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Microemulsion-based hydrogel formulation of ibuprofen for topical delivery

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Abstract

The purpose of this study was to construct microemulsion-base hydrogel formulation for topical delivery of ibuprofen. Ethyl oleate (EO) was screened as the oil phase of microemulsions, due to a good solubilizing capacity of the microemulison systems and excellent skin permeation rate of ibuprofen. The pseudo-ternary phase diagrams for microemulsion regions were constructed using ethyl oleate as the oil, Tween 80 as the surfactant, propylene glycol as the cosurfactant. Various microemulsion formulations were prepared and the abilities of various microemulsions to deliver ibuprofen through the skin were evaluated in vitro using Franz diffusion cells fitted with porcine skins. The in vitro permeation data showed that microemulsions increased the permeation rate of ibuprofen 5.72–30.0 times over the saturated solution. The optimum formulation consisted of 3% ibuprofen, 6% EO, 30% Tween 80/PG (2:1) and water, showed a high permeation rate of 38.06 $\mu g\,cm^{-2}\,h^{-1}$. Xanthan gum as a gel matrix was used to construct the microemulsion-based hydrogel for improving the viscosity of microemulsion for topical administration. The studied microemulsion-based hydrogel showed a good stability. These results indicate that the studied microemulsion-based hydrogel may be a promising vehicle for topical delivery of ibuprofen.

Keywords: Microemulsion; Hydrogel; Ibuprofen; Xanthan gum; Ethyl oleate; Topical delivery

1. Introduction

Microemulsion is defined as a dispersion consisting of oil, surfactant, cosurfactant and aqueous phase, which is a single optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually within the range of 10–100 nm (Tenjarla, 1999). Microemulsions have several advantages such as enhanced drug solubility, good thermodynamic stability, enhancing effect on transdermal ability over conventional formulations (Lawrence and Rees, 2000). There are several permeation enhencement mechanisms of microemulsions such as an increased concentration gradient and thermodynamic activity toward skin and the permeation enhancement activity of the components of microemulsions (Peltola et al., 2003). So far, much attention has been focused on the topical delivery of drugs such as estradiol and lidocaine using microemulsions (Peltola et al., 2003; Sintov and Shapiro, 2004). Recently, different hydrogel matrices such as carbomer 940, xanthan gum and carrageenan have been used to increase the viscosity of microemulsion for topical application (Lapasin et al., 2001; Peltola et al., 2003; Špiclin et al., 2003, Valenta and Schultz, 2004; Gulsen and Chauhan, 2005). The addition of hydrogel matrix into the microemulsion resulted in the formation of the microemulsion-based hydrogel, which is more suitable for topical application when compared with microemulsion.

Ibuprofen, a non-steroidal anti-inflammatory drug (NASAID) is very effective for the systemic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Ibuprofen was formulated into many topical preparations to reduce the adverse side effects and avoid the hepatic first-pass metabolism. But it is difficult to maintain effective concentrations by topical delivery of ibuprofen due to its poor skin permeation ability (Yano et al., 1986). In order to enhance the permeation of ibuprofen, supersaturated solutions, eutectic systems, mucoadhesive patches and vehicle containing non-ionic surfactants or fatty acid have been explored (Stott et

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al., 1998; Park et al., 2000; Irevolino et al., 2001; Heard et al., 2003; Perioli et al., 2004).

The long-term goal of this work is to develop topical microemulsion-based hydrogel. In present study, the present study was focused on the screening of ibuprofen-loaded microemulsions and construction of microemulsion-based hydrogel formulation.

2. Materials and methods

2.1. Materials

Ibuprofen [2-(4-isobutylphenyl)-propionic acid], were purchased from Zhongtian. Isopropyl myristate (IPM), isopropyl palmitate (IPP), oleic acid (OA), ethyl oleate (EO) and propylene glycol (PG) were purchased from Shanghai Chemical Reagent Corporation (Shanghai, China). Tween 80 was obtained from Tianjin Bodi Chemical Company. Other chemicals are HPLC or analytical grade.

