest.

The extent and rate of skin permeation of ketoprofen from prepared microemulsions were determined using Franz diffusion cells fitted with excised rat skins. The effective diffusional area was 1.77 cm^2. The receptor compartment was filled with 11.5 ml of pH 7.4 phosphate buffer (0.01 M) and its temperature was maintained at 37 ± 0.5 °C using a thermostatic water pump (Fine Scientific Instrument, Korea, Model FT-101) and stirred at 600 rpm throughout the experiment. After 2 ml of the microemulsion was applied on the epidermal surface of the skin, 0.2 ml of the receptor medium was withdrawn every hour up to 9 h after the application, and replaced immediately with an equal volume of fresh phosphate buffer equilibrated at 37 ± 0.5 °C.

2.6. Data analysis

The cumulative amount of ketoprofen permeated through excised rat skins was 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).

2.7. HPLC analysis of ketoprofen

The amount of ketoprofen permeated into the receptor medium was determined with a slight modification of the HPLC method reported previously (Satterwhite and Boudinot, 1988). The HPLC system consisted of an isocratic pump (Hitachi, Japan, Model L-7110), an autosampler (Hitachi, Japan, Model L-7200), an UV/Visible detector (Hitachi, Japan, Model L-7400) and an integrator (Hitachi, Japan, Model D-7500). The column used was a C_{18} column (Cosmosil, 4.6×150 mm, 5 μm particle size, Nacalai Tesque, Japan). The mobile phase was a mixture of acetonitrile and pH 7.4 phosphate buffer (78:22 V/V). The flow rate of the mobile phase was 1 ml/min and the detection wavelength was set at 258 nm. After the receptor medium was mixed with an

equal volume of the mobile phase, 50 μl of the mixed sample was injected onto the column. All operations were carried out at ambient temperature.

2.8. Statistics

All the skin permeation experiments were repeated three times and their mean values with standard error were presented. Student's *t*-test was performed to see any significant difference in the permeation rate of ketoprofen between the microemulsion containing permeation enhancers and the control without enhancer. Two-way ANOVA was used to test the statistical difference in the permeation rate among microemulsions of different composition.

3. Results and discussion

3.1. Screening of oils for microemulsion

The solubility of ketoprofen determined in various oils is shown in Table 1. The drug solubility was highest in triacetin (81.0 ± 5.6 mg/ml), followed by Myvacet, oleic acid and IPM. Vegetable oils resulted in solubilities ranging from 4 to 5 mg/ml, and the drug solubility in mineral oil was only 0.25 mg/ml.

Microemulsions containing 3% ketoprofen were prepared using the oils showing high drug solubility (triacetin, Myvacet, oleic acid and IPM), and the permeation rate of the drug through excised rat skin from microemulsions containing each of the oils was determined. The microemulsion consisted of 15% oil, 15% Labrasol, 15% Cremophor RH 40, and 52% water. Labrasol and Cremophor RH 40 were used as the surfactant and the cosurfactant, respectively, based on the preliminary results (data not shown). The cumulative amounts of ketoprofen permeated across excised rat skins from the microemulsions prepared with four different oils are shown in Fig. 1. Oleic acid showed the highest permeation rate (8.44 ± 0.86 μg/cm^2/h) followed by IPM (5.92 ± 0.39 μg/cm^2/h), Myvacet (2.21 ± 0.19 μg/cm^2/h) and triacetin (1.22 ± 0.29 μg/cm^2/h). Takahashi et al. (1991) found that the skin permeation was inhibited as the affinity to vehicle became greater due to a slow release of the drug and/or a poor transfer from the vehicle to the skin. In this study, however, oleic acid, which has less solubilizing capacity of ketoprofen than IPM, resulted in the higher skin permeation rate of the drug than IPM. This may be due to the permeation enhancing effect of oleic acid, which is a powerful enhancer for many drugs (Büyüktimkin et al., 1997) including ketoprofen (Kim et al., 1993). The enhancing mechanism of oleic acid may involve the increased fluidity of lipid portion of the stratum corneum (Kanikkannan et al., 2000). Oleic acid was subsequently used as the oil phase for the formulation of microemulsion containing ketoprofen in this study.

Table 1
Solubility of ketoprofen in various oils at 20° C

Oils	Solubility (mg/ml)
Cotton seed oil	4.89 ± 0.35[a]
Corn oil	4.66 ± 0.62
Sesame oil	4.08 ± 0.64
Olive oil	4.26 ± 0.45
Mineral oil	0.25 ± 0.04
Squalene	0.53 ± 0.08
Oleic acid	20.58 ± 2.09
Myvacet	41.13 ± 2.09
IPM	10.73 ± 0.17
Triacetin	81.04 ± 5.60

[a] Mean ± S.D. ($n = 3$).

