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The enhancement effect of surfactants on the penetration of lorazepam through rat skin

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Abstract

Lorazepam is an anxiolytic, antidepressant agent, having suitable feature for transdermal delivery. The percutaneous permeation of lorazepam was investigated in rat skin after application of a water:propylene glycol (50:50%v/v). The enhancing effects of various surfactants (sodium lauryl sulfate (SLS), cetyltrimethylammonium bromide (CTAB), benzalkonium chloride or Tween 80) with different concentrations on the permeation of lorazepam were evaluated using Franz diffusion cells fitted with rat skins. Flux, K_p, lag time and enhancement ratios (ERs) of lorazepam were measured over 24 h and compared with control sample. Furthermore, lorazepam solubility in presence of surfactants was determined. The in vitro permeation experiments with rat skin revealed that the surfactant enhancers varied in their ability to enhance the flux of lorazepam. The permeation profile of lorazepam in presence of the cationic surfactant, CTAB, reveals that an increase in the concentration of CTAB results in an increase in the flux of lorazepam in comparison with the control. But an increase in concentration of CTAB or benzalkounium chloride from 0.5 to 1% w/w or from 1 to 2.5% w/w resulted in a reduction in ER, respectively. Benzalkonium chloride which possessed the highest lipophilicity (log $P = 1.9$) among cationic surfactants provided the greatest enhancement for lorazepam flux (7.66-fold over control) at 1% w/w of the surfactant. CTAB (log $P < 1$) and sodium lauryl sulphate at a concentration of 5% w/w (the highest concentration) exhibited the greatest increase in flux of lorazepam compared with control (9.82 and 11.30-fold, respectively, over control). This is attributed to the damaging effect of the cationic and anionic surfactants on the skin at higher concentration. The results also showed that the highest ER was obtained in presence of 1% w/w surfactant with the exception of SLS and CTAB. The increase in flux at low enhancer concentrations is normally attributed to the ability of the surfactant molecules to penetrate the skin and increase its permeability. Reduction in the rate of transport of the drug present in enhancer systems beyond 1% w/w is attributed to the ability of the surfactant molecules to form micelles and is normally observed only if interaction between micelle and the drug occurs.

Keywords: Solubility; Skin absorption; Enhancer; Surfactants; Lorazepam

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1. Introduction

Transdermal delivery of drugs promises many advantages over oral or intravenous administration, such as a better control of blood levels, a reduced incidence of systemic toxicity, an absence of hepatic first-pass metabolism, etc. Unfortunately, drug delivery via the skin is not a simple task; the outermost layer of the skin, the stratum corneum (SC), is a formidable barrier both to water transport out of the body and to inward chemical permeation. The SC, of the skin comprising keratin-rich cells embedded in multiple lipid bilayers. In fact, the majority of drugs do not appear to penetrate the skin at a rate sufficiently high for therapeutic efficacy and only the most potent ones with appropriate physicochemical characteristics are valid candidates for transdermal delivery. Many strategies have been suggested in order to overcome the low permeability of drugs through the skin. A popular approach is the use of penetration enhancers (or accelerants) which reduces reversibly the permeability barrier of the SC (Barry, 1983). These agents partition into, and interact with the SC constituents to induce a temporary, reversible increase in skin permeability. In this way, many compounds, such as isopropyl myristate (Naito and Tominagaa, 1985), nicotinic acid esters (Yasukawa et al., 1985), hydrogenated Soya phospholipid (Nishihata et al., 1987), essential oils (Williams and Barry, 1989) ethanol (Nishihata et al., 1988; Obata et al., 1993), *n*-octanol and decanol (Takahashi et al., 1991a,b), terpenes (Arellano et al., 1996) and surfactants (Sarpotdar and Zatz, 1986a,b; Cappel and Kreuter, 1991; Iwasa et al., 1991; Lopez et al., 2000; Park et al., 2000; Shin et al., 2001; Shokri et al., 2001) have been reported to enhance the permeability of drugs.

