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Enhancing effect of polyoxyethylene alkyl ethers on the skin permeation of ibuprofen

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Abstract

The influence of polyethoxylated non-ionic surfactants on the transport of ibuprofen across rat skin was investigated. The skin permeation of ibuprofen from a series of 17 polyoxyethylene (POE) alkyl ethers containing 5% ibuprofen was determined using Franz diffusion cells fitted with excised rat skins. Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR) were performed for the physicochemical characterization of ibuprofen–surfactant interaction. In vitro transdermal flux through excised rat skin was found in the decreasing order of POE(5)cetyl/oleyl ether (110.24 $\mu g/cm^2/h$) > POE(2)lauryl ether (99.91 $\mu g/cm^2/h$) > POE(2)oleyl ether (67.46 $\mu g/cm^2/h$) > POE(10)stearyl ether (66.19 $\mu g/cm^2/h$). POE(2)oleyl ether showed the longest lag time (2.47 h). The enhancers containing the EO chain length of 2–5, HLB value of 7–9 and an alkyl chain length of C16–C18 were effective promoters of ibuprofen flux. FT-IR and DSC studies to probe the nature of the interaction between the ibuprofen and surfactant indicated that the hydrogen bonding state of ibuprofen was changed from the dimeric form to the carbonyl-hydroxyl (C=O–HO) hydrogen bond form in the presence of excess POE alkyl ether. These results indicated that this new system may be used in developing a transdermal formulation with improved skin permeation of ibuprofen.

Keywords: Transdermal drug delivery; Ibuprofen; Polyoxyethylene alkyl ethers; Non-ionic surfactant

1. Introduction

The advantages of transdermal drug delivery over other conventional routes of administration include avoidance of the hepatic first-pass metabolism, enhanced therapeutic efficacy, better patient medication compliance and reduced systemic side effects (Kydoneieus and Berner, 1987). Absorption via the transdermal route is limited by a poor penetration of drugs across the stratum corneum comprising the keratin-rich dead cells embedded in a complex lipid matrix. Factors influencing the drug transport through the skin include lipophilicity (Barry, 1983), solubility, molecular weight or size, and hydrogen bonding ability (Potts and Guy, 1995). Manipulation of these physicochemical properties and incorporation of the penetration enhancers may accelerate the percutaneous absorption of drugs.

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Penetration enhancers that interact with the lipids of the outermost layer of the skin, the stratum corneum, allow for better penetration of coadministered drugs. A wide variety of non-ionic surfactants, least irritating and usually considered to be the most acceptable for transdermal drug delivery, have been shown to increase the percutaneous absorption of drugs (Krasowska, 1978; Sarpotdar and Zatz, 1987; Bialik et al., 1993).

A series of papers have shown that certain polyoxyethylene (POE) ethers were the effective enhancers for rectal insulin absorption when incorporated into suppositories containing 0.5% surfactant in corn oil (Ichikawa et al., 1980). In these studies, C12/POE(9) was found to be the most effective enhancer for insulin absorption, as indicated by lowering blood glucose levels. The surfactants studied varied in the length of both alkyl chain (hydrophobic part) and POE chain (hydrophilic part). For a fixed C12 alkyl chain with varying POE chain, C12/POE(6) was also effective, while C12/POE(3), C12/POE(25) or C12/POE(40) were ineffective. C12/POE(3) was presumably too water-insoluble, while C12/POE(25) and C12/POE(40) were too hydrophilic. For a fixed POE chain of 9 with varying alkyl chain, C12/POE(9) was most effective, followed by C16/POE(9) then C18/POE(9) = C10/POE(9).

Florence (1981) noted that one unique aspect of the C12 chain is its intermediate solubility between oil and water. A medium length alkyl chain surfactant may penetrate the lipid bilayer easily, because of its proper aqueous solubility and higher critical micelle concentration than a longer alkyl chain surfactant. By increasing the length of the alkyl chain, one would expect to improve membrane penetration, but the monomer concentration would be reduced, perhaps offsetting the improvement in penetration (Schott, 1973; Florence, 1981). It is interesting to note that among the anionic fatty acid soaps, sodium laurate (C12) was more active than soaps with shorter or longer chain lengths with respect to the disruption of the membrane integrity in cultured mammalian cells (Ferguson and Prottey, 1976).

While the C12 alkyl chain appears especially well suited for membrane permeabilization, Guarini and Ferrari (1984) found the C16 and C18 ethers were more effective than C12 ethers in the absorption of orally administered heparin in rats. They also found that C16, C18 ethers with POE(10) or POE(20), and C12/POE(10) were effective, but C12/POE(9) was not.

These observations indicate that the absorption enhancement by non-ionic surfactants is complicated by the failure to distinguish between model drugs that have some degree of lipid solubility and, therefore, could be solubilized in the hydrophobic environment of a micelle, and very polar model drugs, which are not solubilized in micelles. The hydrophilic–lipophilic balance (HLB) alone is not a reliable predictor of the absorption enhancing capability, but the size and shape of both the alkyl chain and the polar group (e.g. POE) influence absorption-enhancing ability.