2.2. Screening of oils for microemulsions

To find out the suitable oil which can be used as the oil phase in microemulsion and provide excellent skin permeation rate of ibuprofen, the solubility of ibuprofen in various oils including IPM, IPP, OA and EO was measured. The solubility of ibuprofen in oily mixtures was also measured. The oily mixture was obtained with 1:10:5 mixture of oil:Tween 80:PG. An excess amount of ibuprofen was added to each oil and oily mixtures, and then mixed by magnetically stirring. After stirring for 72 h at 25 °C, the equilibrated sample was centrifuged for 10 min at 12,000 rpm to remove the excess amount of ibuprofen undissolved. Then the supernatant was filtered through a membrane filter, properly diluted with methanol and the concentration of ibuprofen was determinated by HPLC.

The various oils were also used in the preparation of various microemulsions containing 3% ibuprofen, 3% oil, 30% Tween 80, 15% PG and 49% water and their effect on the skin permeation of ibuprofen from the prepared microemulsions was also evaluated in vitro using pig-skin.

2.3. Construction of pseudo-ternary phase diagrams

In order to find out the concentration range of components for the existence range of microemulsions, pseudo-ternary phase diagrams were constructed using H_2O titration method at ambient temperature (25 °C). Three phase diagrams were prepared with the 1:1, 2:1 and 3:1 weight ratios of Tween 80 to PG, respectively. For each phase diagram at specific surfactant/cosurfactant weight ratio, the ratios of EO to the mixture of surfactant and cosurfactant were varied as 0.5:9.5, 1:9, 1.5:8.5, 2:8, 2.5:7.5, 3:7, 3.5:6.5, 4:6, 4.5: 5.5, 5:5, 5.5:4.5, 6:4, 6.5:3.5, 7:3, 7.5:2.5, 8:2, 8.5:1.5, 9:1, 9.5:0.5. The mixtures of oil, surfactant and cosurfactant at certain weight ratios were diluted with H_2O dropwise, under moderate magnetic stirring. After being equilibrated, the mixtures were assessed visually and determined as being microemulsions, crude emulsions or gels. Gels were claimed for those clear and highly viscous mixtures that did not show a change in the meniscus after tilted to an angle of 90°.

Table 1
Compositions of the selected microemulsion formulations (%, w/w)

Vehicle	Ibuprofen	EO	Tween 80	PG	Water
A	3	3	40	20	34
B	3	6	20	10	61
C	3	6	30	15	46
D	3	6	40	20	31

2.4. Preparation of microemulsions and microemulsion-based hydrogel

2.4.1. Preparation of ibuprofen-loaded microemulsions

Ibuprofen was added to the mixtures of oil, surfactant, and cosurfactant with varying component ratio as described in Table 1, and then an appropriate amount of water was added to the mixture drop by drop and the microemulsion containing ibuprofen was obtained by stirring the mixtures at ambient temperature. All microemulsions were stored at ambient temperature.

The saturated solution of ibuprofen as the control (Vehicle E) was prepared by dissolving sufficient ibuprofen in 7.4 PBS.

2.4.2. Preparation of microemulsion-based hydrogel

Xanthan gum was selected as the gel matrix to prepare the microemulsion-based hydrogel formulation. Xanthan gum was slowly mixed with microemulsion under stirring. After xanthan gum was entirely dissolved in the microemulsion, the clear microemulsion-based hydrogel was obtained.

2.5. Characterization of microemulsions

The average size and polydispersity index of the microemulsion droplets were determinated by photon correlation spectroscopy (Nano ZS90, Malvern Instruments, U.K.). The measurement was performed using a He–Ne laser at 633 nm. All measurements were performed at 25 °C.

To characterize the conductivity of the microemulsions, a DDS-11A conductometer (Shanghai Second Instruments Factory, Shanghai, China) was used.

The viscosities of samples were measured at 25 °C using a NDJ-8S digital viscometer (Shanghai Precision and Scientific Instrument, Shanghai, China) with a No. 4 rotor set at 6 rpm.