Surfactants are used as emulsifier and as physical stabilising, wetting and suspending agents in many topical pharmaceutical formulations, cosmetic and food products. Moreover, it is well known that surfactants have effects on the permeability characteristics of several biological membranes, including skin (Florence et al., 1994; Lopez et al., 2000) and for this reason they can enhance the skin penetration of other compounds present in the formulation. Therefore, in recent years they have been employed to enhance the permeation rates of several drugs (Chowan and Pritchard, 1978; Aungst et al., 1986).

To evaluate the benzodiazepines transdermal ability, different authors studied their in vitro percutaneous absorption. For instance, the skin permeation profiles of midazolam maleate (Touitou, 1986) and diazepam (Touitou, 1986) were studied through hairless mouse skin from various solvents systems, besides Hori et al., (1991), Shokri et al. (2001) investigated the enhancement of diazepam penetration through rat skin in vitro by different monoterpenes and surfactants, respectively. Carelli et al. (1992) determined the enhancement effects of oleic and linoleic acid on the skin permeation of alprazolam through hairless mouse skin. Other authors studied the percutaneous absorption of clonazepam from a series of alcoholic-gel or emulsion-gel formulation containing various enhancing agents (Mura et al., 1989, 1997; Ogiso et al., 1989; Puglia et al., 2001) using artificial membranes (Mura et al., 1989, 1993, 1996) or natural ones (rabbit ear skin) (Ogiso et al., 1989; Mura et al., 1996). Since therapy using benzodiazepins often involves long term administration, the transdermal rout of drug administration would have a potential merit over conventional dosage form.

The objective of the present study was to examine the influence of different concentrations of surfactants with different chemical structures on the in vitro permeation of lorazepam through abdominal rat skin.

2. Materials and methods

2.1. Chemicals and reagents

Lorazepam was provided by Industrial Zahravi Pharmaceutical (Tabriz, Iran). Sodium lauryl sulfate (SLS), cetyltrimethylammonium bromide (CTAB), benzalkonium chloride and Tween 80 (Merck, Germany) were used.

2.2. Solubility studies

Saturated solubilities of lorazepam in water–propylene glycol (50:50 v/v) and in the solvent containing different concentrations of various surfactants were evaluated. Saturated solutions were prepared by adding excess drug to the vehicles and shaking for 24 h at 37 °C. After this period the solutions were filtered, diluted and analysed by HPLC. Three determinations were carried out for each sample to calculate the solublity of lorazepam. The apparent solubility ERs of diazepam in vehicles were calculated using the following equation: solubility $ER = C_0/C_s$ where C_0 is the lorazepam concentration in the presence of surfactant and C_s is the saturation solubility of lorazepam in the control sample (no surfactant).

2.3. Skin membrane preparation

The abdominal hair of wistar male rats, weighing 160 ± 25 g, was shaved using electric and hand razors 24 h before treatment. After anaesthetising the rat with ether, the abdominal skin was surgically removed from the animal, and adhering subcutaneous fat was carefully cleaned. To remove extraneous debris and leachable enzymes, the dermal side of the skin was in contact with a saline solution for 1 h before starting the diffusion experiment.

2.4. Permeation studies

A system employing improved Franz diffusion cells with a diffusional area of 5.3 cm^2 was used for permeation studies. The excised rat skin was set in place with the SC facing the donor compartment and the dermis facing the receptor. Five millilitre of the saturated solution of lorazepam (water:-propylene glycol was 50:50% v/v with or without surfactant) was placed on the skin surface in the donor compartment that was sealed from the atmosphere using a plastic film (Parafilm). The receptor compartment of the cell was filled with 25 ml of phosphate buffer (pH 7.4). During the experiments, the solution in receptor side was maintained at 37 ± 0.5 °C and stirred at 800 rpm with Teflon-coated magnetic stirring bars. After application of the test formulation on the donor side, 0.25 ml aliquots were collected from the receptor side at designated time intervals (0.25, 0.5, 1, 2, 4, 6, 8, 10, 18 and 24 h), and 0.25 ml of the phosphate buffer was added into the receptor side immediately after each sample collection. To determine the effect of the surfactant on the skin permeability, different concentrations of surfactants ranging from 0 to 5% w/w were used. The results are the mean and standard deviations of at least three determinations.