Ibuprofen ((±)-2-(*p*-isobutylphenyl)propionic acid), a potent non-steroidal anti-inflammatory drug (NSAID) with pronounced analgesic properties, is used in the long-term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis (Adams et al., 1975; Arendt-Nielsen et al., 1994). Although the systemic treatment of such disease with NSAID has proven to be efficient, dose-dependent side effects, especially gastrointestinal irritation, bleeding, ulceration or perforation after oral administration, are commonly seen. Considering the fact that ibuprofen is often used for a long-term period, transdermal delivery might be more appropriate to reduce the side effects while maintaining its therapeutic blood concentration (Gennaro, 1985). However, it is difficult to maintain effective blood concentrations by transdermal delivery of ibuprofen due to its intrinsically poor skin permeability (Yano et al., 1986). Therefore evaluation of the potential for enhancement of the skin permeation of ibuprofen is of great practical importance. Many factors affecting the in vitro skin permeation of ibuprofen have been investigated. Permeation enhancement of ibuprofen by supersaturated solutions (Iervolino et al., 2000), eutectic systems (Stott et al., 1998) and vehicle composition (Irwin et al., 1990) as well as chemical enhancers (Bialik et al., 1993) have been reported. The use of chemical permeation enhancers to enable transdermal delivery of a drug is the most cost-effective ap-

proach to optimize the delivery of active agents into or through the skin. Ideally, permeation enhancers should be pharmacologically inert, non-toxic, non-irritating and non-allergenic; have a rapid and reversible onset of action, compatible with the formulation components; and be cosmetically acceptable (Barry, 1987; Ranade, 1991). However, all of these ideal requirements are rarely ever achieved, therefore, the search for improved enhancers continues.

The non-ionic surfactants POE alkyl ethers are a series of polyoxyethylene glycol ethers of *n*-alcohols (lauryl, myristyl, cetyl and stearyl alcohol) that are widely used in topical and cosmetic formulations primarily as emulsifying agents for water-in-oil and oil-in-water emulsions (Wade and Weller, 1994). In this study we systematically investigated the effect of POE alkyl ethers on the skin permeation of ibuprofen. The selected surfactants have linear alkyl chain lengths greater than C12 with the ethylene oxide (EO) chain length of 2–100. Our results provide some insight into the selectivity of certain penetration enhancers.

2. Materials and methods

2.1. Materials

Ibuprofen and oxaprozin (Sigma, MO, USA), polyoxyethylene alkyl ethers of the Emulgin series (Goldschmidt, VA, USA) and Brij series (ICI, DE, USA) were used as received. Acetonitrile (Merck, Darmstadt, Germany), phosphoric acid (Shinyo Pure Chemical, Osaka, Japan), monosodium phosphate and disodium phosphate (Junsei, Tokyo, Japan) were of analytical grade. Physicochemical properties of the surfactants used are indicated in Table 1.

2.2. Preparation of ibuprofen vehicles

The vehicles containing 5% w/w ibuprofen were fabricated by the following procedures: (1) Ibuprofen (5 g) and 15 g of POE alkyl ether were melted in a water bath at 80°C. (2) Pre-heated water (80°C) was slowly added into the mixture to make up the weight to 100 g. This mixture was then stirred for 10 min at 2000 rpm using a homogenizer (model ST-HG, Matsushita Electric, Co., Japan). (3) The pH of the mixture was then adjusted to 5.0 using triethanolamine with mechanical stirring. A 5% ibuprofen aqueous suspension containing no POE alkyl ether was used as the control vehicle.

2.3. Solubility studies

Saturated solubilities of ibuprofen in the prepared vehicles were evaluated. Saturated solutions were prepared by adding excess drug to the vehicles and shaking for 48 h at 32°C. After this period the solutions were filtered, diluted and analysed by HPLC.

2.4. In vitro skin permeation study

The permeation of ibuprofen through rat skin from the vehicles, along with the control vehicle, was determined using Franz diffusion cells fitted with excised rat skins. The skin surface area available for the permeation was 1.75 cm^2. The recep-

Table 1
Physicochemical information of the POE alkyl ethers used in the study[a]

Surfactants	Hydrophobic portion	EO chain length	HLB
Emulgin B1	Cetyl/stearyl	12	13.0
Emulgin B2	Cetyl/stearyl	20	15.0
Emulgin B3	Cetyl/stearyl	30	17.0
DLS2	Lauryl	2	7.0
Emulgin 05	Cetyl/oleyl	5	9.0
Emulgin 010	Cetyl/oleyl	10	13.0
Brij 35	Lauryl	23	16.9
Brij 52	Cetyl	2	5.3
Brij 58	Cetyl	20	15.7
Brij 72	Stearyl	2	4.9
Brij 78	Stearyl	20	15.3
Brij 98	Oleyl	20	15.3
Brij 30	Lauryl	4	9.7
Brij 92	Oleyl	2	4.9
Brij 56	Cetyl	10	12.9
Brij 76	Stearyl	10	12.4
Brij 700	Stearyl	100	18.8

[a] Data reproduced with permission of Goldschmidt Chemical Company and ICI Company.

tor compartment was filled with pH 7.4 phosphate buffer (0.02 M) and its temperature was maintained at 37 ± 0.5°C using a thermostatic water pump (model HDT6, ERWEKA, Germany). The cells were allowed to equilibrate overnight.

