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Surfactant effects in percutaneous absorption I. Effects on the transdermal flux of methyl nicotinate

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Summary

We have investigated the effects of a series of surfactants on the permeability of human skin *in vitro* using methyl nicotinate as a model drug. The surfactants used were cetyl trimethyl ammonium bromide, sodium lauryl sulphate, decyl methyl sulphoxide and Brij 36T. These surfactants have a linear alkyl chain of 10–12 units linked to different hydrophilic groups. We found that while the ionic surfactant exerted a greater effect on the flux of methyl nicotinate, the nonionic surfactants had a smaller but more immediate effect on the flux. This is consistent with the hypothesis that for compounds to disturb the permeability barrier of the stratum corneum they must first penetrate it themselves. Ionic compounds can be expected to penetrate this lipophilic barrier more slowly than nonionic compounds of a similar structure and therefore will take longer to elicit their effects.

Introduction

The principal barrier to the percutaneous absorption of almost all compounds is the stratum corneum. This layer is composed of keratinised cells in a highly ordered lipid matrix (Elias and Friend, 1975). It is generally accepted that compounds penetrate the stratum corneum by travelling through this intercellular lipid region (Elias et al., 1981; Elias, 1983). Compounds which interact with the lipids of the stratum corneum can greatly reduce the barrier function of the skin.

There are many reports of a wide variety of surfactants enhancing the penetration of compounds across biological membranes (Riegelman and Crowell, 1958a–c; Aguiar 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). Cetyl trimethyl ammonium bromide (CTAB, cationic) and sodium lauryl sulphate (SLS, anionic) cause extensive damage to skin that is accompanied by 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

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effect on transdermal flux is comparatively small (Hwang and Danti, 1983).

We previously reported an investigation on the effect of surfactants on the percutaneous absorption of methyl nicotinate (MN) in humans (Ash-ton et al., 1988). MN is a potent vasodilator which causes erythema when applied to the skin. The time of onset of erythema is related to the speed of penetration of MN. Solutions containing 4% MN and 1.5% surfactant were applied to the forearm of volunteers. The surfactants used were Brij 36T (B36T, nonionic) and SLS (anionic). In apparent contradiction to previously published work (Aguiar and Weiner, 1969; Hwang and Danti, 1983) we found that B36T reduced the time of onset of erythema but SLS had no apparent effect. We have now investigated the time course of surfactant effects on the flux of MN across human skin *in vitro*. The surfactants studied were B36T, SLS CTAB and decyl methyl sulphoxide (DMS).

Materials and Methods

Brij 36T and MN were purchased from Sigma Chemical Co. (MO). CTAB, SLS (specially pure) and NaCl were obtained from BDH Chemicals, U.K. DMS was obtained from Cyclo Products (CA). Vertical glass diffusion cells were donated by Fisons Pharmaceuticals (U.K.). Full thickness human abdominal skin was obtained at autopsy and stored at -20°C until used. Male and female donors of a mean age of 67 years were used (age range 47–83 years).

Full thickness excised human skin was mounted in diffusion chambers with the dermis facing the receptor compartment. The receptor (capacity 5 ml) was filled with normal buffered saline and maintained at 37°C . 1 ml of 4% w/v solutions of MN containing 1.5% B36T, 1.5% SLS (5.4 mM) 5.4 mM CTAB or 5.4 mM DMS were applied to the donor compartments. Controls were performed by applying 1 ml of 4% MN to the surface both with and without prior treatment with chloroform. 0.5 ml samples of the receptor were periodically removed over 8 h and replaced with fresh buffer. After 24 and 48 h both the donor and

receptor phases were replaced with fresh solutions and the flux of MN monitored for a further 8 h. Experiments were repeated up to 12 times.

MN in the receptor phase was detected by GLC analysis using a Packard 437 GLC with flame ionisation detection linked to a 301 computing integrator. 2 μl samples were injected onto a 2 m \times 2 mm i.d. 2% OV17 on AWD MCS 80/100 chromosorb W column maintained at 120°C .

The pseudo-steady state flux of MN was measured and the permeability constant of MN was calculated. The percentage change in the permeability constant caused by the inclusion of each surfactant was determined for each of the 3 days the skin was exposed.