2.5. Analytical procedure

The HPLC apparatus (Ceceil 1100, UK) equipped with a 20 μm loop and a variable-wavelength UV detector. The column was Spherisorb C18 (150×4 mm, 5 μm, Hichrom). The mobile phase for lorazepam was methanol–water (60:40). The flow rate was1.2 ml min^{-1} and detection was performed at 230 nm (Puglia et al., 2001).

2.6. Data treatment

According to Fick's second law of diffusion, the total amount of drug (Q_t) appearing in the receptor solution in time t is expressed as:

$$Q_t = AKLC_0\left[\left(\frac{Dt}{L^2}\right) - \left(\frac{1}{6}\right) - \left(\frac{2}{\pi^2}\right)\Sigma\frac{(-1)^n}{n^2}\right] \times \exp\left(\frac{D^n 2\pi^2 t}{L^2}\right) \quad (1)$$

where A, is the effective diffusion area, C_0, represents the drug concentration which remains constant in the vehicle, D is the diffusion coefficient, L denotes the thickness of the membrane and K is the partition coefficient of the drug between membrane and vehicle. At steady-state, Eq. (1) is expressed as follows:

$$\frac{Q_t}{A} = KLC_0\left[\left(\frac{Dt}{L^2}\right) - \left(\frac{1}{6}\right)\right] \quad (2)$$

The flux, J, was determined from the slope of the steady-state portion of the amount of the drug

permeated divided by A versus time. The lag time values were determined from the x-intercept of the slope at steady-state.

From Eq. (2) the flux is expressed as:

$$J = \frac{C_0 KD}{L} = C_0 K_p \quad (3)$$

where K_p is the permeability coefficient.

The ER was calculated from following equation (Williams and Barry, 1989)

$$ER = \left(\frac{K_p \text{ with pretreatment}}{K_p \text{ without pretreatment}} \right) \quad (4)$$

The values reported are mean ratios from a minimum of three replicates.

3. Results and discussion

Table 1 shows the solubility of lorazepam in presence of various surfactants in vehicles. The drug has a relatively low solubility in water: propylene glycol mixture (2.481 mg ml^{-1}); the addition of surfactant enhanced the solubility of lorazepam in water:propylene glycol significantly (Table 1). The vehicle containing 5% SLS showed the highest solubility (15.744 mg ml^{-1}), which is over 6-fold the solubility of lorazepam in water:PG (50:50% v/v).

Figs. 1–4 show the permeation profiles of lorazepam in presence of Tween 80 (a nonionic surfactant), benzalkonium chloride and CTAB (cationic surfactants) and SLS (an anionic surfactant) through rat skin, respectively. The flux, J, permeability coefficient, K_p, lag time and ER for each of the different concentrations of the surfactant according to Eqs. (2)–(4) are tabulated in Table 2. The table shows that all the surfactants used in the study increase the permeation rate of lorazepam. The results showed that surfactant concentration plays an important role in the ER. To determine the effect of a non-ionic surfactant on the permeation of lorazepam, Tween 80 with

Table 1
Effect of surfactants on the lorazepam solubility in water–propylen glycol (50:50) at 37 °C (the results are the mean of at least three determinations)

Surfactant concentration (%w/w)		Solubility (mg ml^{-1})	ER_{sol}[a]
Control		2.48	1.00
Tween 80			
	0.5	3.61	1.46
	1.0	4.39	1.77
	2.5	5.75	2.32
	5.0	5.97	2.41
Benzalkonium chloride		4.72	1.90
	0.5	5.29	2.13
	1.0	6.99	2.82
	2.5	11.69	4.71
	5.0		
CTAB		6.63	2.67
	0.5	6.68	2.69
	1.0	8.39	3.38
	2.5	10.72	4.32
	5.0		
SLS			
	0.5	4.36	1.76
	1.0	7.01	2.83
	2.5	8.58	3.46
	5.0	15.74	6.35

[a] ER_{sol}, enhancement ratio of lorazepam solubility.