2.6. HPLC analysis of ibuprofen

Ibuprofen was analyzed by reversed phase HPLC using Agilent 1100 series (Agilent, German). The HPLC system consisted of quaternary pump, an autosampler, a diode array detector (DAD detector) and workstation. The column was a Lichrospher C_{18} column (5 μm, 4.6 mm × 25 cm, Hanbang, China). The mobile phase was an acetonitrile–sodium acetate buffer solution (pH 2.5) (70:30) (v/v) mixture. The flow rate of the mobile phase was fixed at 0.8 ml/min and the detection wavelength was set at 264 nm. The retention time of ibuprofen was

about 7.5 min. The assay was linear in the concentration range of 0.1–200.0 μg/ml. The recovery rate ranged from 99.5 to 100.5%. The R.S.D. value for precision is below 0.3%. No interference from the formulation or skin tissue was observed. All samples should be filtered through an aqueous 0.45 μm pore size filter membrane in order to protect the column.

2.7. In vitro skin permeation study

The full-thickness porcine ear skin was used for the permeation experiments. After hair was moved with a depilatory and examined for integrity, the skin was rinsed with physiological saline and then washed with PBS (pH 7.4). The skin was clamped between the donor and the receptor chamber of vertical diffusion cell with an effective diffusion area of 2.8 cm^2 and a 7 ml cell volume. The receptor chamber was filled with freshly PBS. The diffusion cell was maintained at 37 °C using a re-circulating water bath and the solution in the receptor chambers was stirred continuously at 300 rpm. The formulation (1.0 g) was gently placed in the donor chamber. At 1, 2, 3, 4, 5, 6, 7, and 8 h, 0.5 ml of the solution in the acceptor chamber was removed for HPLC determination and replaced immediately with an equal volume of fresh PBS. No interference of the other formulation components was observed. All experiments were performed in triplicate.

The cumulative amount of ibuprofen permeated through porcine ear skins was plotted as a function of time. The permeation rate of ibuprofen at the steady state (J, $\mu g\,cm^{-2}\,h^{-1}$) and lag time were calculated from the slope and intercept of the straight line obtained by plotting the amount of ibuprofen permeated versus time in steady state conditions. The skin permeation coefficient (P) was calculated by dividing the skin flux by the ibuprofen donor concentration.

2.8. Stability of microemulsion-based hydrogel

The stability of the studied microemulsion-based hydrogel containing ibuprofen was studied via clarity and phase separation observation and HPLC assay of ibuprofen at 40 °C for 3 months. The centrifuge tests were also carried out to assess the physical stability. The studied microemulsion-based hydrogel were centrifuged for 15 min at 10,000 rpm.

2.9. Statistical analysis

All skin permeation experiments were repeated three times and data were expressed as the mean value ± S.D. Statistical data were analyzed by one-way analysis of variance (ANOVA). A multiple comparison test was used to compare different formulations, and a P value of 0.05 was considered to be significant.

3. Results and discussion

3.1. Solubility of ibuprofen

To develop microemulsion formulations for topical delivery of poorly water-soluble ibuprofen, the optimum oil need to be chosen. The solubility of ibuprofen in the various oils and oily mixtures is shown in Table 2. The solubility of ibuprofen was highest in OA (0.207 ± 0.012 g/ml), followed by IPM, EO and IPP. The solubility of ibuprofen in the oily mixture containing IPM was decreased slightly when compared with that in IPM. But the solubility of ibuprofen in the other oily mixture was significantly increased when compared with that in oil. The solubility of ibuprofen in oily mixture containing EO reached a maximum (0.439 ± 0.017 g/ml), which was three times higher than the figure in EO. However, the oily mixtures with IPP and OA only showed 42.18%, 30.43% increase in the solubility of ibuprofen. It indicated that the addition of Tween 80 and PG to oil led to a different change in drug solubility. The high solubility of ibuprofen in oily phase was advantage to increase that in microemulions.

