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Investigation of microemulsion system for transdermal delivery of meloxicam

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Abstract

A new oil-in-water microemulsion containing 0.375% meloxicam was developed in order to improve the skin permeability of meloxicam. Among various surfactants and cosurfactants investigated in the microemulsion system, polyoxyethylene sorbitan trioleate (Tween 85) showed excellent solubility and ethanol expressed skin permeation enhancing effect for meloxicam. The microemulsion existence ranges were defined through the construction of the pseudo-ternary phase diagram. The effect of the content of isopropyl myristate (IPM) and the effect of the mass ratio of the surfactant/cosurfactant (Km) on skin permeation of meloxicam were evaluated with excised rat skins. The optimum formulation with the highest skin permeation rate (5.40 μg/cm^2/h) consisted of 0.375% meloxicam, 5% IPM, 50% Tween 85/ethanol (1:1) and water.

Keywords: Meloxicam; Microemulsion; Transdermal; IPM; Phase diagram; Skin permeability

1. Introduction

Meloxicam, 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (Fig. 1), is a potent non-steroidal anti-inflammatory drug (NSAIDs) of the enolic acid class of oxicam derivatives which shows preferential inhibition of cyclo-oxygenase-2 (COX-2) and inhibits prostaglandin synthesis. Turck et al. (1997) reported that the usual oral dosage of meloxicam in clinical treatment was 7.5–30 mg/day, the elimination half life period of meloxicam in plasma was approximately 20 h, and Cmax was 0.993 μg/ml after oral administration of 15 mg meloxicam to 24 healthy male volunteers. It is very efficient for the treatment of rheumatoid arthritis, osteoarthritis, and other joint diseases. Its therapeutic benefits combined with a good gastrointestinal tolerability are well-documented in comparision with other NSAIDs, however, its oral administration can produce some side effects such as bellyache and indigestion, so meloxicam is not suitable for the treatment of rheumatological patients with gastric ulcer (Davies and Skjodt, 1999). In order to avoid the irritation of gastrointestinal tract, minimize systemic toxicity and achieve a better therapeutic effect, one promising method is to administer the drug via skin (McNeill and Potts, 1992). Transdermal dosage forms such as patch (Ji et al., 2005) and gels (Gupta et al., 2002) has been tested for this purpose. In this study a new microemulsion system for transdermal delivery of meloxicam was developed to improve the skin permeation of meloxicam.

Microemulsion typically consist of oil, surfactant, cosurfactant and aqueous phase, which is transparent, thermodynamically stable and has a droplet size <0.15 nm and does not have the tendency to coalesce (Kreilgaard, 2002). Microemulsion has several advantages such as enhanced drug solubility, good thermodynamic stability, ease of manufacturing and enhancement effect on transdermal delivery over conventional formulation (Lawrence and Rees, 2000; Gasco, 1997). Recently, more attention has focused on microemulsions for transdermal delivery of drugs. The transdermal delivery of aceclofenac (Lee et al., 2005), diclofenac diethylamine (Djordjevic et al., 2004), triptolide (Chen et al., 2004), using microemulsion has been reported. In transdermal delivery, the key point of dosage design

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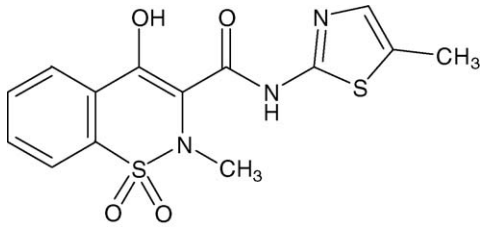

Fig. 1. The structure of meloxicam.

was to solubilize the drug in microemulsion and improved the permeability.