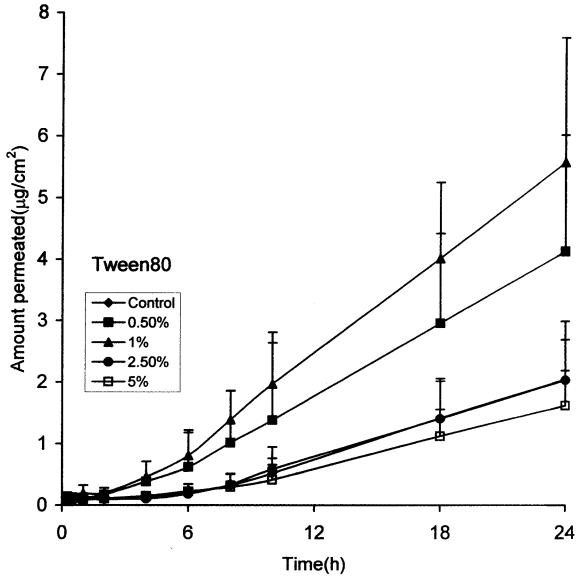

Fig. 1. Permeation profiles of lorazepam in presence of different concentrations of Tween 80 through rat skin.

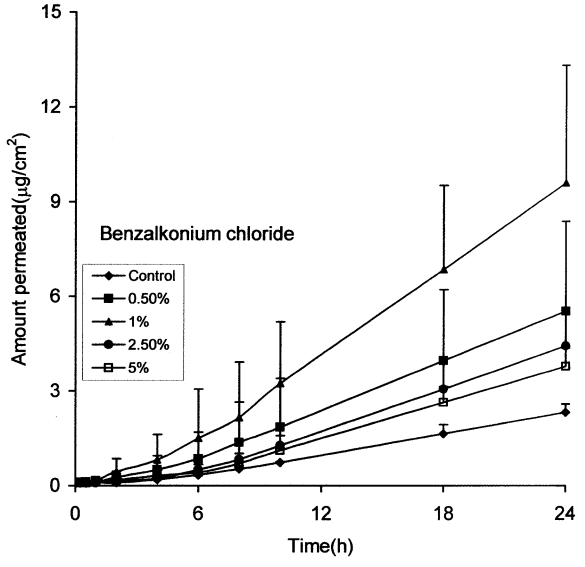

Fig. 2. Permeation profiles of lorazepam in presence of different concentrations of benzalkonium chloride through rat

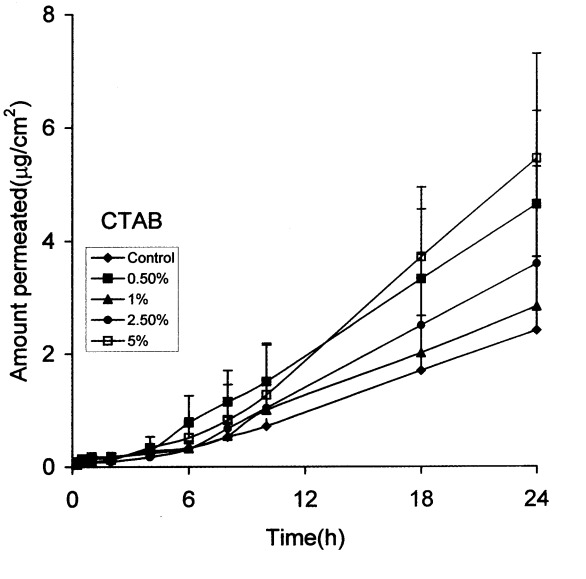

Fig. 3. Permeation profiles of lorazepam in presence of different concentrations of CTAB through rat skin.