Rat skins were harvested from male Sprague–Dawley rats weighing 250 ± 20 g. After careful removal of the hair on the dorsal area using an electric clipper (model 808, Daito Electric, Japan), a 3×3 cm patch of skin was excised from each sacrificed rat and subcutaneous fat and other extraneous tissues were trimmed. The thickness of the prepared skin was measured with a micrometer and the excised rat skins were stored at −20°C prior to use.

After 1.0 g of the vehicles containing 5% w/w ibuprofen was applied under occlusion on the epidermal surface, 200 μl of the receptor medium was withdrawn at predetermined time intervals, 2, 4, 6, 8 and 10 h, and replaced immediately with an equal volume of pre-thermostated (37°C) fresh phosphate buffer. Excess drug (5% w/w dispersion) was used in the donor compartment to maintain infinite dose condition. Analysis of each subsequent sample was performed using HPLC.

HPLC analysis of ibuprofen was performed using a system consisting of an isocratic pump (Waters 600E, Milford, MA, USA), an autoinjector (Waters 715, Milford, MA, USA), and a UV/vis detector (Waters 486, Milford, MA, USA) at a wavelength of 223 nm interfaced with an integrator (Waters IEEE-488, Milford, MA, USA). The HPLC conditions were as follows: mobile phase, acetonitrile: 0.2% (v/v) phosphoric acid with triethylamine, 2×10^{-3} mol (70:30); column, Inertsil® ODS-2 (4.6×150 mm, 5 μm particle size, GL Sciences, Tokyo, Japan); flow-rate, 1.0 ml/min. After the receptor medium was mixed with an equal volume of the internal standard solution (oxaprozin 50 μg/ml in mobile phase), 50 μl of the mixed sample was injected onto the column.

After plotting the cumulative amounts of ibuprofen permeated through excised rat skins as a function of time, permeation parameters were calculated using the following equations (Barry, 1983):

$$J_s = \frac{1}{A}\left(\frac{dQ}{dt}\right)_{ss} = \frac{DKC}{h} = PC$$

$$D = \frac{h^2}{6T_L}$$

where, J_s is the permeation rate (flux) at steady-state (μg/cm^2/h), A is the area of skin (cm^2) through which the permeation of the drug takes place; $(dQ/dt)_{ss}$ is the amount of drug passing through the skin per unit time at steady-state (μg/h), C is the drug concentration in the vehicle (μg/ml), K is the partition coefficient of drug (skin/vehicle), h is the effective path length (cm), P is the permeability coefficient for the drug (cm/h), D is the (apparent) diffusion coefficient of the drug (cm^2/h) and T_L is the lag time (h).

2.5. Statistics

Each experiment was repeated 3–9 times and their mean value with S.D. was presented. Student's t-test was performed to see any significance difference in permeation parameters between the control vehicle and test vehicles containing surfactants.

2.6. Characterization of ibuprofen-surfactant interaction using DSC and FT-IR

Differential scanning calorimetry (DSC) and Fourier transform infra-red spectroscopy (FT-IR) were performed to identify any change in the physicochemical properties of the mixture of ibuprofen and POE alkyl ether. Ibuprofen, POE(5)cetyl/oleyl ether as a surfactant, and their intrinsic mixtures at various ratios (drug:surfactant = 1:1, 1:2 and 1:5% w/w) were employed as samples. The mixtures of ibuprofen and surfactant were prepared by melting together at 80°C with mechanical stirring. When no particles were observed in the mixture, the melts were cooled down to ambient temperature. After storage for at least 24 h, the mixture was pulverized in a mortar and sieved to obtain the fraction of 150–300 μm.

Thermal analysis was performed on the drug and drug-polymer physical mixture using a DSC equipped with a computerized data station (NET-

Table 2
Solubility of ibuprofen in the 15% POE alkyl ether–water vehicles at 32°C

POE-alkyl ethers	Solubility (mg/ml)
Control	0.11 ± 0.02[a]
Emulgin B1	26.89 ± 3.09
Emulgin B2	16.62 ± 0.41
Emulgin B3	15.08 ± 0.97
DLS2	5.12 ± 1.63
Emulgin 05	24.37 ± 2.07
Emulgin 010	15.38 ± 2.16
Brij 35	13.55 ± 1.17
Brij 52	N/A[b]
Brij 58	17.93 ± 1.02
Brij 72	0.56 ± 0.32
Brij 78	19.04 ± 0.45
Brij 98	18.75 ± 1.43
Brij 30	12.14 ± 1.94
Brij 92	N/A[b]
Brij 56	25.26 ± 0.89
Brij 76	2.17 ± 0.16
Brij 700	5.35 ± 0.36

[a] Mean ± S.D., $n = 3$.
[b] Not available.

ZSCH, DSC 200, Germany) in sealed stainless steel pans under a stream of anhydrous nitrogen gas. To fill the DSC pans without the systems melting, the pans were cooled to 0°C for 30 min prior to loading with approximately 10 mg of mixture. DSC was calibrated against an indium reference pan between 20 and 300°C at a heating rate of 20°C/min. Determinations of the transition temperature were carried out via a computerized procedure. The FT-IR spectra were recorded on a Perkin-Elmer model 1750 spectrometer using KBr disks.