There are two basic types of microemulsion systems: oil-in-water (O/W) and water in oil (W/O), while the O/W microemulsion was important to improve the solubility of poorly water-soluble drugs. The traditional way was dissolve the drug in oils firstly and then incorporated into microemulsion, this method can be applied for most drugs such as triptolide (Chen et al., 2004), aceclofenac (Lee et al., 2005), and diclofenac diethylamine (Djordjevic et al., 2004). In this study, due to the higher solubility of meloxicam in surfactants than that in oils, another way was adopted to dissolve poorly water-soluble drugs into O/W microemulsion, which was dissolve the drug in hydrocarbon chain of surfactants firstly and then miroemulsified (Ye et al., 2003). The aim of this work was to formulate a new O/W microemulsion system for transdermal delivery of meloxicam using polyoxyethylene sorbitan trioleate as surfactant, which had low content of surfactants and high skin permeability.

2. Materials and methods

2.1. Materials

Meloxicam (99% purity) was obtained from Taiyang Pharmaceutical Co., Ltd. (Beijing, China). PEG-8 caprylic/capric glycerides (Labrasol®), diethylene glycol monoethyl ether (Transcutol® P) were kindly donated by Gattefosse, France. Isopropyl myristate (IPM), Cremophor® EL (EL) were supplied by Sigma Chemical Co., USA. Oleic acid, ethyl oleate, polyoxyethylene sorbitan trioleate (Tween 85), polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monooleate (Span 80), polyoxyethylene (10) isooctylphenyl ether (Triton X-100; OP) were purchased from Shanghai Chemical Co., China. Water was purified by double distillation in a glass apparatus. All other chemicals and solvents were of analytical reagent grade.

2.2. Determination of the solubility of meloxicam in oils and surfactants

In order to find out appropriate solvents with good solubilizing capacity of meloxicam, the solubility of meloxicam was investigated in some oils such as oleic acid, ethyl oleate and isopropyl myristate, and some surfactants including Tween 80, Tween 85, Tween 20, Cremophor® EL, Labrasol® and OP. An excess amount of meloxicam was added to 5 ml of each selected solvent and was shaken at 20 °C for 72 h. The suspension was filtered through a membrane filter (0.45 μm), and the concentration of meloxicam in the filtrate was determined by HPLC.

2.3. Construction of pseudo-ternary phase diagrams

The pseudo-ternary phase diagrams were constructed by instillation of homogenous liquid mixtures of oil, surfactant, and cosurfactant, with water at ambient temperature (Djordjevic et al., 2004). At desired Km (3:1, 1:1 and 1:3), oily mixtures of oil, surfactant and cosurfactant were prepared. The ratio of oil to the mixture of surfactant and cosurfactant was varied from 9:1 to 1:9. Water was added drop by drop under gentle stirring to each oily mixture. The compositions of microemulsion at which phase seperation from homogeneous microemulsion to heterogenous phases occurred were recorded. The phase inversion of the microemulsion from O/W to W/O was determined based on the change of conductivity (Baroli et al., 2000) which was measured using a conductance meter (Analytical equipment mill, Tianjin, China, model DDS-11C) at 20 ± 0.5 °C. Based on these results, appropriate oil, surfactant and cosurfactant were selected and used in the preparation of microemulsions containing 0.375% meloxicam. The effect of the contents of the oil and the mixture of surfactant and cosurfactant on the permeation of meloxicam through excised rat skins was evaluated.

2.4. Measurement of droplet size

The average droplet size of the microemulsions were measured by dynamic light scattering (DLS) using a Zetasizer Nano-ZS (Malvern Instruments, England). The measurement by backscatter at a fixed angle was 173° at 20 °C.

2.5. Skin permeation study

The skin permeation rates of meloxicam from various microemulsions were determined to evaluate the effect of the formulation factors. The abdominal skins were obtained from male Wistar rats weighing 220 ± 20 g. After hair was shaved carefully with an electric clipper (Oster, USA), the skin was excised from the abdominal region of each sacrificed rat and the subcutaneous fat and other extraneous tissues were trimmed. The excised rat skins were washed, then stored at 4 °C and used within 24 h after the skin harvest.