3.2. Optimization of microemulsion formulation

The construction of phase diagram makes it easy to find out the concentration range of components for the existence range of microemulsions. Fig. 2 shows the phase diagrams, constructed to determine the optimum S/CoS, for the formulation of O/W microemulsion consisting of oleic acid, Labrasol, Cremophor RH 40 and water. S/CoS was varied as 1/2, 1, 3, 5 and 7. As shown in this figure, as S/CoS decreases, the existence area of O/W microemulsion becomes enlarged, reaching a maximum at S/CoS of 1.

Based on this result, O/W microemulsions containing 3% ketoprofen were prepared at S/CoS of

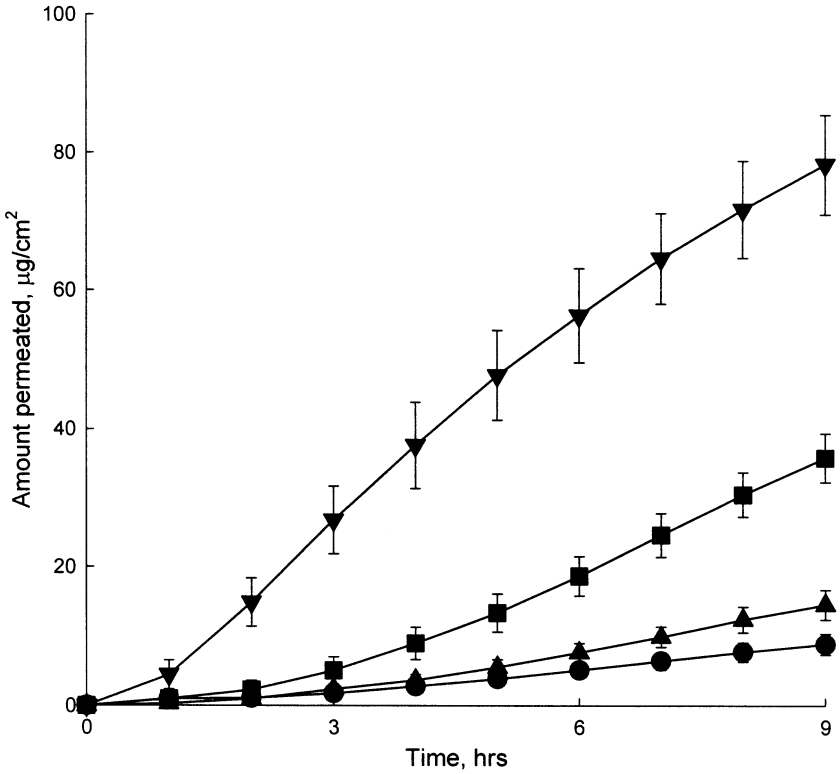

Fig. 1. Permeation profiles of ketoprofen through excised rat skins from microemulsions prepared with different oils (Mean ± S.E., $n = 3$). Key: ●, triacetin; ▲, Myvacet; ▼, oleic acid; ■, IPM.

1. The microemulsions containing ketoprofen resulted in similar phase diagrams as for the microemulsions without the drug. In these formulations, the content of oil phase (oleic acid) was varied as 3, 6 and 12%, while the content of surfactant mixture was varied as 30, 55 and 80%. The detailed composition of nine different O/W microemulsions is shown in Table 2. All these formulations existed inside the area of the O/W microemulsion formation, thus, forming clear microemulsion at the additive concentrations examined.

The effects of the content of oil and surfactant mixture on the skin permeation of ketoprofen were evaluated. The skin permeation profiles are presented in Fig. 3. And the permeation rates of the drug calculated from these profiles in Fig. 3 are shown in Fig. 4. Among the formulations tested, Formula F, which is composed of 3% ketoprofen, 6% oleic acid and 30% Labrasol/Cremophor RH 40 (1/1) mixture, showed the highest permeation profile. The skin permeation rate of ketoprofen from this microemulsion was 9.78 ± 1.02 $\mu g/cm^2/h$.

The content of surfactant mixture in microemulsion affected the skin permeation rate of ketoprofen significantly. As the content of surfactant mixture was decreased from 80 to 30%, the skin permeation rate of ketoprofen was increased 12–23 times. This may be due to an increased thermodynamic activity of the drug in the microemulsion at the lower content of surfactant (Shah, 1994), as ketoprofen is poorly water-soluble, but soluble in the surfactant mixture.