3. Results and discussion

3.1. Solubility studies

The saturated solubility of ibuprofen in the vehicles (15% POE alkyl ether–water) at 32°C are shown in Table 2. The drug has a very low aqueous solubility (0.11 mg/ml), but the addition of POE alkyl ethers enhanced the solubility of ibuprofen in water significantly. The vehicles containing POE(12)cetyl/stearyl ether showed the highest solubility (26.89 mg/ml), which is almost 250-fold over the intrinsic solubility of ibuprofen in water. Since the vehicles containing POE(2)cetyl ether and POE(2)oleyl ether formed a gel, the solubility could not be determined.

3.2. Skin permeation studies

The permeation parameters were determined and are presented in Table 3. The permeation rate of ibuprofen was increased 0.94–5.24 times with the addition of POE alkyl ethers over the control vehicle (21.05 ± 7.49 μg/cm^2/h). POE(5)cetyl/oleyl ether showed the most potent enhancing effect (110.24 μg/cm^2/h, 5.24-fold over the control), followed by POE(2)lauryl ether (99.91 μg/cm^2/h, 4.74-fold), POE(2)oleyl ether (67.46 μg/cm^2/h, 3.20-fold) and POE(10)stearyl ether (66.19 μg/cm^2/h, 3.10-fold). POE(2)oleyl ether showed the longest lag time (2.47 h).

There are two possible mechanisms by which the rate of transport is enhanced using surfactants (Breuer, 1979; Walters et al., 1987). Initially the surfactants may penetrate into the intercellular regions of stratum corneum, increase fluidity and eventually solubilize and extract lipid components. Secondly, penetration of the surfactant into the intracellular matrix followed by interaction and binding with keratin filaments may result in a disruption within the corneocyte.

POE alkyl ethers are thought to enhance the penetration of a drug via both the lipophilic and the hydrophilic molecular mechanisms, and to disrupt the lipid arrangements in the stratum corneum and to increase the water content of the proteins in the barrier (Breuer, 1979; Walters et al., 1987). The structures of POE alkyl ethers are relevant to this role. It consists of an EO and a long hydrocarbon chain. This structure imparts both lipophilic and hydrophilic characteristics to the enhancer, allowing it to partition between lipophilic mortar substance and the hydrophilic protein domains. The POE alkyl ethers may interact with the polar head groups of the lipids and the modification of H-bonding and ionic forces may occur. The enhancer has an effect upon the hydration of spheres of the lipids, resulting in a

disruption of the lipid-packing arrangement. The lipophilic domain becomes fluidized and, therefore, promotes the diffusion of polar penetrants. This perturbation probably fluidizes the lipids in the skin and, hence, allows ibuprofen to pass through. The other possible mechanism related to our studies involves the protein domains (corneocytes). In this case, the targets of the enhancer are the keratin fibrils and their associated water molecules. The disruption caused by the enhancer makes this area more aqueous. With high enough volumes an increase in the solubilizing ability of the aqueous layer could result and actually change the operational partition coefficient of this region of the skin (Barry, 1983). This would then allow for drug transport through the corneocytes. The third mechanism may involve the insertion of the enhancer between the lipophilic tails of the bilayer. This will also disrupt the packing of the lipids, increasing the fluidity of this layer and permitting easier diffusion through the skin. This mechanism, much like the first, will enhance the penetration of ibuprofen across rat skin.

3.3. Effects of EO and alkyl chain length on skin permeation

The effects of the alkyl chain length with varying EO chain lengths, from 2 to 20, on the skin permeation of ibuprofen are illustrated in Figs. 1–3. At a constant EO chain length of 2, POE(2)lauryl ether showed the highest enhancing effect (4.74-fold over the control), followed by POE(2)oleyl ether (3.20-fold), POE(2)stearyl ether (1.61-fold) and POE(2)cetyl ether (0.94-fold). POE(2)oleyl ether showed significantly enhancing effect compared to POE(2)stearyl ether containing the same alkyl chain length. This effect could be explained by the double bond of oleyl ether. The presence of *cis*-double bonds in fatty acids and alcohols has been shown to increase considerably its enhancement potential when compared with

Table 3
Permeation parameters of ibuprofen through excised rat skins after the transdermal application of POE alkyl ethers–water vehicles containing 5% ibuprofen