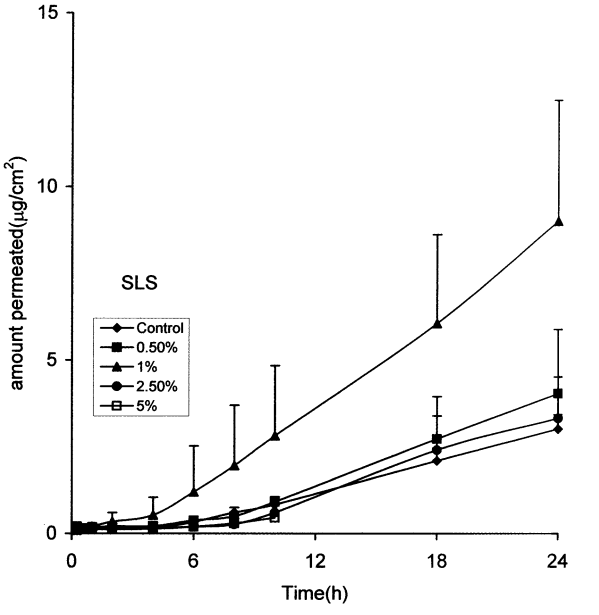

Fig. 4. Permeation profiles of lorazepam in presence of different concentrations of SLS through rat skin.

different concentrations was used and the permeation profile is shown in Fig. 1. In this case, the highest permeation rate was observed with the solution containing 1% w/w of Tween 80. Similar results were reported for diazepam permeation in presence of Tween 80 (Shokri et al., 2001). They are two possible mechanisms by which the rate of transport is enhanced using nonionic surfactants

Table 2
Lorazepam skin permeation parameters in presence of various surfactants (the results are the mean and standard deviation of at least three determinations)

Surfactant concentration (%w/w)		Steady-state flux (μg cm^{-2} h^{-1})	K_p ($\times 10^3$; cm h^{-1})	Lag time (h)	ER
Control		0.12 ± 0.02	0.0510 ± 0.0063	3.82	1.00
Tween 80					
	0.5	0.28 ± 0.15	0.1146 ± 0.0632	2.84	2.29
	1.0	0.47 ± 0.19	0.1878 ± 0.0778	2.74	3.75
	2.5	0.24 ± 0.08	0.0969 ± 0.0312	4.47	1.93
	5.0	0.19 ± 0.09	0.0780 ± 0.0365	4.07	1.56
Benzalkoniumchloride					
	0.5	0.49 ± 0.16	0.1994 ± 0.0633	2.76	3.98
	1.0	0.95 ± 0.36	0.3841 ± 0.1449	2.65	7.66
	2.5	0.62 ± 0.08	0.2516 ± 0.0315	4.04	5.02
	5.0	0.89 ± 0.07	0.3591 ± 0.0298	4.03	7.16
CTAB					
	0.5	0.58 ± 0.18	0.2341 ± 0.0727	2.70	4.67
	1.0	0.38 ± 0.10	0.1513 ± 0.0421	3.55	3.02
	2.5	0.62 ± 0.22	0.2485 ± 0.0888	4.28	4.96
	5.0	1.22 ± 0.51	0.4926 ± 0.2040	4.88	9.82
SLS					
	0.5	0.37 ± 0.03	0.1501 ± 0.0106	5.13	2.99
	1.0	1.25 ± 0.53	0.5039 ± 0.2144	3.66	10.05
	2.5	0.67 ± 0.16	0.2685 ± 0.0629	6.74	5.36
	5.0	1.40 ± 0.13	0.5662 ± 0.0519	7.26	11.30