When the content of surfactant mixture was fixed to 80%, the skin permeation rate of ketoprofen reached a maximum at 3% of oil content. However, the difference in the skin permeation rate of the drug from the microemulsion containing different amount of oil (3, 6 and 12%) was not significant. It is considered that high content of

surfactant mixture in the microemulsion may make the effect of oil on the skin permeation less pronounced. On the other hand, at 30 and 55% surfactant mixtures, the skin permeation rates of ketoprofen were significantly different among three formulations containing different content of oil, reaching a maximum at 6%. This finding is consistent with a previous report that, when oleic acid was added to FAPG bases in the range of 0–60%, maximal enhancement of percutaneous absorption of indomethacin was achieved at 5% (Nomura et al. 1990). The average size of oil droplets in microemulsion of Formula F was 91 nm, with the range 46–130 nm.

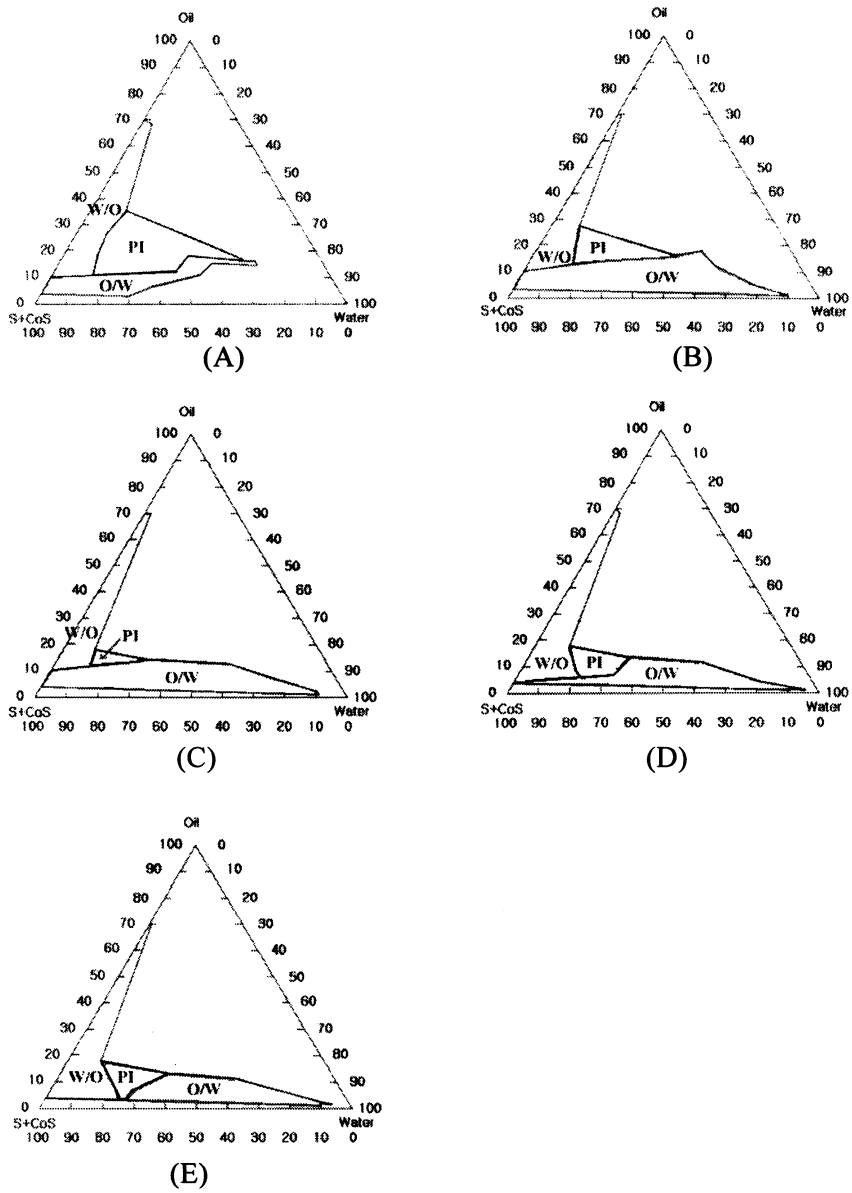

Fig. 2. Pseudoternary phase diagrams of microemulsion composed of oleic acid, surfactant (Labrasol), cosurfactant (Cremophor RH 40) and water. Key: A, S/CoS = 1/2; B, S/CoS = 1; C, S/CoS = 3; D, S/CoS = 5; E, S/CoS = 7.