Surfactants	Permeation parameters[a]			
	T_L (h)	J_s (μg/cm^2/h)	K	$D \times 10^3$ (cm^2/h)
Control	2.32 ± 0.26[b]	21.05 ± 7.49	26.13 ± 3.23	0.75 ± 0.24
Emulgin B1	1.17 ± 0.25*	27.73 ± 0.67	0.071 ± 0.01*	1.48 ± 0.34*
Emulgin B2	0.90 ± 0.26*	26.86 ± 4.17	0.086 ± 0.02*	1.95 ± 0.51*
Emulgin B3	1.07 ± 0.23*	28.89 ± 0.90*	0.116 ± 0.02*	1.68 ± 0.61*
DLS2	1.43 ± 0.23*	99.91 ± 6.06*	1.688 ± 0.37*	1.18 ± 0.17*
Emulgin 05	0.97 ± 0.06*	110.24 ± 5.55*	0.267 ± 0.07*	1.73 ± 0.11*
Emulgin 010	1.93 ± 0.31*	33.93 ± 3.71*	0.257 ± 0.04*	0.88 ± 0.15
Brij 35	1.03 ± 0.15*	20.60 ± 0.95	0.097 ± 0.01*	1.64 ± 0.23*
Brij 52	1.03 ± 0.06*	19.89 ± 1.15	N/A[c]	1.62 ± 0.09*
Brij 58	1.04 ± 0.25*	21.37 ± 0.96	0.073 ± 0.04*	1.68 ± 0.40*
Brij 72	1.02 ± 0.25*	33.86 ± 2.12*	3.739 ± 0.28*	1.65 ± 0.42*
Brij 78	1.30 ± 0.10*	57.84 ± 2.70*	0.240 ± 0.06*	1.29 ± 0.10*
Brij 98	1.80 ± 0.36*	58.53 ± 2.02*	0.335 ± 0.08*	0.95 ± 0.18
Brij 30	2.17 ± 0.15	33.30 ± 0.65*	0.363 ± 0.07*	0.77 ± 0.07
Brij 92	2.47 ± 0.46	67.46 ± 2.84*	N/A[c]	0.69 ± 0.12
Brij 56	2.30 ± 0.17	34.16 ± 2.15*	0.189 ± 0.08*	0.73 ± 0.05
Brij 76	1.20 ± 0.41*	66.19 ± 3.19*	2.226 ± 0.23*	1.40 ± 0.12*
Brij 700	1.33 ± 0.21*	57.47 ± 0.39*	0.864 ± 0.06*	1.27 ± 0.21*

[a] T_L, lag time; J_s, steady-state permeation rate; K, partition coefficient (skin/vehicle); D, diffusion coefficient.
[b] Mean ± S.D., $n = 6$.
[c] Not available.
* Significantly different from the control ($P < 0.05$).

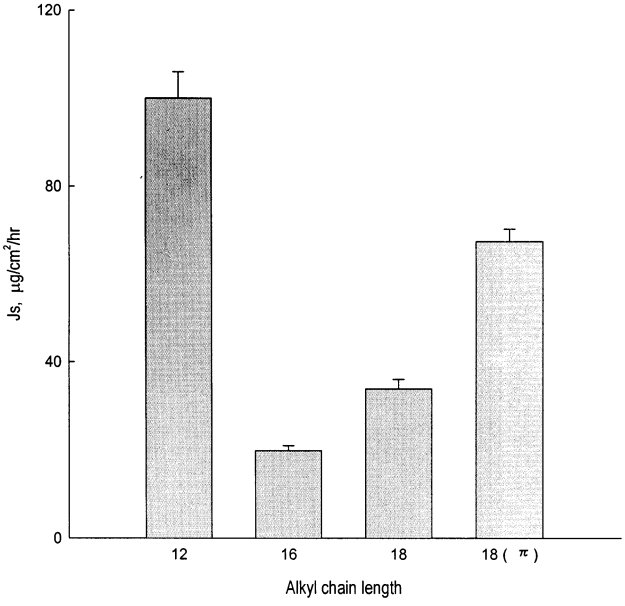

Fig. 1. A histogram showing the dependence of ibuprofen flux (J_s) on alkyl chain length with a constant EO chain length of 2.

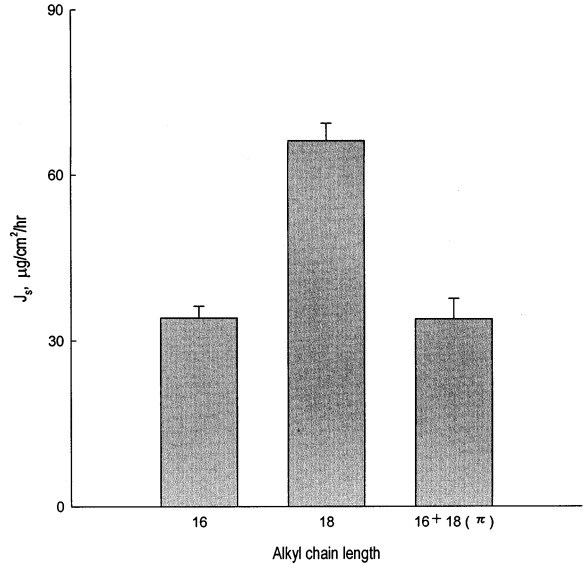

Fig. 2. A histogram showing the dependence of ibuprofen flux (J_s) on alkyl chain length with a constant EO chain length of 10.

saturated *trans*-double bond counterparts (Cooper, 1984; Aungst et al., 1986). Meanwhile, POE(2)lauryl ether (4.74-fold) presented a high enhancing effect despite of short alkyl chain length, which can be explained considering relatively high hydrophile/lipophile balance (HLB) of 7.0. At a constant EO chain length of 10, POE(10)stearyl ether showed the most effective enhancing on ibuprofen flux (3.14-fold over the control), followed by POE(10)cetyl ether, POE(10)cetyl/oleyl ether. At a constant EO chain length of 20, the flux was found in the order POE(20)oleyl ether > POE(20)stearyl ether > POE(20)cetyl/stearyl ether > POE(20)cetyl ether.