(Breuer, 1979; Walters et al., 1987). Initially the surfactants may penetrate into the intercellular regions of SC, increase fluidity and eventually solubilise and extract lipid components. Secondly, penetration of the surfactant into the intercellular matrix followed by interaction and binding with keratin filaments may results in a disruption within the corneocyte. Tween 80 is thought to enhance the penetration of lorazepam via both the lipophilic and the hydrophilic molecular mechanisms, and to disrupt the lipid arrangements in the SC and to increase the water content of the proteins in the barrier. The structure of Tween 80 is relevant to this role. It contains the ethylene oxide 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. Tween 80 may interact with the polar head groups of the lipids and the modification of H-bonding and ionic forces may occur. The other possible mechanism related to our studies involves the protein domains (corneocytes). In this case, 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 solubilising 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.

Shin et al. (2001) recently studied the mechanism of the effect of non-ionic surfactants as permeation enhancers towards piroxicam through rat skins using thermal analysis and histological examination. They indicated that changes in thermal profile seen with surfactant-treated sample were due to its incorporation into the SC resulted in decreased lipid order. They also showed that various enhancers had different fluidising effect on the lipids of the SC. It has been also shown that intact skin is composed of SC, epidermis, dermis and subcutaneous fats and has well-woven struc-

tures. The skin pre-treated with the non-ionic surfactant showed that the SC was loosely layered and that intercellular spaces were wide (Shin et al., 2001).

Table 2 shows that the presence of benzalkonium chloride produced the highest permeation rate at the concentration of 1% w/w. Increasing the concentration of benzalkonium chloride from 1 to 2.5% w/w reduces the permeation rate and beyond 2.5% the flux increased from 0.6241 to 0.8909 μg cm^{-2} h^{-1}. The permeation profile of lorazepam in presence of the other cationic surfactant, CTAB, reveals that an increase in the concentration of CTAB results in an increase in the flux of lorazepam in comparison with the control (Table 2). But an increase in concentration of CTAB or benzalkounium chloride from 0.5 to 1% w/w or from 1 to 2.5% w/w resulted in a reduction in ER, respectively. Similar results were reported on the effect of other cationic surfactant (cetrimide is a cationic surfactant which contains higher percentages of CTAB) on haloperidol permeation through rat skin (Vaddi et al., 2001). They stated that, this reduction in ER may be due to the fact that though the cationic surfactant did not alter lag time significantly from that of the control, cationic surfactant at low concentration had less mean lag time than that of higher concentration (Table 2). Provided the enhancer did not influence the lag time, and such a difference in the lag time may be due to experimental and animal variations and these variations can be minimised either by increasing the sample size or increasing the enhancer concentration difference. As all four concentrations chosen were above the critical micelle concentration (CMC) of the cationic surfactants ($>0.01\%$ in water), therefore, drug solutions would presumably contain an identical number of monomers but different quantities of micelles increasing with the surfactant concentration. Enhancer dose-dependent thermodynamic activity of lorazepam above CMC can be attributed to micelle-dependent solubilisation of skin lipids (Loden, 1990). Though it is generally accepted that micelles do not penetrate the skin on the account of bulkiness, they may solubilise specific components within the intercellular lipid matrix (Ruddy, 1995). So an increase in the thermodynamic activity was proportional to the number of micelles present. Since the enhancer index of CTAB and benzalkonium chloride at 0.5% were 4.67 and 3.98, respectively, monomers probably did show considerable enhancement activity. The highest flux was observed in presence of 5% CTAB. This could be explained by the fact that these surfactants cause extensive damage to the skin that is reported to cause a large increase in transdermal flux at higher concentration of cationic surfactants (Gershbein, 1979). Kushla and Zatz (1991), who worked with three series of cationic surfactants and found that the nature of the surfactant head group has little influence on cutaneous barrier impairment. Other authors (Laughlin, 1978) hypothesise that surfactants with hydrophilic head groups should more effectively enhance the percutaneous penetration of polar molecules, while those of lesser hydrophilicity should be less effective. The results obtained in the present work in agreement with Laughlin's hypothesis because CTAB ($\log P_{oct} < 1$) which is more hydrophillic than benzalkonium chloride ($\log P_{oct} = 1.9$) is less effective in enhancing lorazepam skin penetration. This could be attributed to the lipophilicity of lorazepam.