Results

With no surfactant present the pseudo-steady state flux of MN through the skin was $1.83 \pm 0.15 \mu\text{m cm}^{-2} \text{h}^{-1}$ ($n = 12$) and this did not change significantly over the 3 day experimental duration (Fig. 1). The presence of 1.5% Brij 36T in the donor solution increased the flux to $2.9 \pm 0.58 \mu\text{m cm}^{-2} \text{h}^{-1}$ ($n = 12$) and this also did not change significantly over 3 days. In contrast, the effects of SLS increased with the duration of exposure. Over the first 8 h, the flux of MN from

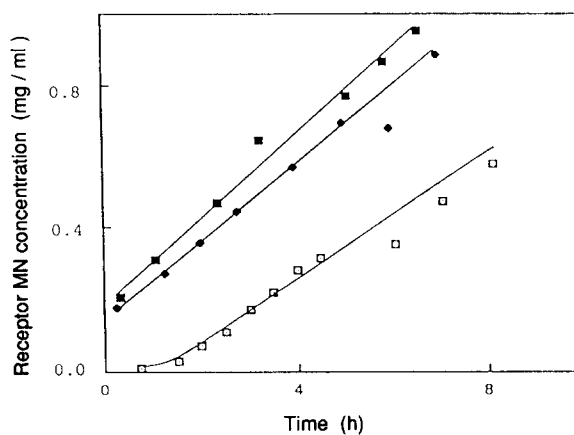


Fig. 1. Flux of MN through full thickness human skin from a 4% aqueous solution over a 3 day period. (\square) Day 1; (\blacklozenge) day 2; (\blacksquare) day 3.

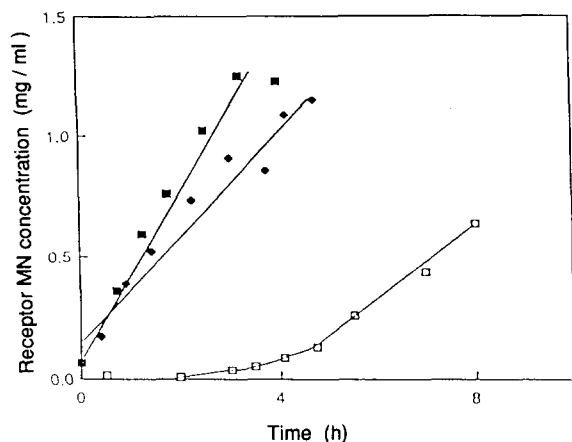


Fig. 2. Flux of MN through full thickness skin from a 4% aqueous solution containing 1.5% SLS over 3 days. (□) Day 1; (◆) day 2; (■) day 3.

a solution containing 1.5% SLS was greater than that from deionised water ($2.3 \pm 0.32 \mu\text{m cm}^{-2} \text{h}^{-1}$, $n = 8$). However, the lag time was longer and in some cases the flux increased in a nonlinear manner throughout the first 8 h. The flux further increased to $4.19 \pm 0.58 \mu\text{m cm}^{-2} \text{h}^{-1}$ after 24 h exposure to SLS and to $6.02 \pm 0.6 \mu\text{m cm}^{-2} \text{h}^{-1}$ after 48 h (Fig. 2). The effects of CTAB and DMS were similar but larger than that of SLS with increases in flux on each of the 3 days.

The percentage change in flux for each surfactant on each day of the experiment is shown in Table 1.

TABLE 1

Percentage increase in transdermal flux with duration of surfactant treatment (standard deviations are indicated in parentheses for 1, $n = 6$; 2, $n = 12$)

Surfactant treatment	Percentage increase in flux		
	Day 1	Day 2	Day 3
CTAB ¹	60 (20)	160 (17)	404 (20)
SLS ²	26 (10)	104 (17)	289 (15)
DMS ¹	171 (20)	360 (26)	414 (40)
B36T ²	67 (14)	65 (16)	92 (22)

Discussion

B36T acted rapidly on the skin to produce small increases in the penetration of MN but did not subsequently produce large changes in permeability. Nonionic compounds are comparatively lipophilic and could be expected to penetrate skin readily and to interact with the lipid matrix of the stratum corneum. In contrast, CTAB and SLS are ionic and can be expected to penetrate the stratum corneum slowly (Blank et al., 1964). These surfactants appear to penetrate the stratum corneum decreasing its barrier function. This increases the penetration of both surfactant and MN. The permeability of the skin therefore markedly increases over time. Although DMS is structurally similar to SLS it is not ionic and can be expected to penetrate the skin more readily and thus exert its effects sooner.

The above hypothesis is consistent with the *in vivo* data previously published (Ashton et al., 1988). In this work Brij 36T was found to increase the permeation of MN across human skin while SLS had no apparent effect. Presumably the time for dilation (less than 20 min) is too short for SLS to penetrate the SC and increase the permeability.

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