In Figs. 4–7, the influence of EO chain length at a constant alkyl chain length of 12, 16 and 18 on the permeation rate of ibuprofen is expressed. At a constant alkyl chain length of 12, POE(2)lauryl ether showed the highest enhancing effect (4.74-fold), followed by POE(4) lauryl ether and POE(23)lauryl ether. The enhancing effect was inversely proportional to the HLB values of these surfactants. At a constant alkyl chain length of 16, POE(10)cetyl ether showed the highest enhancing effect (1.62-fold), followed by POE(20)cetyl ether and POE(2)cetyl ether in the rank order. At a constant alkyl chain length of 18,

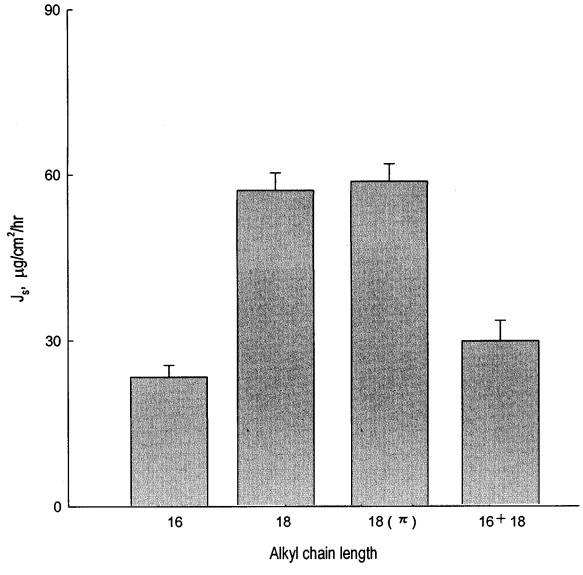

Fig. 3. A histogram showing the dependence of ibuprofen flux (J_s) on alkyl chain length with a constant EO chain length of 20.

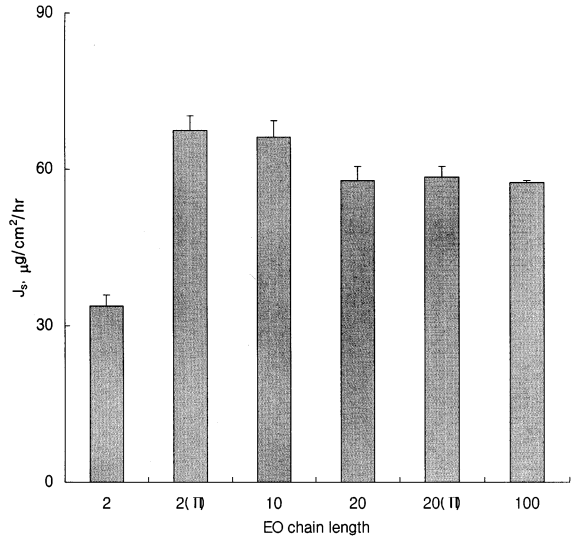

Fig. 6. A histogram showing the dependence of ibuprofen flux (J_s) on alkyl chain length with a constant EO chain length of 18.

Fig. 4. A histogram showing the dependence of ibuprofen flux (J_s) on alkyl chain length with a constant EO chain length of 12.

POE(2)oleyl ether and POE(10)stearyl ether showed the enhancing effect (3.20-fold). These cases showed a similar pattern regardless of EO chain length except for POE(2)stearyl ether. From these results, it may be concluded that surfactants with alkyl chain length of 18 comparatively increased ibuprofen flux through rat skin. Consequently, the surfactants with EO chain length 2–5, HLB value 7–9 and an alkyl chain length C16–C18 showed effective penetration enhancement of ibuprofen.

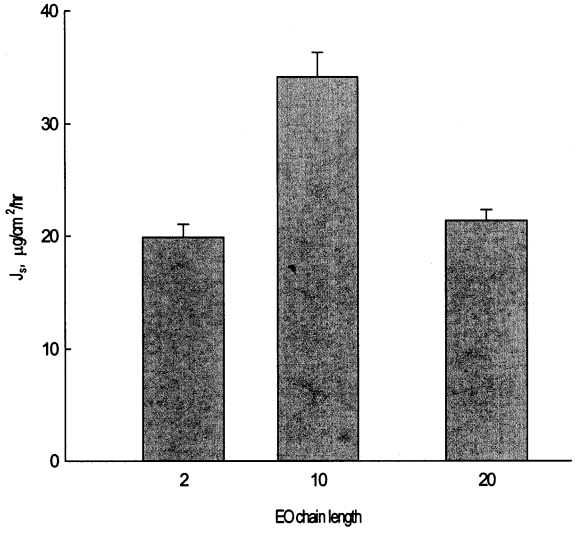

Fig. 5. A histogram showing the dependence of ibuprofen flux (J_s) on alkyl chain length with a constant EO chain length of 16.

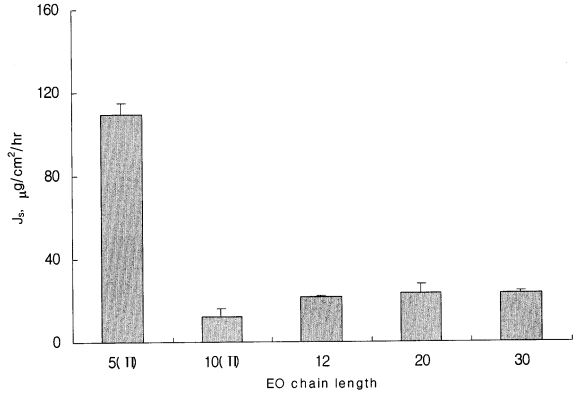

Fig. 7. A histogram showing the dependence of ibuprofen flux (J_s) on alkyl chain length with a constant EO chain length of 1:1 mixture of C16 and C18.