The permeation experiments were performed using Franz diffusion cells fitted with excised rat skins at 37 °C. The effective diffusion area was 2.27 cm^2 (17 mm diameter orifice), and the receptor compartment was filled with 13.5 ml of 20% ethanol in pH 7.4 phosphate buffer. It was constantly stirred at 600 rpm throughout the experiment. After meloxicam-loaded microemulsion (2 g) was applied on the epidermal surface of the skin, the receptor medium was withdrawn every hour for up to 10 h after the application. An equal volume of the fresh phosphate buffer was immediately replenished after each sampling. Collected samples were filtered through 0.45 mm polyvinyl

difluoride filters, and meloxicam was quantified by HPLC analysis as described below.

2.6. HPLC assay

The amount of meloxicam in the receptor phase was quantified with a modified HPLC method reported previously (Xu et al., 2001). The Hewlett-Packard 1100 Series HPLC system (Agilent, USA) was consisted of a G 1311A quaternary pump, a G1314A UV detector, a vacuum degasser unit. The column used was a Zorbax SB C18 column (150 mm × 4.6 mm i.d., 5 μm, Agilent, USA). The mobile phase consisted of methanol–acetonitrile–0.05 mol/L phosphate buffer (10:30:66, v/v) was delivered at a flow rate of 1 ml/min. The detection wavelength was 361 nm. All operations were carried out at ambient temperature.

2.7. Data analysis of skin permeation

The cumulative drug permeation per unit of skin surface area (Q_t) was calculated from the following equation:

$$Q_t = \frac{V_r C_t + \sum_{i=0}^{t-1} V_s C_i}{A}$$

where C_t is the drug concentration of the receiver solution at each sampling time, C_i the drug concentration of the i th sample, and V_r and V_s the volumes of the receiver solution and the sample, respectively, A represents the skin surface area. The skin permeation rate at steady-state (J_s, μg/cm^2/h) was calculated from the slope of the linear portion of the plots of Q_t against time. Meanwhile the Student's t-test was performed to see if there was any significant difference in the permeation rate of meloxicam among microemulsions of different composition.

3. Results and discussion

3.1. Determination of the solubility of meloxicam in oils and surfactants

It was very important to find out an appropriate solvent to dissolve meloxicam and then formed microemulsion, because only the dissolved drug can permeate skin. Meloxicam cannot be dissolved in water and is sparingly soluble in common solvents such as ethanol and acetone. In order to screen appropriate solvents for the preparation of microemulsions, the solubility of meloxicam in various oils and non-ionic surfactants were measured and the results were shown in Table 1. Oleic acid showed the solubility of meloxicam of 1.26 ± 0.08 mg/ml, which was the best among the oil investigated, but still much lower than Tween 85 which was tested to have the solubility of meloxicam of 20 mg/ml. Besides, Tween 85 had wide pharmaceutical applications owing to its good biological acceptance (Kibbe, 2000), and exhibited the maximum solubilizing capacity for meloxicam (20.1 ± 0.54 mg/ml), therefore, it was selected as the surfactant in this study.

Table 1
Solubility of meloxicam in various surfactants and oils at 20 °C

Surfactants and oils	Solubility (mg/ml)
Tween 85	20.10 ± 0.54
Tween 80	7.90 ± 0.15
Tween 20	14.31 ± 0.10
Labrasol®	1.61 ± 0.60
EL	5.00 ± 0.07
OP	6.49 ± 0.16
Oleic acid	1.26 ± 0.08
IPM	0.98 ± 0.03
Ethyl oleate	0.43 ± 0.01

3.2. Phase diagram preparation

The phase diagram facilitated the determination of the components concentration range for the existence of microemulsion. According to the conductivity measurements, the investigated microemulsion can be divided into W/O and O/W. In the region of low water composition, the W/O microemulsion was formed and the conductivity of the microemulsion was about 50 μs/cm. As the fraction of water increased, the O/W microemulsion was formed, and the conductivity reached above 100 μs/cm. It has been previously reported that O/W microemulsions have relatively high conductivity as compared with W/O microemulsions (Baroli et al., 2000).