In the case of SLS an increase in the concentration of the surfactant resulted in an increase in the permeation rate of lorazepam and the highest permeation rate was obtained from the solution containing 5%w/w SLS. Table 2 also shows that increasing the concentration of SLS from 1 to 2.5% w/w caused a reduction in the ER. Beyond 2.5% an increase in ER was observed. It has been reported that anionic surfactants, like SLS, can penetrate and interact strongly with the skin, producing large alterations in the barrier properties (Walters, 1989; Cheon Koo et al., 1994). In particular, SLS is able to produce variations in the structural organisation of lipids when it is used above the critical micellar concentration (Ribaud et al., 1994), and similar effects on organisation of skin lipids have been described for other permeation enhancers such as Laurocapram (Goodman and Barry, 1989). Borras-Blasco et al., 1997 reported that SLS was able to increase the penetration rates of compounds that have values of lipophilicity lower than an optimum lipophili-

city value (log $P_{oct} < 3$) but do not affect penetrants with a log P_{oct} above this optimum. Lorazepam has a log P_{oct} value of about 2.4 and the effect observed in this study is similar to that reported for other hydrophilic compounds (Cheon Koo et al., 1994; Borras-Blasco et al., 1997). This could be explained by the fact that below log $P_{oct} = 3$, the penetrant could be controlled by diffusion across the lipid bilayers, which is rate controlling. If the enhancer disrupts the lipid bilayers, the diffusion coefficient improves and hence the flux increases. Therefore, if the rate determining step above log P_{oct} 3 changes such that interfacial transfer across the polar head groups of the lipid bilayers is slow, then the enhancer will have no effect. An additional mechanism for the skin penetration enhancement by SLS could involve the hydrophobic interaction of the SLS alkyl chain with the skin structure which leaves the end sulphate group of the surfactant exposed, creating additional sites in the membrane which leads to permit an increase in skin hydration (Rhein et al., 1986; Gibson and Teall, 1983).

Comparing different concentrations of various surfactants, it is clear from Table 2 that the solution containing 5% w/w SLS leads to the highest flux value of lorazepam (1.4049 μg cm^{-2} h^{-1}). The ERs of different concentrations of surfactants were 1.56–11.30. With SLS showing the most potent enhancing effect (1.4049 μg cm^{-2} h^{-1}, 11.30-fold over the control), followed by CTAB (1.222 μg cm^{-2} h^{-1}, 9.82-fold) and benzalkonium chloride (0.9528 μg cm^{-2} h^{-1}, 7.66-fold) and Tween 80 (0.4659 μg cm^{-2} h^{-1}, 3.75-fold) with concentration of 5, 5, 1 and 1% w/w, respectively.

The plot of ER versus concentration of the surfactants is shown in Fig. 5. The figure showed that in all cases, except CTAB and SLS, the greatest enhancement of the skin transport occurs at low concentrations of the enhancer (1% w/w), but this is seen to decrease at higher concentrations. Reduction of the rate of transport of the drug present in enhancer systems is attributed to the ability of the surfactant to form micelles and is normally observed only if interaction between micelle and the drug occurs. Solubilisation of the drug species by surfactant micelles decreases the thermodynamic activity of the drug and, hence, decreases the driving force of the drug absorption. The increase in flux at low enhancer concentrations is normally attributed to the ability of the surfactant molecules to penetrate the skin and increase its permeability. Therefore, the overall effect of a surfactant on the rate of drug permeation across a membrane will be a combination of the influence of these two opposing effects. In this study the saturated solutions of lorazepam have been used and the driving forces are expected to be similar (The CMC of SLS and Tween 80 are 0.03 and 0.01% w/w in water, respectively). Although 1% w/w is above CMC of the surfactants, it has been shown that the presence of propylene glycol increases the CMC of the nonionic surfactants up to ten times where the concentration of propylene glycol is 40% v/v (Sarpotdar and Zatz, 1986a).