Table 2
Solubility of ibuprofen in various oils, oily mixtures and microemulsion formulations at 25 °C (mean ± S.D., $n = 3$)

Vehicle	Solubility (g/ml)
IPM	0.160 ± 0.015
IPP	0.147 ± 0.011
OA	0.207 ± 0.012
EO	0.153 ± 0.009
Oily mixture containing IPM	0.157 ± 0.021
Oily mixture containing IPP	0.209 ± 0.016
Oily mixture containing OA	0.270 ± 0.022
Oily mixture containing EO	0.439 ± 0.017

According to the solubility of ibuprofen, EO should be the most appropriate oil for the development of microemulsion. In order to verify the selection of oil, the various oils were used in the preparation of microemulsions and the skin permeation rate of ibuprofen from the microemulsions containing 3% ibuprofen, 3% oil, 30% Tween 80, 15% PG and 49% water was also determinated in vitro using porcine skin. Tween 80 and PG were used as the surfactant and cosurfactant, respectively. The permeation rates of ibuprofen across porcine ear skins from the microemulsions are shown in Fig. 1. EO showed the highest permeation rate (10.62 ± 0.63 $\mu g\,cm^{-2}\,h^{-1}$), followed by OA (3.96 ± 0.47 $\mu g\,cm^{-2}\,h^{-1}$), IPP (1.83 ± 0.35 $\mu g\,cm^{-2}\,h^{-1}$) and IPM (1.82 ± 0.31 $\mu g\,cm^{-2}\,h^{-1}$). EO resulted in the highest permeation rate of this drug. This may be due to the permeation enhancing effect of EO. Though IPP, IPM and OA have also been frequently used as powerful permeation enhancers, EO acted as a more effective permeation enhancer for topical delivery of ibuprofen in microemulsion system. So EO was subsequently used as the oil of microemulsions.

3.2. Phase studies

The aim of the construction of pseudo-ternary phase diagrams was to find out the existence range of microemulsions. The pseudo-ternary phase diagrams with various weight ratios of Tween 80 to PG are described in Fig. 2. The translucent microemulsion region is presented in phase diagrams. No

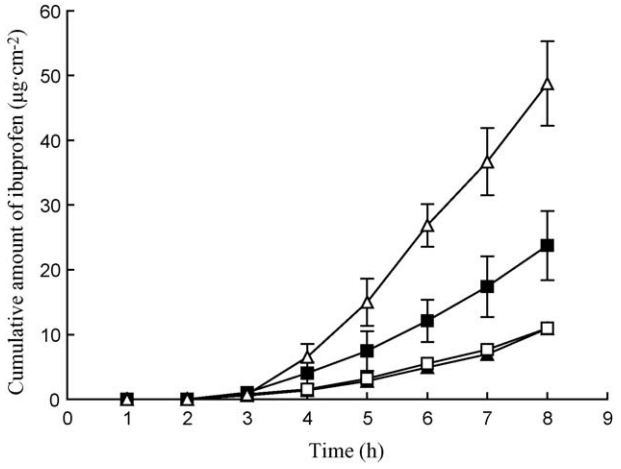

Fig. 1. Permeation profiles of ibuprofen through excised porcine ear skins from microemulsions prepared with different oils (mean ± S.D., $n = 3$). Symbols: (▲) IPM, (□) IPP, (■) OA, (△) EO.

distinct conversion from water-in-oil (w/o) to oil-in-water (o/w) microemulsions was observed. The rest of the region on the phase diagram represents the turbid and conventional emulsions based on visual observation. No liquid crystalline structure was observed using cross polarizer. The area of microemulsion isotropic region changed slightly in size with the increasing ratio of surfactant to cosurfactant.

3.3. Preparation and characterization of buprofen-loaded microemulsions

Various microemulsions were selected from the 2:1 phase diagram. In the previous study, we found that the order of the addition of the ingredients had significant influence on the preparation of microemulsions when microemulsions had low concentrations of surfactant and cosurfactant (Vandamme, 2002; Chen et al., 2004). In this work, the influence of ibuprofen on the preparation of microemulsions was studied. Vehicle B had only 20% Tween 80 and 10% PG. When ibuprofen was dissolved into the oily phase, the clear microemulsion could be quickly obtained by dispersing the oily phase into the aqueous phase. However, when ibuprofen was solubilized into the drug-free Vehicle B, a relatively long time was required to obtain transparent Vehicle B under magnetic stirring. Additionally, drug-free Vehicle B had a larger average diameter when compared with drug-loaded Vehicle B. Ibuprofen had a significant influence on the equilibrium time and particle size of microemulsion. Currently, there is no clear mechanism elucidating the influence. However, it is possible that ibuprofen might act as an emulsifying agent or a cosurfactant by deposition of drug molecule at interface of microemulsion (Martin, 1993; Park and Kim, 1999; Podlogar et al., 2005). In addition, PG cannot be solubilized in EO. The distribution of PG between the oily phase and the aqueous phase might require more time to obtain the equilibrium. It is concluded the order of the addition of ibuprofen might change the physicochemical properties of the microemulsions and should be a very important factor for the preparation of microemulsions,