3.3. Screening of cosurfactant

Cosurfactants can decrease interfacial tension between oil and water in microemulsion, adjust the flexility of interfacial membrane and reduce the required amount of surfactant sometimes. The short-chain alcohols and Transcutol P were widely used as cosurfactant (Lee et al., 2003; Gao et al., 1998). In this experiment, ethanol, isopropyl alcohol and Transcutol P as the cosurfactant were investigated with IPM as the oil phase, Tween 85 as the surfactant at the fixed Km of 1:1. Two factors need to be considered, one was the existence region of the microemulsion, and the other was the skin permeation rate. Fig. 2 showed that the area of O/W microemulsion with ethanol and isopropyl alcohol were significantly higher than that of Transcutol P which proposed that short-chain alcohols were suitable as cosurfactant, this was because the small volume of short-chain alcohols could insert into the interfacial layer and formed tight interfacial film. The skin permeation rate from the microemulsion containing ethanol and isopropyl alcohol was 5.40 and 4.23 μg/cm^2/h, respectively (Fig. 3). Ethanol were widely used as a permeation enchancer for many drugs (Gao and Singh, 1998), and it had lower irritant and toxicity, so ethanol was chosen as the cosurfactant. An ethanol cosurfactant was necessary to maintain O/W emulsion stable, which was consistent with previous work about microemulsion systems where cosurfactants (usually short chain alcohols) are necessary to maintain a single phase (Lee et al., 2003).

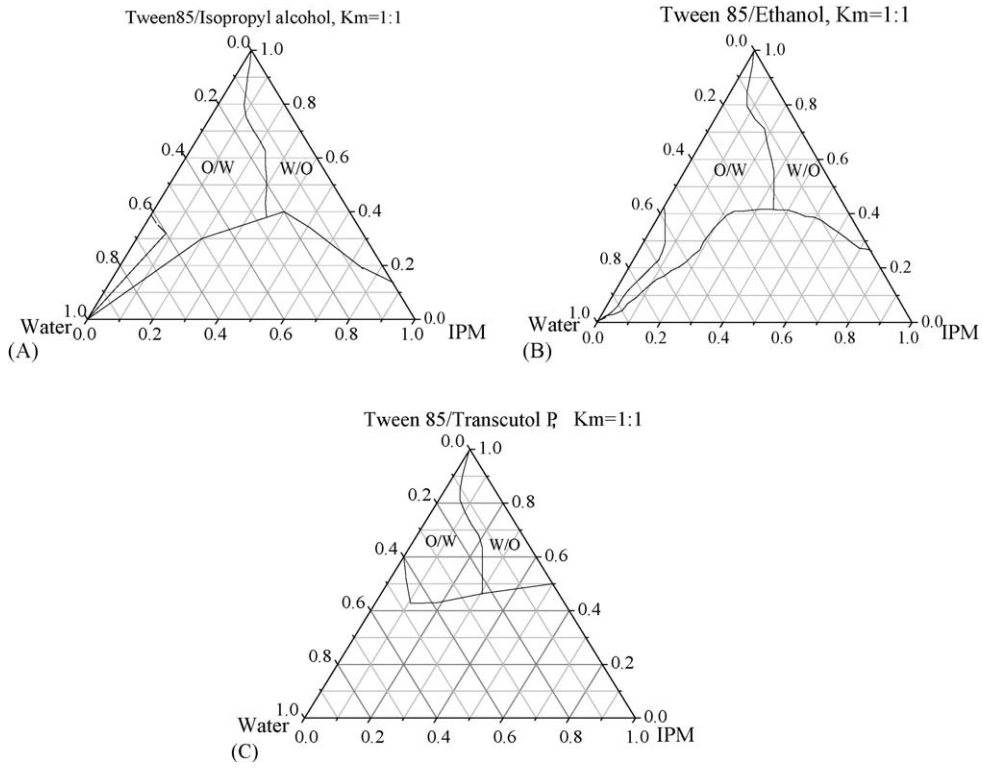

Fig. 2. Pseudo-ternary phase diagrams of microemulsion composed of IPM, surfactant (Tween 85), water and different cosurfactant (A) Isopropyl alcohol; (B) Ethanol; (C) Transcutol® P at Km 1:1.

