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Research Article

# The Enhancement Effect of Surfactants on the Penetration of Nitrendipine through Rat Skin

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**ABSTRACT**

Nitrendipine (NDP), a dihydropyridines calcium antagonist which has a very low solubility *in vitro* was used as a poorly water-soluble model drug. The percutaneous permeation of nitrendipine 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 such as sodium lauryl sulphate (SLS), benzalkonium chloride and Tween 80 with different concentrations on skin permeability were evaluated. Flux, Kp, lag time and enhancement ratios (ERs) of nitrendipine were measured over 12 h and compared with that of control sample. Furthermore, 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 nitrendipine and the flux of benzalkonium chloride provided the greatest enhancement for nitrendipine flux (5.858±0.145 μg/cm$^2$/h, 3 fold over control) at 1% w/w of the surfactant. SLS at a concentration of 5% w/w (the highest concentration) exhibited the greatest increase in flux of nitrendipine compared with control (6.103±0.221 μg/cm$^2$/h, 3.5 fold over control). Tween 80 at a concentration of 1% w/w exhibited significant increase in flux of nitrendipine compared to control (5.607±0.187, 1.9 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. 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. The results showed that the nature of enhancer greatly influences cutaneous barrier impairment. The surfactants have shown ability to enhance the permeation of nitrendipine across rat skin.



## 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. 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 [1]

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These agents partition into, and interact with the SC constituents to induce a temporary, reversible increase in skin permeability. 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 [2,3] 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 [4,5].The objective of the present study was to examine the influence of different concentrations of surfactants on the *in vitro* permeation of nitrendipine through abdominal rat skin.

## MATERIALS AND METHODS

Nitrendipine (NDP) was a kind gift from U.S. Vitamins, Mumbai, India. Sodium lauryl sulphate (SLS), Benzalkonium chloride and Tween 80 (Hi-Media, India) were used. All other reagents are of analytical grade.

### Solubility Studies

Saturated solubilities of nitrendipine 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 analyzed by HPLC. The apparent solubility enhancement ratios (ERs) of nitrendipine in vehicles were calculated using the following equation: solubility enhancement ratio=C /C , 0 s where C is the nitrendipine concentration in the presence of surfactant and C is the saturation solubility 0 s of nitrendipine in the control sample (no surfactant).

### Skin Membrane Preparation

The abdominal hair of Wister male rats, weighing 160±25 g, was shaved using 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. All surgical and experimental procedures were reviewed and approved by the animal and ethics review committee of Sri Venkateswara College of Pharmacy, R.V.S.Nagar, Chittoor, Andhra Pradesh, India.

### *Ex-vivo* Permeation Studies

A system employing improved Franz diffusion cells with a diffusional area of 3.56 $cm^2$ was used for permeation studies. The excised rat skin was set in place with the stratum corneum facing the donor compartment and the dermis facing the receptor. Two ml of nitrendipine (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 (Para film). The receptor compartment of the cell was filled with 12 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, 100 µl aliquots were collected from the receptor side at designated time intervals. The amount of NDP in receptor fluids were analyzed by HPLC.

### HPLC Analysis of Nitrendipine

Mobile phase was prepared by mixing acetonitrile, freshly prepared double distilled water and glacial acetic acid in the ratio of 60:40:0.1v/v/v. Mobile phase was degassed with the help of bath sonicator. The chromatographic system consisted of a Shimadzu LC-10AT solvent delivery pump equipped with a 20 l loop and rheodyne sample injector. Wakosil II 5C18RS (SGE) (25cm X 4.6 mm ID) analytical column was used. Detector used was SPD- 10A VP dual wavelength UV-Visible detector (Shimadzu) and the eluate was monitored at 235 nm. The sensitivity was set at 0.001 AUFS. Flow rate was kept at 1ml / min. The data was recorded using Winchrome Software.

### Data Treatment

Nitrendipine fluxes through the skin were calculated by plotting the cumulative amount of drug penetrating the skin against time and determining the slope of the linear portion of the curve and the x- intercept values (lag time) by linear regression analysis. Drug fluxes (µg/$cm^2$ per h), at steady-state, were calculated by dividing the slope of the linear portion of the curve by the area of the skin surface through which diffusion took place. The lag time values were determined from the x-intercept of the slope at steady state J= C Kp. 0 where C represents the drug concentration which remains constant in the vehicle, Kp is the permeability 0 coefficient. The ER was calculated from the following equation [1,6],

$$ER = \frac{\text{Kp with pretreatment}}{\text{Kp without pretreatment}}$$

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

## RESULTS AND DISCUSSION

The drug has a relatively low solubility in water–propylene glycol mixture (1.67 mg/ml); the addition of surfactant enhanced the solubility of nitrendipine in water–propylene glycol significantly. The vehicle containing 5% SLS showed the highest solubility (12.6694 mg/ml), which is over 6-fold the solubility of nitrendipine

in water–PG (50:50% v/v). The permeation profiles of nitrendipine in presence of SLS (an anionic surfactant), benzalkonium chloride, Tween 80 (a nonionic surfactant) through rat skin are shown in Figs. 1–3 respectively.