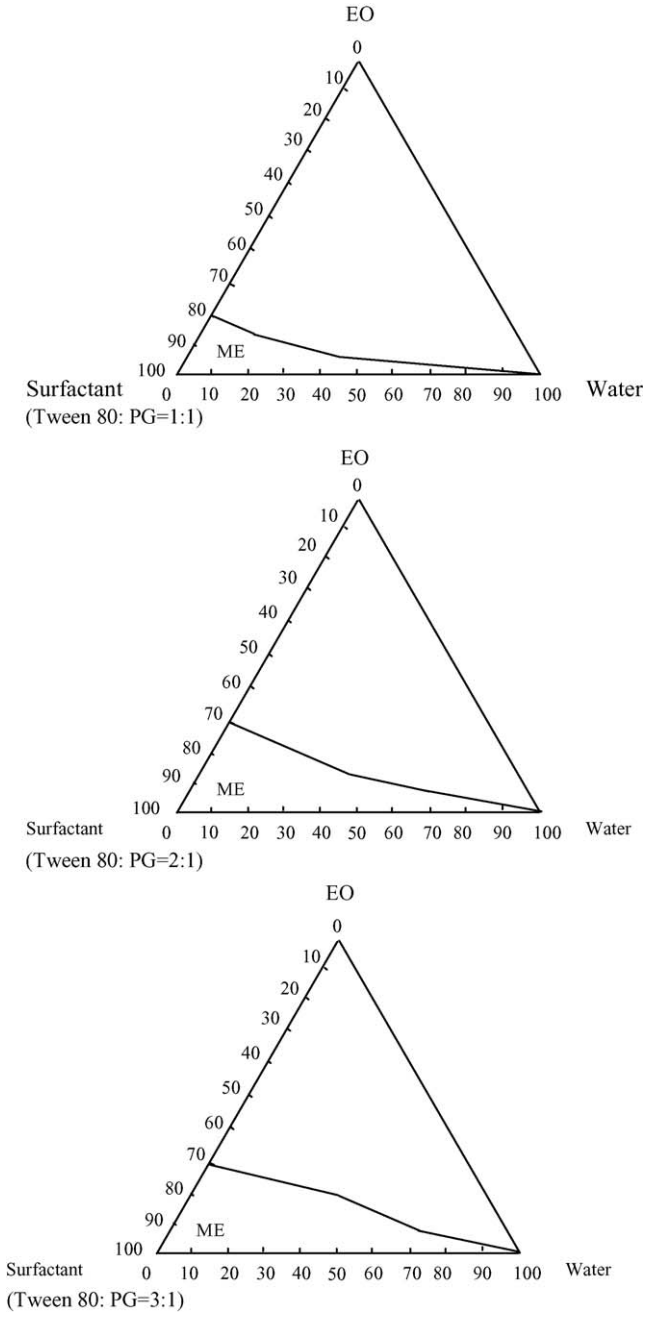

Fig. 2. The pseudo-ternary phase diagrams of the oil-surfactant-water system at the 1:1, 2:1, and 3:1 weight ratios of Tween 80 to PG at 25 °C (ME represents microemulsion region).

when microemulsions had low concentrations of surfactant and cosurfactant. In this work, ibuprofen was added into oily phase and the drug-loaded microemulsions were prepared by mixing oily phase containing ibuprofen with water.