3.4. Screening of oils

Oleic acid, Ethyl oleate and IPM as oil phase were investigated with Tween 85 and enthanol as surfactant and cosurfactant, respectively, at fixed Km of 1:1, and the phase diagrams were shown in Fig. 4. Based on the results, IPM was an excellent enhancer in transdermal delivery as previously reported (Lee et al., 2003) for its maximum area of O/W microemulsion, and it was selected as the oil phase. Although oleic acid was also regarded as one of the powerful permeate enhancers and has the higher solubility than the other two oils studied, O/W microemulsion area was so small that little proportional change of composition will cause the deviation from microemulsion region, this was because different oils require different HLB, which was introduced by Griffin as an empirical scale intended to describe the balance of the size and strength of the hydrophilic and lipophilic groups on the emulsifier molecule. The optimal oil for a desired microemulsion of a given surfactant can be chosen by a simple "emulsion comparison" method (Kloet et al., 2002). It is well known that the HLB value of IPM (11.1) was similar to that of Tween 85 (11.0). It was consistent with the previously reported that the emulfied effect was the best when HLB of oils were equal to that of selected surfactant (Kloet et al., 2002), and previous reports also confirmed that IPM was an excellent enhancer for transdermal delivery (Lee et al., 2003).

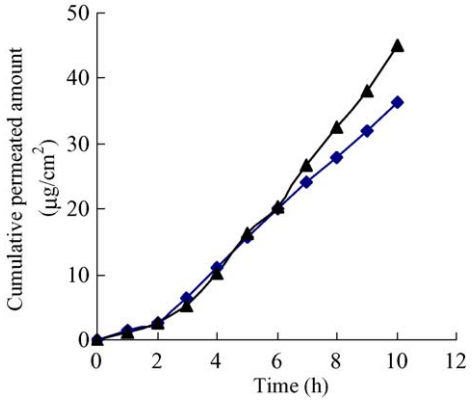

Fig. 3. Permeation profiles of meloxicam through excised rat skins from microemulsions containing different cosurfactants ($n=3$). Symbols: (▲) isopropyl alcohol; (♦) ethanol.

3.5. Optimization of microemulsion formulation

In order to find out the optimum O/W microemulsion region, the effect of the three different Km, 3:1, 1:1, and 1:3, respectively (Fig. 5) were determined in the systems of IPM/Tween 85/ethanol/water. The transparent or translucent W/O or O/W microemulsion area was presented in the phase diagrams. Significant difference can be observed in the three phase diagrams of microemulsions with different Km. The areas of O/W microemulsion made at different Km are presented in Fig. 6, and the optimum surfactant/cosurfactant ratio of microemulsion systems was found at Km 1:1. The emulfied area was low at Km 3:1, it was because ethanol is a polar solvent with the tendency to highly incorporate into water, and the relatively lower ethanol content in the microemulsion systems decreased the hydrophilic-