Table 2
Ketoprofen microemulsion of different compositions used for optimization

Formulations	Components			
	Ketoprofen	Oil	Surfactant mixture[a]	Water
A	3[b]	3	80	14
B	3	3	55	39
C	3	3	30	64
D	3	6	80	11
E	3	6	55	36
F	3	6	30	61
G	3	12	80	5
H	3	12	55	30
I	3	12	30	55

[a] Labrasol + Cremophor RH 40 (1:1, weight).
[b] % w/w.

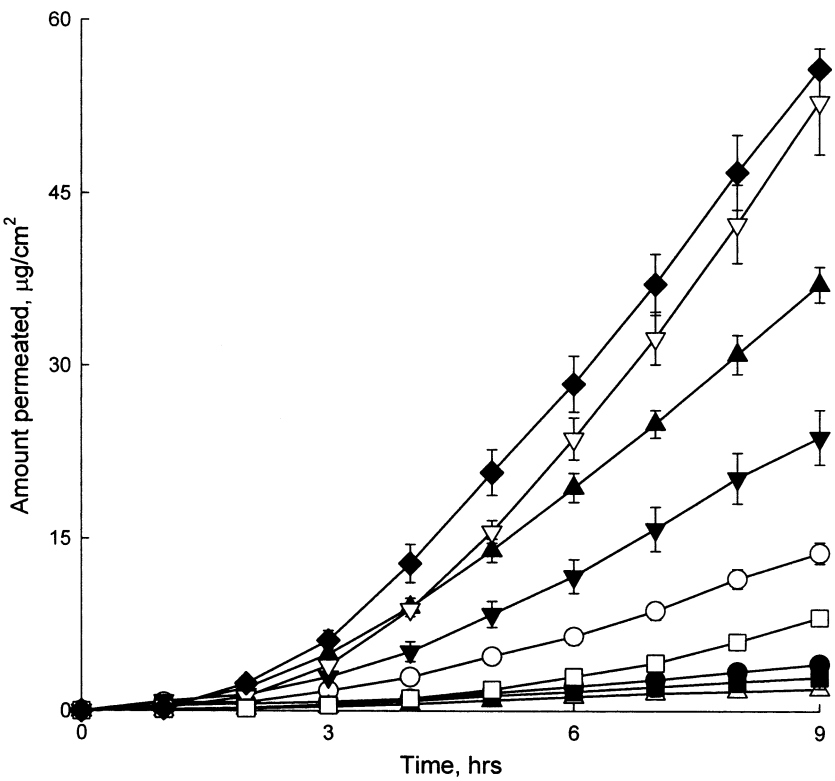

Fig. 3. Permeation profiles of ketoprofen through excised rat skins from 3% ketoprofen microemulsions of different compositions (Mean ± S.E., $n = 3$). Key: ●, A; ○, B; ▲, C; △, D; ▼, E; ▽, F; ■, G; □, H; ◆, I.

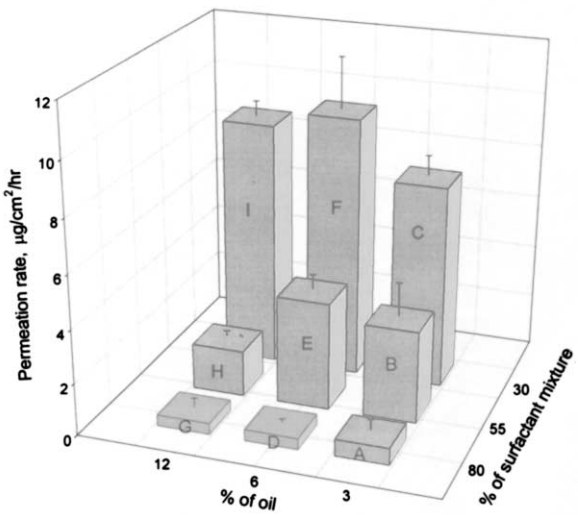

Fig. 4. Permeation rates of ketoprofen through excised rat skins from 3% ketoprofen microemulsions of different compositions. Values represent the mean ± S.D. ($n = 3$).

3.3. Effect of permeation enhancers

To improve the permeation rate of ketoprofen from microemulsions, various terpenes (limonene, menthol, cineole and camphor) were added to the microemulsion of Formula F. At the terpene concentration of 5%, the physical property of microemulsions was not changed. The obtained permeation profiles are shown in Fig. 5. Limonene showed the most pronounced enhancing effect on the permeation rate of ketoprofen. The permeation parameters calculated from the profiles are presented in Table 3. While limonene increased the permeation rate of ketoprofen by ~3-fold compared to the control containing no enhancer, other terpenes did not increase the skin permeation rate of the drug significantly.