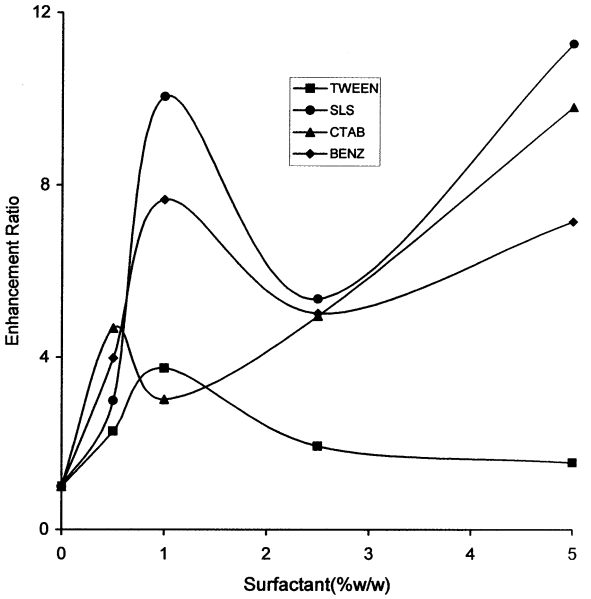

Fig. 5. The effect of surfactant concentration on the ER of lorazepam through rat skin.

It has been reported that above the CMC of the surfactant the flux of the drug should be reduced. However, Fig. 5 shows that as the concentration of SLS, CTAB and benzalkonium chloride increases

from 2.5 to 5% w/w the ER increases. This could be explained by the fact that these surfactants cause extensive damage to the skin that is reported to cause a large increase in transdermal flux (Gershbein, 1979). In contrast, nonionic surfactants such as Brij 36T cause comparatively little damage to the skin and their effect on transdermal flux is comparatively small (Hwang and Danti, 1983; Shokri et al., 2001). This could be a reason for the increase in flux in higher concentrations (above CMC of the surfactants) of SLS, CTAB or benzalkonium chloride. There are many reports of a wide variety of surfactants enhancing the penetration of compounds across biological membranes (Riegelam and Crowell, 1958a,b,c; Augiar and Weiner, 1969; Walters et al., 1981). In general cationic surfactants are more damaging and cause a greater increase in flux than anionic surfactants. Anionic surfactants cause greater enhancement and damage than nonionic surfactants (Stoughton, 1982; Cooper, 1984).

Dalvi and Zatz (1981) found that skin permeability was not increased by nonionic surfactants in purely aqueous media. However, Shahi and Zatz (1978) did report that Tween 80 was responsible for enhancement of hydrocortisone penetration from isopropyl alcohol:water mixtures. The authors hypothesised that the nature of the medium could influence the interaction between nonionic surfactants and the skin barrier (Sarpotdar and Zatz, 1986b). Further investigations employing lidocaine solutions in propylene glycol–water vehicles supported this assumption (Sarpotdar and Zatz, 1986a). It has been shown that at concentrations of 0.5 and 1% Tween 80 increased the skin penetration of chloramphenicol (Augiar and Weiner, 1969). It is apparent that propylene glycol and Tween 80 interact to affect the skin barrier so as to promote the penetration of lorazepam. It was evident from surface tension studies that the addition of propylene glycol raised the CMC of the nonionic surfactants by approximately a factor of 10. The increase in monomer concentration might be an explanation for observed synergistic effect of propylene glycol and Tewen 80.

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