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International Journal of Pharmaceutics 228 (2001) 99–107

international journal of pharmaceutics

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# The effect of surfactants on the skin penetration of diazepam

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Received 18 April 2001; received in revised form 2 July 2001; accepted 10 July 2001

**Abstract**

The percutaneous permeation of diazepam was investigated in rat skin after application of a water–propylene glycol (50:50% v/v) using a diffusion cell technique. The effect of various surfactants (sodium lauryl sulfate (SLS), cetyltrimethylammonium bromide (CTAB), benzalkonium chloride or Tween 80) with different concentrations on skin permeability were evaluated. Flux, $K_p$, lag time and enhancement ratios (ERs) of diazepam were measured over 10 h and compared with control sample (containing no surfactant). Furthermore, diazepam 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 diazepam. Benzalkonium chloride which possessed the highest lipophilicity ($\log P = 1.9$) among cationic surfactants provided the greatest enhancement for diazepam flux (7.98-fold over control). CTAB ($\log P < 1$) at a concentration of 1% w/w exhibited no significant increase in flux of diazepam compared to control (1.16-fold over control). 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 to form micelles and is normally observed only if interaction between micelle and the drug occurs. The results showed that the nature of enhancer greatly influences cutaneous barrier impairment. 

*Keywords:* Skin absorption; Enhancer; Surfactants; Diazepam

## 1. Introduction

Transdermal delivery of drugs promises many advantages over oral or intravenous administration. 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. Many strategies have been sug-

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0378-5173/01/$ - see front matter 
PII: S0378-5173(01)00805-5

gested 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), terpens (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) have been reported to enhance the permeability of drugs.

Surfactants are used as emulsifier and as physical stabilizing, 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).

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 diazepam through abdominal rat skin.

## 2. Materials and methods

### 2.1. Chemicals and reagents

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

### 2.2. Solubility studies

Saturated solubilities of diazepam 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. The apparent solubility enhancement ratios (ERs) of diazepam in vehicles were calculated using the following equation: solubility enhancement ratio $= C_0/C_s$, where $C_0$ is the diazepam concentration in the presence of surfactant and $C_s$ is the saturation solubility of diazepam in the control sample (no surfactant).

### 2.3. Skin membrane preparation

The abdominal hair of wistar male rats, weighing $160 \pm 25$ g, was shaved using electric and hand razors 24 h before treatment. After anesthetizing 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 milliliter of the saturated solution of diazepam (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 $37 \pm 0.5$ °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 and 10 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.

### 2.5. Analytical procedure

Diazepam in samples was determined using HPLC apparatus (Ceceil 1100, UK) equipped with a variable-wavelength UV detector. The column was Spherisorb C18 (150 × 4 mm, 5 μm, Hichrom). HPLC mobile phase was prepared by adding methanol and acetonitrile to a 0.056 M sodium acetate buffer which had been adjusted to pH 4 with glacial acetic acid (50:5:45, v/v/v); the flow rate was 1.2 ml/min. Detection was performed at 240 nm (Lau et al., 1987).

### 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:

$$Q_t = AKLC_0\left[(Dt/L^2) - (1/6) - (2/\pi^2)\sum((-1)^n/n^2)\exp(D^n 2\pi^2 t/L^2)\right], \quad (1)$$

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:

$$Q_t/A = KLC_0[(Dt/L^2) - (1/6)]. \quad (2)$$

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:

$$J = C_0KD/L = C_0K_p, \quad (3)$$

where $K_p$ is the permeability coefficient.