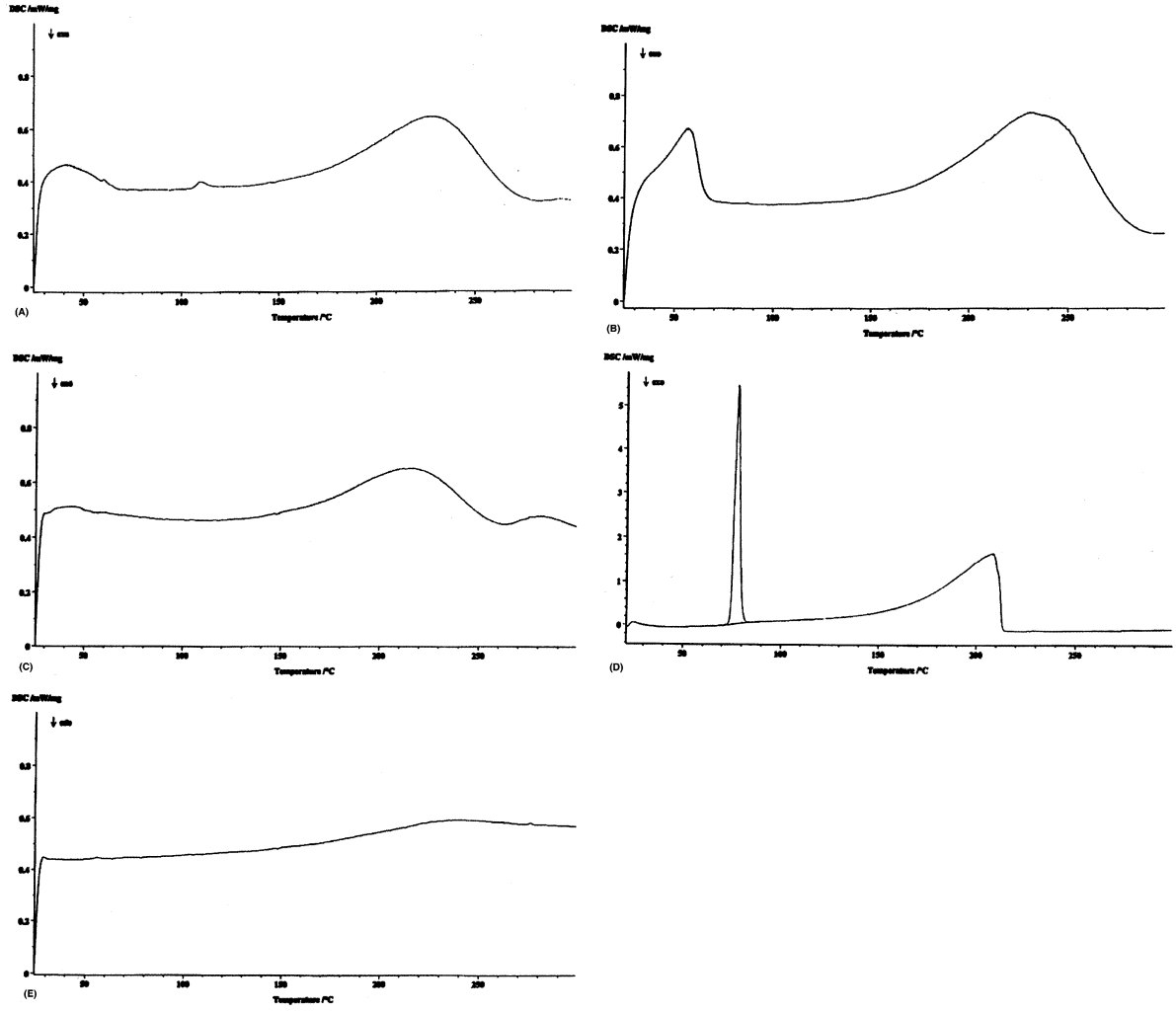

Fig. 8. Differential scanning calorimetry traces for ibuprofen:POE(5) cetyl/oleyl ether. (a) 1:2; (b) 1:1; (c) POE(5) cetyl/oleyl ether; (d) neat ibuprofen and (e) 1:5.

3.4. Characterization of ibuprofen–POE alkyl ether interaction using DSC and FT-IR

The DSC traces for ibuprofen:POE(5)cetyl/oleyl ether are shown in Fig. 8. As POE(5)cetyl/oleyl ether is a liquid at ambient temperature, there was no distinct peak in its thermogram. Ibuprofen displays two endothermic peaks at 77.8 and at 208.3°C with decomposition at around 213°C. The DSC curves of ibuprofen dispersions show one or two endothermic peaks depending on the ratio of drug-to-surfactant. At each ibuprofen–POE(5)cetyl/oleyl ether ratio, the endothermic peak corresponding to the melting of ibuprofen and surfactant shifted to a lower temperature but lost its sharpness. The disappearance of the endothermic peak supports the increase of amorphousness following fusion and recrystallization.