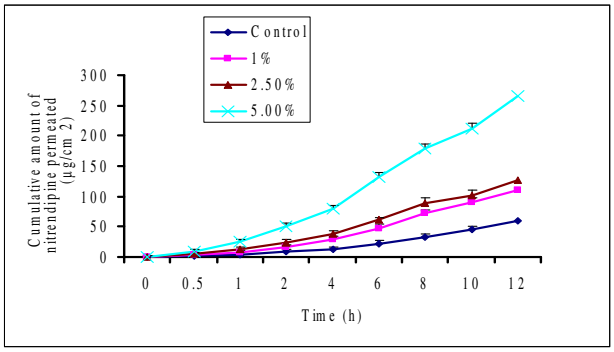


**Figure1:** Permeation profile of nitrendipine in presence of different concentrations of SLS through rat skin (Mean ±SD; n=3)

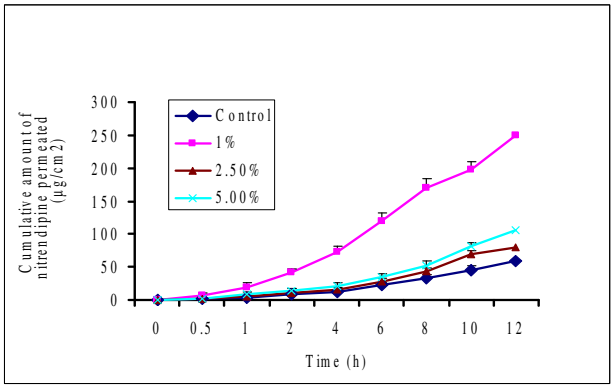


**Figure 2:** Permeation profile of nitrendipine in presence of different concentrations of benzalkonium chloride (Mean ±SD; n=3)

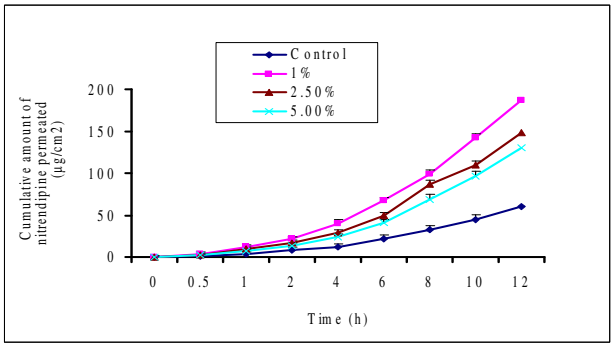


**Fig.3.** Permeation profile of nitrendipine in presence of different concentrations of tween 80 through rat skin (Mean ±SD; n=3)

The flux, J, permeability coefficient, Kp, lag time and ER for each of the different concentrations of the surfactant were shown in the Table 1. The table shows that all the surfactants used in the study increase the permeation rate of nitrendipine. 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 nitrendipine 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 [7,8]. 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. To determine the effect of a nonionic surfactant on the permeation of nitrendipine, Tween 80 with different concentrations was used and the permeation profile is shown in Fig. 3. 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 [9]. Initially, the surfactants may penetrate into the intercellular regions of SC, increase fluidity and eventually solubilize and extract lipid components. Tween 80 is thought to enhance the penetration of nitrendipine via both the lipophilic and the hydrophilic molecular mechanisms [10]. 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. Tween 80 may interact with the polar head groups of the lipids and the modification of H-bonding and ionic forces may occur. Comparing different concentrations of various surfactants, it is clear from the table that the solution containing 5% w/w SLS leads to the highest flux value of nitrendipine (6.103±0.221 µg/cm$^2$/h)[11]. The ERs of different concentrations of surfactants were 1.43 –3.6. With SLS showing the most potent enhancing effect (6.103±0.221 µg/cm$^2$/h, 3.5 fold over the control), followed by benzalkonium chloride (2.242 µg/cm$^2$ / h, 3.2 fold) and Tween 80 (5.607±0.187 µg/cm$^2$/h, 1.9 fold) with concentration of 1%w/w, respectively. The plot of ER versus concentration of the surfactants is shown in Fig. 4.

**Table 1:** Nitrendipine skin permeation parameters for various formulations

| Formulation | Steady state flux (μg/cm²/h) | Kp (x $10^{-3}$ cm/h) | Lag time (h) | ER |
|---|---|---|---|---|
| **Control** | 1.768±0.089 | 0.1768±0.061 | 0.664 | 1 |
| **SLS** | | | | |
| 1% | 2.861±0.091 | 0.2861±0.094 | 1.011 | 1.61 |
| 2.5% | 3.061±0.171 | 0.3061±0.092 | 0.817 | 1.73 |
| 5.0% | 6.103±0.221 | 0.6103±0.129 | 2.02 | 3.45 |
| **Benzalkonium chloride** | | | | |
| 1.0% | 5.858±0.145 | 0.5858±0.091 | 1.903 | 3.33 |
| 2.5% | 2.544±0.095 | 0.2544±0.068 | 0.59 | 1.43 |
| 5.0% | 3.442±0.079 | 0.3442±0.087 | 0.305 | 1.94 |
| **Tween 80** | | | | |
| 1.0% | 5.607±0.187 | 0.5607±0.085 | 0.598 | 3.17 |
| 2.5% | 4.488±0.134 | 0.4988±0.058 | 0.581 | 2.53 |
| 5.0% | 4.146±0.109 | 0.4146±0.033 | 0.345 | 2.34 |

Mean ±SD; n=3

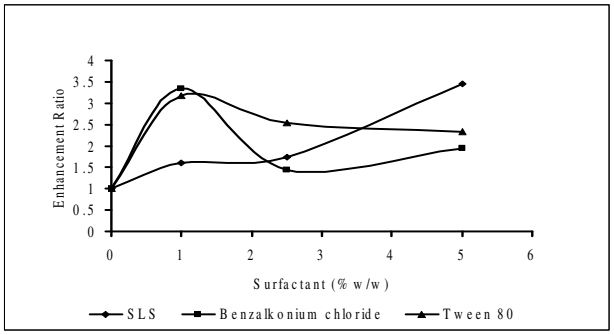


**Figure 4:** Effect of surfactant concentration on the ER of nitrendipine through rat skin

The figure showed that in all cases, except 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.

## CONCLUSION

The surfactants have shown ability to enhance the permeation of nitrendipine 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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