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

$$\text{ER} = (K_p \text{ with pretreatment}/K_p \text{ without pretreatment}). \quad (4)$$

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

## 3. Results and discussion

The solubility of diazepam in presence of surfactants in vehicles is shown in Table 1. The drug has a relatively low solubility in water–propylene glycol mixture (1.53 mg/ml); the addition of surfactant enhanced the solubility of diazepam in water–propylene glycol significantly (Table 1). The vehicle containing 5% SLS showed the

Table 1
Effect of surfactants on the diazepam solubility in water–propylene glycol (50:50) at 37 °C

| Surfactant | Solubility (mg/ml) | $ER_{sol}$[a] |
|---|---|---|
| Control | 1.5300 | 1.0000 |
| *SLS* | | |
| 0.5 | 2.1710 | 1.4190 |
| 1.0 | 3.4616 | 2.2625 |
| 2.5 | 7.1366 | 4.6644 |
| 5.0 | 12.3674 | 8.0833 |
| *Benzalkonium chloride* | | |
| 0.5 | 1.8290 | 1.1942 |
| 1.0 | 2.6152 | 1.7093 |
| 2.5 | 4.2992 | 2.8099 |
| 5.0 | 8.9060 | 5.8209 |
| *CTAB* | | |
| 0.5 | 2.1444 | 1.4016 |
| 1.0 | 3.5898 | 2.3463 |
| 2.5 | 5.5552 | 3.6310 |
| 5.0 | 8.1964 | 5.3573 |
| *Tween 80* | | |
| 0.5 | 2.4614 | 1.6088 |
| 1.0 | 2.5214 | 1.6482 |
| 2.5 | 3.3418 | 2.1742 |
| 5.0 | 3.6582 | 2.3910 |

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

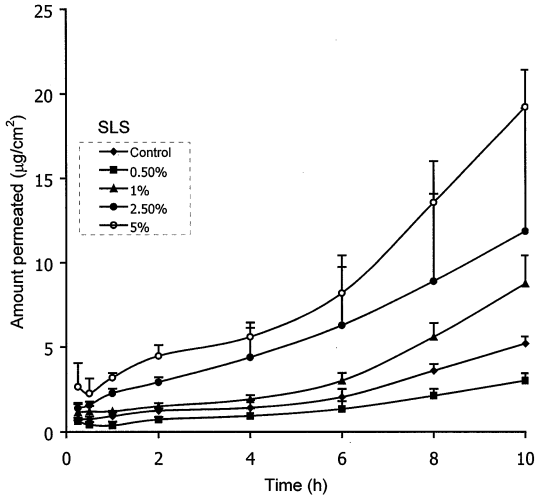


Fig. 1. Permeation profiles of diazepam in presence of different concentrations of SLS through rat skin.

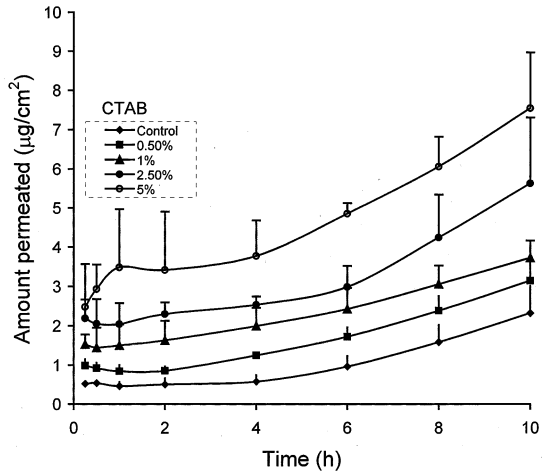


Fig. 3. Permeation profiles of diazepam in presence of different concentrations of CTAB through rat skin.

highest solubility (12.3674 mg/ml), which is over 8-fold the solubility of diazepam in water–PG (50:50% v/v).

The permeation profiles of diazepam in presence of SLS (an anionic surfactant), benzalkonium chloride and CTAB (cationic surfactants) and Tween 80 (a nonionic surfactant) through rat skin are shown in Figs. 1–4 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 diazepam. The slightly higher concentration observed with the first sample, containing higher concentration of surfactants (5% w/w), taken at 0.25 h than that observed with the second sample could be due to the burst transportation that is sometimes caused by surfactants (Figs. 1 and 4). This is often followed by the drug

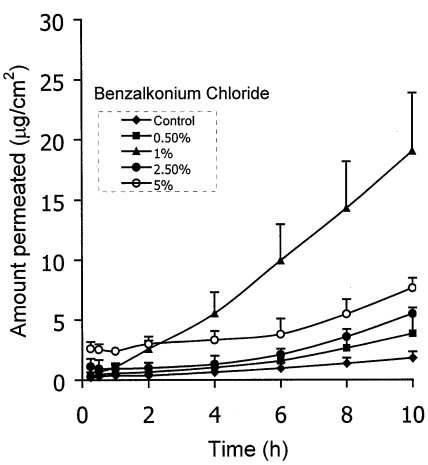


Fig. 2. Permeation profiles of diazepam in presence of different concentrations of benzalkonium chloride through rat skin.