Terpenes have been used to increase the skin permeation of a large number of compounds (Büyüktimkin et al., 1997). They have been reported to increase the drug diffusivity in stratum

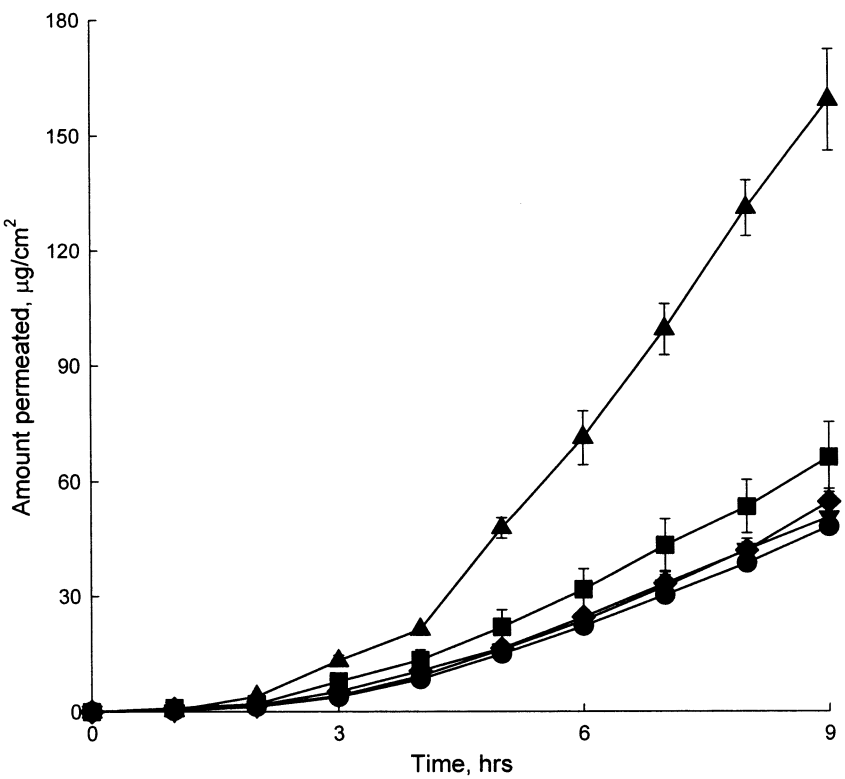

Fig. 5. Permeation profiles of ketoprofen through excised rat skins from 3% ketoprofen microemulsions containing different terpenes at the level of 5% (Mean ± S.E., $n = 3$). Key: ●, control; ▲, limonene; ▼, menthol; ■, cineole; ◆, camphor.

Table 3
Permeation parameters of ketoprofen through excised rat skins from 3% ketoprofen microemulsions containing different permeation enhancers at the level of 5%

Enhancers	Permeation parameters[a]	
	T_L (h)	J_s (μg/cm^2/h)
Control (None)	3.44 ± 0.35[b]	8.58 ± 1.04
Limonene	3.63 ± 0.13	29.56 ± 3.39[c]
Menthol	3.45 ± 0.40	9.03 ± 0.82
Cineole	3.25 ± 0.54	11.36 ± 2.17
Camphor	4.63 ± 1.96	9.89 ± 1.38

[a] T_L: lag time, J_s: permeation rate.
[b] Mean $\pm$ S.D. ($n = 3$).
[c] Significantly different from the control ($P < 0.05$).

corneum and also drug partitioning into stratum corneum by disrupting the intercellular lipid bilayers (Cornwell et al., 1996). The intensity of their effects depends mainly on the lipophilicity of the drug and vehicle used (Williams and Barry, 1991; Büyüktimkin et al., 1997).

For all the enhancers studied, there was no significant change in the lag time for the skin permeation of ketoprofen, unlike other report, in which terpenes enhanced the permeation rate of diclofenac sodium and resulted in longer lag time than the control containing no enhancer (Arellano et al., 1996).

4. Conclusion

An O/W microemulsions containing ketoprofen was formulated for transdermal application. The components and their concentration ranges for the formation of microemulsion were obtained using the construction of pseudoternary phase diagram. Their concentrations were optimized after the evaluation of their effect on skin permeation of the drug. The optimum formulation of the microemulsion consisted of 3% ketoprofen, 6% oleic acid, 30% Labrasol/Cremophor RH 40 (1:1) and water. The addition of limonene to the microemulsion further increased the skin permeation rate of ketoprofen.

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