The parameters of microemulsions were presented in Table 3. All the microemulsions had small average droplet diameters between 12 and 17 nm. The droplet size of all microemulsions ranged from 10 to 100 nm. The polydispersity index showed that all the microemulsions had narrow size distribution. The high conductivities reveal the o/w structure of microemulsions.

Table 3
Physicochemical parameters of the tested microemulsions (mean ± S.D., $n = 3$)

Vehicles	Polydispersity index	Droplet size (nm)	Conductivity (μS/cm)	pH
A	0.186 ± 0.021	12.4 ± 0.3	118.0 ± 2.0	5.70 ± 0.03
B	0.132 ± 0.027	16.9 ± 0.3	299.0 ± 5.0	5.19 ± 0.03
C	0.122 ± 0.012	12.6 ± 0.1	207.0 ± 1.0	5.42 ± 0.02
D	0.162 ± 0.010	13.4 ± 0.6	306.0 ± 6.0	5.79 ± 0.01

Table 4
The permeation parameters of the ibuprofen-loaded microemulsions and saturated solution

Vehicle	J (μg cm^{-2} h^{-1})	P ($\times 10^{-3}$ cm h^{-1})	Lag time (h)
A	9.76 ± 0.66	1.95 ± 0.13	2.57 ± 0.23
B	38.06 ± 1.04	7.61 ± 0.21	1.47 ± 0.15
C	23.80 ± 0.78	4.76 ± 0.16	1.84 ± 0.31
D	11.07 ± 0.45	2.21 ± 0.09	2.63 ± 0.38
E	1.05 ± 0.11	–	–

3.4. In vitro skin permeation studies

The permeation ability of the various microemulsions was evaluated using the in vitro permeation experiments. The permeation parameters of the tested microemulsion and control formulations were presented in Table 4. The permeation profiles of ibuprofen through porcine ear skins from various vehicles are shown in Fig. 3. A steady increase of ibuprofen in the receptor chambers with time was observed. The permeation profiles of microemulsions followed zero order release kinetics. Statistical comparison of the flux throughout 8 h showed that all the microemulsions provided fluxes ($P < 0.01$) higher than the saturated solution of ibuprofen (Vehicle E). Vehicle E had only a low accumulative amount of ibuprofen about 8.52 μg cm^{-2} at 8 h. The accumulative amounts of ibuprofen at 8 h from Vehicle A, B, C and D were 5.72–30.0 times higher when compared with Vehicle E. Vehicle B had the highest permeation rate of 38.06 μg cm^{-2} h^{-1}. Vehicle C had a higher permeation rate of 23.80 ± 0.78 when compared with Vehicle D.

Theoretically, the saturated solution of ibuprofen should have high permeation rate. The equation of $J = PC/h = DKC/h$ can be expressed as an alternative form, $J = (D \times C_s/h) \times (C/C_m)$, where K can be defined as the ratio of saturated concentration in the skin (C_s) to the saturated concentration in the microemulsion (C_m) and C/C_m can be defined as the extent of saturation, which directly indicates the thermodynamic activity of drug in vehicle. Then the saturated solution should have the highest thermodynamic activity and has a high permeation rate (Higuchi, 1960). The thermodynamic activity of drug in the formulation is a significant driving force for the release and penetration of the drug into skin (Walters et al., 1998). Ibuprofen had a high P of 0.0066 cm h^{-1} at pH 7.0 (Hadgraft and Claudia, 2000). According to the data from Watkinson et al., the saturated solution at pH 7.4 should have a higher P due to the high partition coefficient between solution and skin (Watkinson et al., 1993). However, the low solubility of ibuprofen in PBS resulted in a low permeation rate, because overall factors such as D, C, C_s and C_m may control the penetration of ibuprofen. In this work, the microemulsions had high concentrations of ibuprofen and permeation coefficient, so the high permeation rate of ibuprofen could be obtained. This phenomenon accorded with the results reported by Peltola et al. (Peltola et al., 2003). Even though the saturated solution of estradiol had a high permeation coefficient when compared with estradiol-loaded microemulsions, obviously the permeation rate was lower than those of microemulsions due to the low solubility in water. Park also studied the effect of polyoxyethylene alkyl ethers on the skin permeation of ibuprofen (Park et al., 2000). Polyoxyethylene alkyl ethers could increase the solubility of ibuprofen in water and then resulted in a high permeation rate, even though the permeation coefficient is lower than that of the saturated solution without polyoxyethylene alkyl ethers. So, the solubility acted as the requisite condition for enhancing the permeation rate and the microemulsion system provide a powerful solubilization of ibuprofen.