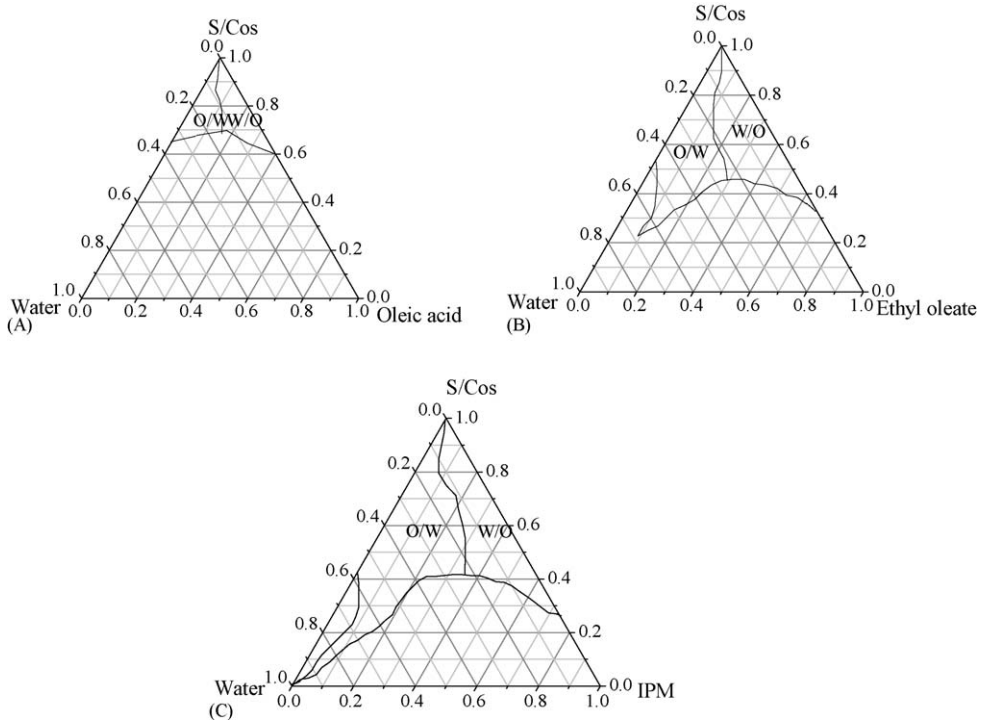

Fig. 4. Pseudo-ternary phase diagrams of microemulsion composed of surfactant (Tween 85), cosurfactant (ethanol) (Km = 1:1), water and different oils (A) Oleic acid; (B) Ethyl oleate; (C) IPM.

ity of the mix-surfactant, so the area of O/W microemulsion was small. In contrast, at the ratio of 1:3, the low concentration of surfactant reduced the amount of micelle, which consequently decreased the solubilization capacity of microemulsion. In brief, system at Km 1:1 formed a larger single phase region than the systems at other Km. It was reported that at the optimum Km value, the cosurfactant was insert into the cavities between the surfactant molecules exactly, and the formed microemul-

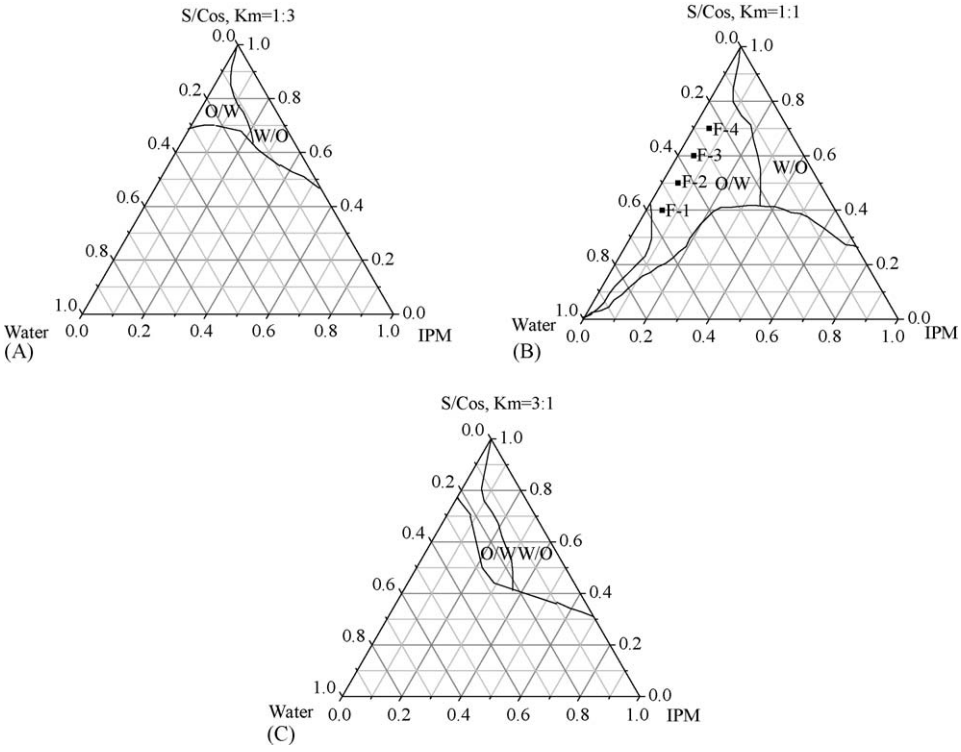

Fig. 5. Pseudo-ternary phase diagrams of microemulsion composed of oil (IPM), surfactant (Tween 85), cosurfactant (ethanol), water and different Km (A) 1:3; (B) 1:1; (C) 3:1.