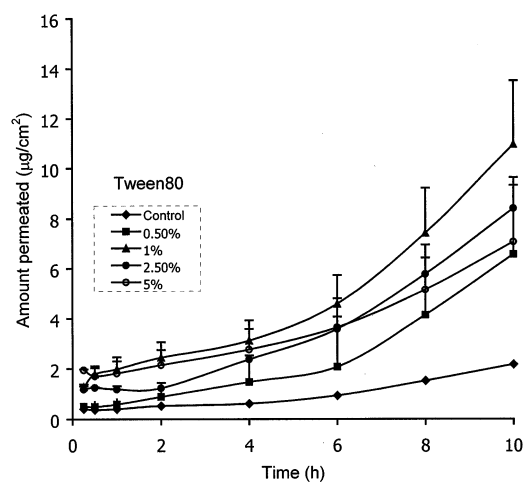


Fig. 4. Permeation profiles of diazepam in presence of different concentrations of Tween 80 through rat skin.

Table 2
Diazepam skin permeation parameters for various formulations

| Formulation | Steady-state flux (μg/cm$^{-2}$ per h) | $K_p$ ($\times 10^6$; cm h$^{-1}$) | Lag time (h) | ER |
|---|---|---|---|---|
| Control | 0.281 ± 0.062 | 0.184 ± 0.041 | 3.33 | 1.00 |
| *SLS* | | | | |
| 0.5 | 0.416 ± 0.131 | 0.272 ± 0.085 | 2.80 | 1.48 |
| 1.0 | 1.437 ± 0.304 | 0.942 ± 0.199 | 3.97 | 5.12 |
| 2.5 | 1.394 ± 0.954 | 0.913 ± 0.624 | 0.52 | 4.96 |
| 5.0 | 2.756 ± 0.015 | 1.805 ± 0.010 | 3.18 | 9.81 |
| *Benzalkonium chloride* | | | | |
| 0.5 | 0.562 ± 0.313 | 0.368 ± 0.105 | 3.21 | 2.00 |
| 1.0 | 2.242 ± 1.016 | 1.468 ± 0.564 | 1.38 | 7.98 |
| 2.5 | 0.844 ± 0.008 | 0.552 ± 0.005 | 4.37 | 3.00 |
| 5.0 | 0.960 ± 0.116 | 0.629 ± 0.076 | 4.00 | 3.42 |
| *CTAB* | | | | |
| 0.5 | 0.356 ± 0.080 | 0.234 ± 0.052 | 0.27 | 1.27 |
| 1.0 | 0.325 ± 0.022 | 0.213 ± 0.014 | 0.00 | 1.16 |
| 2.5 | 0.526 ± 0.294 | 0.344 ± 0.102 | 2.20 | 1.87 |
| 5.0 | 0.626 ± 0.375 | 1.280 ± 0.245 | 0.00 | 2.23 |
| *Tween 80* | | | | |
| 0.5 | 1.124 ± 0.264 | 0.736 ± 0.173 | 3.70 | 4.00 |
| 1.0 | 1.597 ± 0.346 | 1.045 ± 0.226 | 3.10 | 5.68 |
| 2.5 | 1.209 ± 0.105 | 0.791 ± 0.069 | 3.00 | 4.30 |
| 5.0 | 0.856 ± 0.352 | 0.561 ± 0.230 | 1.81 | 3.05 |

uptake by the skin that allows a lower concentration in the receptor phase compared to the previous sample. The surfactant concentration plays an important role in the ER. In the case of SLS an increase in the concentration of the surfactant resulted in an increase in the permeation rate of diazepam and the highest permeation rate was obtained from the solution containing 5% w/w SLS. 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 organization of lipids when it is used above the critical micellar concentration (CMC) (Ribaud et al., 1994), and similar effects on organization 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 lipophilicity value ($\log P_{oct} < 3$) but do not affect penetrants with a $\log P_{oct}$ above this optimum. Diazepam has a $\log P_{oct}$ value of about 2.7 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 sulfate 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).