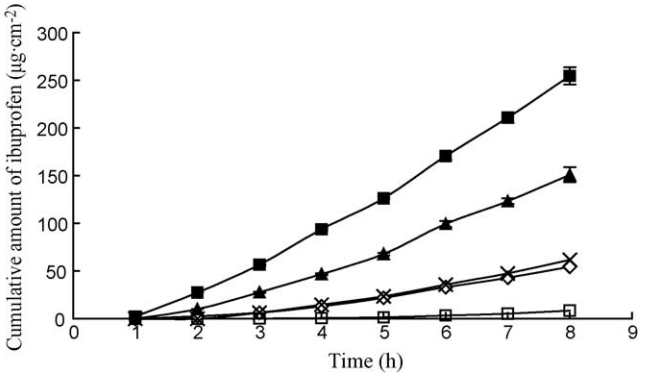

Fig. 3. Permeation profiles of ibuprofen through excised porcine ear skins from microemulsion formulations (mean ± S.D., $n = 3$). Symbols: (◊) A, (■) B, (▲) C, (×) D, (□) E.

The high permeation rate of microemulsions might attribute to several factors. Firstly, the high concentration (3%) of ibuprofen in microemulsions resulted in high concentration gradient, which might be the main permeation mechanism of ibuprofen into the skin from these microemulsions. Microemulsions could act as drug reservoirs where drug is released from the inner phase to the outer phase and then further onto the skin (Peltola et al., 2003).

Secondly, due to the small droplet size, droplets settled down to close contact with the skin and a large amount of inner EO in microemulsions might penetrate into skins (Peltola et al., 2003). EO and propylene glycol as permeation enhancers had strong permeation enhancing effect. They could enhance the solubility of ibuprofen in the skin and partition coefficient might not be necessary to decrease with increasing the solubility of drug in

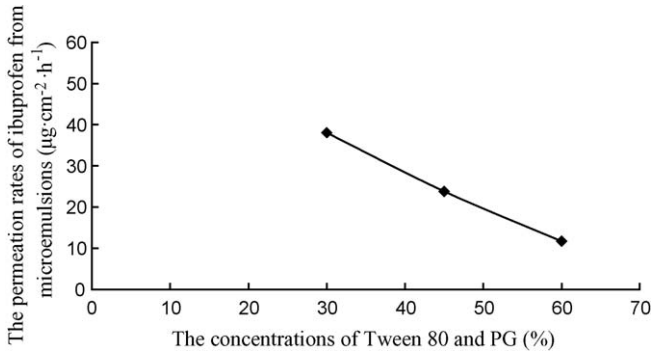

Fig. 4. The correlation between the permeation rates of ibuprofen through excised porcine ear skins from Vehicle B, C, D and the concentrations of Tween 80 and PG in Vehicle B, C, D.

the formulation. Then P could be increased due to permeation enhancers.

In addition, Due to the small droplet diameters of microemulsions, the likely mechanism may also be the permeation of ibuprofen directly from the droplets into the stratum corneum without microemulsion fusion to the stratum corneum and subsequent permeation enhancement.