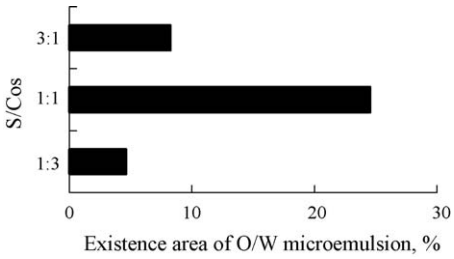

Fig. 6. Existence area of O/W microemulsion formulated with different Km in the pseudo-ternary phase diagrams.

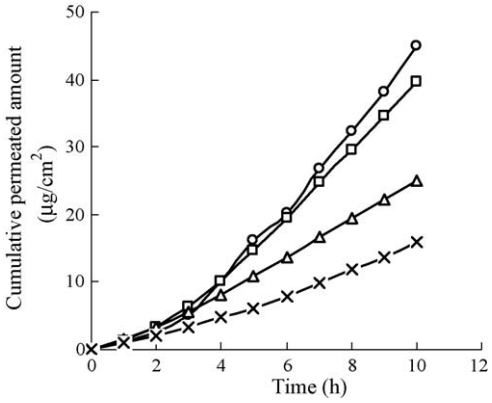

Fig. 7. Permeation profiles of meloxicam through excised rat skins from microemulsions containing different contents of IPM ($n = 3$). Symbols: (◯) 5% oil; (□) 10% oil; (△) 15% oil; (×) control.

sion had the maximum solubilization capacity (Kawakami et al., 2002).

The content of oil also played an important role in microemulsion formulation and it affected the skin permeation rate directly. Fig. 7 showed the effect of the content of IPM ranged from 5% to 15% on the skin permeation of meloxicam, while the content of surfactant and cosurfactant mixture Km (1:1) was fixed at 50%. The calculated skin permeation rates of meloxicam were presented in Table 2. The skin permeation rate of meloxicam was the highest when the percentage concentration of IPM was 5% and the skin permeation rate was 3.3 times of the control group (25% surfactant and 25% ethanol micelle solution containing 0.5% meloxicam without oil). The results suggested that microemulsion as a new transdermal permeation carrier had better penetrable ability through skin compared to the micelle solution. And the skin permeation rate would increase with the decreasing oil content, it is because the water in microemulsion could hydrate skin and caused the corneous cell to swell thus made drug channels wide, therefore with the increasing

Table 2
Permeation rate of meloxicam through excised rat skin from microemulsion containing different content of IPM at 20 °C

Content of IPM (%)	J_s (μg/cm^2/h)
0 (control)	1.66 ± 0.16
5	5.40 ± 0.36
10	4.66 ± 0.75
15	2.75 ± 0.55

Table 3
The average droplet sizes of microemulsion containing different contents of IPM at 20 °C

Content of IPM (%)	Droplet sizes (nm)
5	37.0
10	46.9
15	61.9

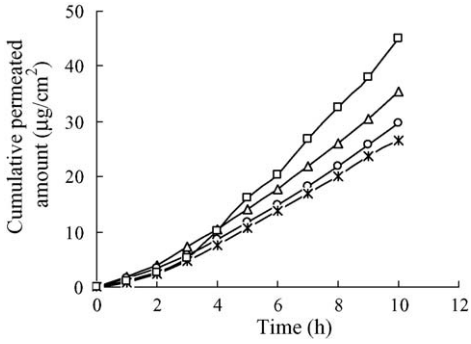

Fig. 8. Permeation profiles of meloxicam through excised rat skins from microemulsions containing different contents of surfactant mixture ($n = 3$). Symbols: (x) 40% S/Cos; (□) 50% S/Cos; (△) 60% S/Cos; (◯) 70% S/Cos.