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 5% w/w reduces the permeation rate. The permeation profile of diazepam in presence of the other cationic surfactant, CTAB, reveals that an increase in the concentration of CTAB results in a slight increase in the flux of diazepam in comparison with the control (Table 2). 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) hypothesize 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 hydrophilic than benzalkonium chloride ($\log P_{oct} = 1.9$) is less effective in enhancing diazepam skin penetration. This could be attributed to the lipophilicity of diazepam.

To determine the effect of a nonionic surfactant on the permeation of diazepam, Tween 80 with different concentrations was used and the permeation profile is shown in Fig. 4. In this case, the highest permeation rate was observed with the solution containing 1% w/w of Tween 80. There are two possible mechanisms by which the rate of transport is enhanced using nonionic surfactants (Breuer, 1979; Walters et al., 1987). Initially, the surfactants may penetrate into the intercellular regions of SC, increase fluidity and eventually solubilize 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 diazepam 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 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.

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 diazepam (2.756 μg/cm$^2$ per h). The ERs of different concentrations of surfactants were 1.16–9.81. With SLS showing the most potent enhancing effect (2.756 μg/cm$^2$ per h, 9.81-fold over the control), followed by benzalkonium chloride (2.242 μg/cm$^2$ per h, 7.98-fold) and Tween 80 (1.597 μg/cm$^2$ per h, 5.68-fold) with concentration of 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 enhancement of the skin transport occurs at low concentrations of the enhancer (1% w/w), but this is seen to decrease at higher concentrations. 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 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. Solubilization of the drug species by surfactant micelles decreases the thermodynamic activity of the drug and, hence, decreases the driving force of the drug absorption. Therefore, the overall effect of a sur-

factant 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 diazepam 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).

According to Fig. 5, increasing the concentration of SLS or CTAB results in a continuous increase in the ERs. 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). This could be a reason for the increase in flux in higher concentrations (above CMC of the surfactants) of SLS and CTAB. 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).

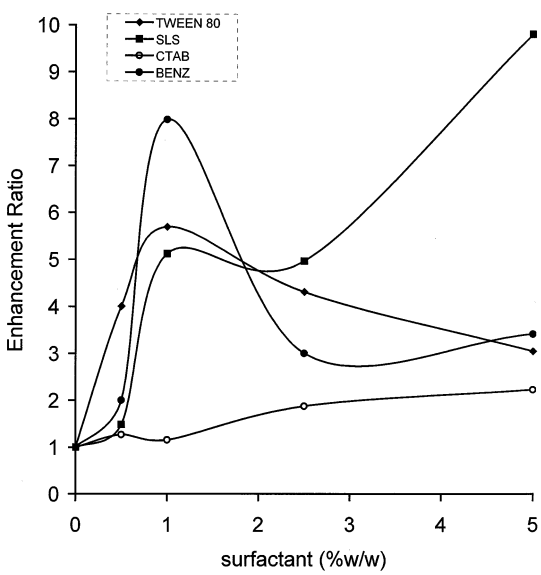


Fig. 5. The effect of surfactant concentration on the ER of diazepam through rat skin.

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 hypothesized 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 diazepam. 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 Tween 80.

## 4. Conclusion

The surfactants have shown ability to enhance the permeation of diazepam across rat skin. The nature of the enhancer seems to exert an important influence on cutaneous barrier impairment. The highest permeation rate is obtained with anionic surfactant, SLS, and the lowest permeation rate in absence of the surfactant. This study also shows that the enhancer concentration has significant effect on skin permeability.

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