According to Tables 1 and 4, we constructed the correlation between the permeation rates of ibuprofen through excised porcine ear skins from Vehicle B, C and D and the concentrations of surfactant and cosurfactant in Vehicle B, C and D. The correlation was showed in Fig. 4. The concentration of the mixtures of Tween 80 and PG in Vehicle B, C and D were 30%, 45%, 60%, respectively. Fig. 4 showed that the permeation rates were decreased with the increase of the concentrations of the mixture of Tween 80 and PG. The regression equation is $J = -0.8997C + 64.8$ ($r^2 = 0.9989$), where C is the concentration of the mixtures of Tween 80 and PG, J is the permeation rate. There is a good linear relation between the permeation rates and concentrations. According to an alterative form $J = (D \times C_s/h) \times (C/C_m)$, a plot of J versus the extent of saturation (or thermodynamic activity) should be linear if $(D \times C_s/h)$ is assumed to be constant for those three microemulsion formulations. This means that the influence of three microemulsion formulations on three factors was similar and the collective term $(D \times C_s/h)$ can be recognized as a constant. Then J for microemulsion formulation only becomes a function of its thermodynamic activity. So the concentrations of Tween 80 and PG influenced on the permeation rates of ibuprofen significantly.

In order to evaluate effect of EO on the permeation rates, different microemulsions were compared. The microemulsion containing 3% EO, 30% Tween 80 and 15% PG had the permeation rate of $10.62\,\mu g\,cm^{-2}\,h^{-1}$ and Vehicle C had $23.80 \pm 0.78\,\mu g\,cm^{-2}\,h^{-1}$. The increase of EO in Vehicle C resulted in a significant increase of permeation rate. However, the increase of the concentration of EO in Vehicle D showed no significant increase of permeation rate when compared with Vehicle A. It is possible that the high concentration of surfactant and cosurfactant in Vehicle A and D might result in a relatively low thermodynamic activity. Even though Vehicle D have higher concentration of EO than Vehicle A, the low thermodynamic activity might did not increase the penetration of EO into skins (Tenjarla, 1999). So the relatively high concentration of EO in Vehicle D did not enhance the permeation rate when compared with Vehicle A. However Vehicle C had a relatively lower concentration of Tween 80 and PG when compared with A and D. EO might serve as the important factor enhancing the permeation rate, because the high thermodynamic activity might contribute to the penetration of EO into skins.

3.5. Preparation of microemulsion-based hydrogel

Recently, the gel matrices such as carbomer 940, xanthan gum and carrageenan have been used to prepare the microemulsion-based hydrogel for improving the viscosity of microemulsion (Peltola et al., 2003; Špiclin et al., 2003). In this work, carbomer 940 and xanthan gum were added to vehicle B to prepare the microemulsion-based hydrogel. However, after carbomer 940 was swelled in Vehicle B, only an ivory-white hydrogel was obtained and the microemulsion structure was disturbed. So it is concluded that carbomer 940 was not a suitable gel matrix for this microemulsion system. We found that xanthan gum could increase the viscosity of microemulsion and maintain the microemulsion structure and was a good matrix for vehicle B. The oily droplets in microemulsion might be distributed in three-dimensional gel network (Lapasin et al., 2001).

The viscosity of microemulsion-based hydrogel was increased with the increase of the concentration of xanthan gum. However, 2% xanthan gum resulted in a too high viscosity of 35.40 ± 0.45 Pa S and 1% xanthan gum led to a low viscosity of 11.69 ± 0.3 Pa S. The microemulsion-based hydrogel containing 1.5% xanthan gum had a suitable viscosity of 22.88 ± 0.38 Pa S for topical application.

The microemulsion-based hydrogel with 1.5% xanthan gum were stable at 40 °C. No change of phase separation and degradation of ibuprofen was observed during 3 months. The centrifuge test showed that the microemulsion-based hydrogel had a good physical stability. The microemulsion-based hydrogel with 1.5% xanthan gum might be a promising vehicle for topical delivery of ibuprofen.

4. Conclusions

EO was used as the oily phase of microemulsion due to powerful solubilization and permeation enhancing effect for ibuprofen. Microemulsions could increase the topical delivery of ibuprofen 5.72–30.0 times when compared with the control. The optimum permeation rate (Vehicle B) was mainly due to the high concentration gradient of ibuprofen and the permeation enhancing ability of EO. The addition of xanthan gum into microemulsions resulted in the significant increase of viscosity. The microemulsion-based hydrogel formulation containing 3% ibuprofen with a suitable viscosity for topical administration was constructed by swelling 1.5% xanthan gum in microemulsion system. The influence of the addition of xanthan gum on the microstructure and permeation ability of microemulsion would be further investigated.

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