amount of the water content in the system, the cumulative permeation amount was improved, this was consistent with the previous study. (Thacharodi and Rao, 1994; Alvarez-Figueroa and Blanco-Mendez, 2001). Microemulsion was a swelled micelle so that the amount of meloxicam loaded was increased compared with that of micelle and the drugs in microemulsions can penetrate skins in the form of microemulsion droplet not as free one. From Table 3, the average droplet sizes were found to increase significantly with more oil, which can be attributed to the expansion of oil drop of microemulsion by further addition of the oil. This finding was consistent with a previous report that, the average droplet sizes of triptolide microemulsion containing 1.5% and 6% oil were 12.7 and 59.8 nm, respectively (Chen et al., 2004). Small droplet size was preferred in the term of skin penetration, so the oil content was selected as 5%.

When the oil content was at 5%, the formula 1, 2, 3 and 4 (F-1, F-2, F-3, F-4) in which the contents of surfactant mixture were 40, 50, 60 and 70% (Km = 1:1), respectively were investigated (Fig. 5(B)). The profiles of cumulative permeation amount versus time were shown in Fig. 8 and the skin permeation rate data were calculated and listed in Table 4. In the study, the skin permeation rate of meloxicam was increased as the content of surfactant mixture decreasing from 70 to 50%, this may be due to an increased thermodynamic activity of the drug in

Table 4
Permeation rate of meloxicam through excised rat skin from microemulsion containing different contents of surfactant mixtures at 20 °C

Content of surfactant mixtures (%)	J_s (μg/cm^2/h)
40	3.08 ± 0.35
50	5.40 ± 0.36
60	3.92 ± 0.15
70	3.30 ± 0.31

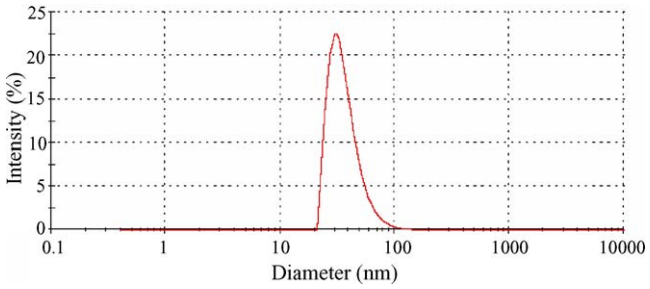

Fig. 9. Average droplet size in microemulsion containing 0.375% meloxicam, 5% oil, 25% surfactant (Tween 85), and 25% cosurfactant (ethanol) measured by dynamic light scattering method.

microemulsion at the lower content of surfactant (Shah, 1994). This finding was consistent with previous reports that when the content of surfactant mixture was decreased from 80 to 36%, the skin permeation rate of ketoprofen was increased 12–23 times (Rhee et al., 2001). However, the skin permeation rate of F-1 was lowest, which was not accordant with the above rule, this was because F-1 was at the border of microemulsion region, so that it was unstable and the turbidity of microemulsion could be observed in the experiment. Meanwhile, high content of surfactant will increase the irritation to skin, therefore F-2 that has the highest skin permeation rate and low content of surfactants was selected as the optimum formula.

In this study, a new O/W microemulsion system for transdermal delivery of meloxicam using polyoxyethylene sorbitan trioleate as surfactant were constructed, various formulation factors were evaluated to find out an optimum microemulsion vehicle that had the low surfactants and high skin permeation of the drug. The optimum formulation consisted of 0.375% meloxicam, 5% IPM, 50% Tween 85/ethanol (1:1) and water exhibited the highest skin permeation rate (5.40 $\mu g/cm^2/h$). The average droplet of the selected microemulsion by dynamic light scattering determination was 37.0 nm (Fig. 9).

Acknowledgement

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