Further investigation was performed with FT-IR. Generally, carboxylic acids are characterized by FT-IR spectroscopy by bands from the OH stretch, the OH in-plane and out-of-plane stretch, and the C=O asymmetrical wag (Stott et al.,

1998). These bands are all sensitive to the hydrogen bonding of the COOH group that exists either as the unbonded monomer, the carboxylic acid dimer, or in a hydrogen-bonded polymeric form. The carboxylic acid monomer has a characteristic strong absorbance between 1800 and 1740 cm^{-1}. When two C=O groups are present with a center of symmetry as in a carboxylic acid dimer this peak shifts to 1720–1680 cm^{-1}. When the carbonyl C=O is hydrogen bonded, but not dimerised as in alcohol-carbonyl bonding, a band is seen near 1730–1705 cm^{-1} (Najib et al., 1986; Colthup et al., 1990).

FT-IR analysis of ibuprofen, POE(5)cetyl/oleyl ether, and the mixtures of ibuprofen-POE(5)cetyl/oleyl ether of various concentration ratios (1:1, 1:2, 1:5% w/w) are shown in Fig. 9. In the carbonyl frequency region, ibuprofen shows a strong absorbance at 1720 cm^{-1}, which confirms that in the condensed state it exists in the dimeric from. With the ibuprofen:POE(5)cetyl/oleyl ether mixture the hydrogen bonding state of ibuprofen changes from the dimeric form to a carbonyl-hydroxyl (C=O–HO) hydrogen-bonded form in the presence of excess POE alkyl ether, which gives the shift of CO stretch in the carboxylic group to higher wave number. This is shown by an upward shift of the C=O asymmetrical stretch peak from 1720 to 1740 cm^{-1} for the ibuprofen:POE(5)cetyl/oleyl ether of 1:5. The ratio of the absorbance of the 1740 and 1720 cm^{-1} peaks provides a measure of the relative amounts of the two hydrogen-bonded forms. When POE(5)cetyl/oleyl ether is in excess, the hydroxyl-hydrogen bonded form predominates and when ibuprofen is in excess, both the hydroxyl and dimeric forms exist.

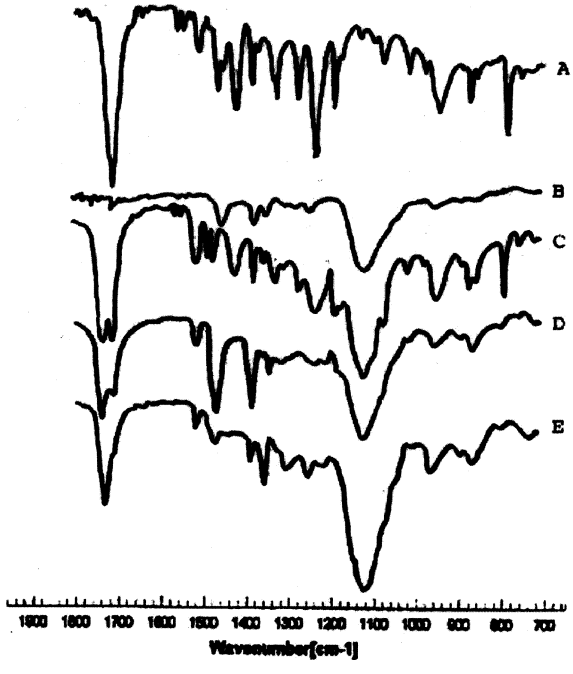

Fig. 9. FT-IR traces showing absorption in the carbonyl (C=O) stretching region for neat ibuprofen and a range of ibuprofen:POE(5) cetyl/oleyl ether mixtures. (A) Ibuprofen; (B) POE(5); (C) ibuprofen:POE(5)cetyl/oleyl ether 1:1; (D) 1:2; (E) 1:5.

In the low frequency region 600–1600 cm^{-1}, the bands observed in the mixture are both for the ibuprofen and POE(5)cetyl/oleyl ether, but some bands for the ibuprofen are either disappeared or significantly reduced in intensity. In case of the strong band at 810 cm^{-1} with ibuprofen, the band is disappeared in the mixtures. It can be concluded from the spectroscopic studies that in the mixture, a significant change in the total symmetry of the ibuprofen molecule in the POE(5)cetyl/oleyl ether matrix has occurred since ibuprofen interacts with POE(5)cetyl/oleyl ether mainly through hydrogen bonding between the carboxylic acid group of the drug and the surfactant (El-Hinnawi and Najib, 1987). The data presented demonstrates that this new system provides a more efficient way of improving the percutaneous absorption of ibuprofen. Further work is warranted to optimize the gel preparation containing ibuprofen using the factorial design and its in vitro/in vivo drug release behaviours.

4. Conclusion

POE alkyl ethers have shown ability to enhance the permeation of ibuprofen across rat skin. The enhancers containing EO chain length of 2–5, HLB value 7–9 and an alkyl chain length C16–C18 are the very effective promoters for the skin permeation of ibuprofen.

In addition to HLB, the size and shape of both the alkyl chain and the POE group, physicochem-

ical changes between drug and surfactant were found to be important factors for the enhancement of skin permeation of ibuprofen. IR and DSC studies indicate that the hydrogen bonding state of ibuprofen changes from the dimeric form to carbonyl-hydroxyl (C=O–HO) hydrogen bonded form in the presence of excess POE alkyl ether enhanced the skin permeation of ibuprofen.

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