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Non-ionic Surfactant Effects on Hairless Mouse Skin Permeability Characteristics

KENNETH A. WALTERS, MICHAEL WALKER AND OREST OLEJNIK†

Fisons plc, Pharmaceutical Division, Bakewell Road, Loughborough, LE11 0RH, UK

Abstract—The influence of a range of polyethoxylated non-ionic surfactants upon the transport of methyl nicotinate across hairless mouse skin in-vitro was investigated using standard two-compartment diffusion cells. Those surfactants having a linear alkyl chain greater than C8 and an ethylene oxide chain length of less than E14 caused significant increases in the flux of methyl nicotinate. Surfactants having branched or aromatic moieties in the hydrophobic portion were ineffective. Maximum enhancement of flux was obtained using polyoxyethylene (10) lauryl ether (Brij 36T). Two possible modes of surfactant action are proposed. Initially the surfactant may penetrate into the intercellular regions of the stratum corneum, increase fluidity and eventually solubilise and extract lipid components. Secondly, penetration of the surfactant into the intracellular matrix followed by interaction and binding with the keratin filaments may result in a disruption of order within the corneocyte. The structural specificity required for the latter mechanism may explain, to some extent, the maximum activity obtained with the C12 surfactant.

The successful management of motion sickness, hypertension and angina using transdermal drug delivery systems has stimulated interest in the use of this route for the therapeutic management of several diverse conditions. Of particular interest are those diseases in which parenteral drug delivery is, at present, the principal mode of therapy (e.g. diabetes), and syndromes requiring the long-term oral administration of potential gastrointestinal irritants (e.g. chronic rheumatoid arthritis). Many of the existing drugs, however, do not possess the requisite physicochemical characteristics for efficient percutaneous absorption and therapeutic blood levels cannot be attained. For this reason, increasing the penetration and permeation of drug substances across the skin has recently attracted much attention. Many substances are capable of altering the barrier properties of the stratum corneum. These compounds, collectively known as penetration enhancers, include water (Behl et al 1980), dimethylsulphoxide (DMSO; Chandrasekaran et al 1977), *N*,*N*-diethyl-*m*-toluamide (Windheuser et al 1982), *N*-methyl-2-pyrrolidone (Barry et al 1984), 1-dodecylazacycloheptan-2-one (Stoughton & McClure 1983), calcium thioglycolate (Kushida et al 1984), oleic acid (Cooper 1984) and various synthetic surface active agents (Attwood & Florence 1983; Ashton et al 1986). The wide structural variability of these compounds implies that the mechanisms of action are complex and may involve different routes of transdermal permeation. Thus, oleic acid enhances the penetration of lipophilic compounds whereas DMSO is more effective with hydrophilic permeants. The latter can be rationalized, to some extent, in that the more lipophilic permeants will have a decreased chemical potential in the organic solvent. However, experiments using vehicles saturated with permeant (i.e. of equal thermodynamic activity) have demonstrated that decylmethylsuphoxide can enhance the rate of skin permeation of ionized salicylic acid to a much greater extent than the undissociated species (Cooper 1984). Although this enhancer appears to operate by decreasing the diffusional resistance to polar molecules, the exact mechanism of action remains unknown but may be dependent on the nature of the hydrophobic portion of the enhancing surfactant molecule.

The influence of the surfactant alkyl chain on transport properties has been well established in various membrane systems including erythrocytes (Zaslavsky et al 1978), gastric mucosa (Walters et al 1981) and goldfish gill epithelium (Walters et al 1982a). In the experiments described here, non-ionic surfactants of the polyoxyethylene alkyl or aryl ether type have been evaluated for their ability to enhance the permeability of methyl nicotinate across hairless mouse skin. Relationships between surfactant structure and enhancement activity are established for this permeant and possible modes of action are outlined.

Materials and Methods

Female hairless mice (Strain MF1-hr/hr/Ola) in the age range 10–14 weeks were used. The animals were allowed free access to food and water. Polyoxyethylene alkyl ethers of the Brij series (Table 1) were obtained from ICI United States Inc., Wilmington, Delaware, except for polyoxyethylene (10) lauryl ether which was obtained from Sigma Ltd., Poole, Dorset, UK. Surfactants of the Texofor series were obtained from ABM Chemicals, Stockport, UK. Polyoxyethylene (10) alphanol 79 was obtained from ICI Organics Division, Manchester, UK. Rewopal HV10 was obtained from Rewo Chemicals Ltd., Maryport, UK and Arosurf 66-E10 from Sherex Chemical Co. Inc., Dublin, Ohio, USA. Triton X100 and methyl nicotinate were obtained from Sigma UK. All surfactants were used as supplied. All other reagents were AR grade.

Interaction between surfactants and the permeant

To assay whether there was interaction of methyl nicotinate with the non-ionic surfactants, non-equilibrium dialysis at 37°C was used. Two 4 mL capacity glass half-cells were separated by a Visking Cellophane membrane. This type of cellulose membrane is generally considered to be permeable

Correspondence and present address: K. A. Walters, Controlled Therapeutics (Scotland) Ltd., 1 Redwood Place, Peel Park Campus, East Kilbride, G74 5PB, UK.

† Present Address: Iolab Corp. (J & J), Claremont, CA. 91711, USA.

Table 1. Structures of the surfactants used in this study.

Surfactant	Hydrophobic portion	Ethylene oxide chain length
Alphanol 10	octyl	10
Brij 36T	lauryl	10
Brij 56	cetyl	10
Brij 76	stearyl	10
Brij 96	oleyl	10
Arosurf 66E10	iso-stearyl	10
Triton X100	octyl phenol	10
Rewopal HV10	nonyl phenol	10
Brij 52	cetyl	2
Texofor A6	cetyl	6
Texofor A14	cetyl	14
Brij 58	cetyl	20
Texofor A30	cetyl	30
Texofor A45	cetyl	45
Texofor A60	cetyl	60

to small molecules but not to surfactant micelles (Barry & El Eini 1976). Before use the membrane was placed in boiling distilled water for 5 min and allowed to cool. Methyl nicotinate (0·1%w/v) in surfactant solution (0·1 or 0·5%w/v) was placed in the donor half-cell, 0·9%NaCl (saline) in the other half-cell and the rate of transfer of permeant into the receptor half-cell determined over 2 h and compared with the rate of transfer in the absence of surfactant. The concentration of methyl nicotinate in the receptor solution was analysed spectrophotometrically at 264nm and, in all cases, the increase in concentration with time was linear.

Skin permeation experiments

Hairless mice were killed by cervical dislocation and the abdominal skin excised and adhering fat and other visceral tissue removed. The skin was then placed as a barrier between the two halves of a standard two-compartment glass diffusion cell. The area available for diffusion between compartments was 1·77cm^2 and each half-cell volume was 4 mL. The donor compartment, which bathed the epidermal side of the membrane, was charged with varying concentrations of methyl nicotinate (0·1–1·0%w/v) in saline. In all cases the receptor (dermal) compartment contained saline. Except for the hydration studies, the experiments were started immediately, no more than 5 min elapsing between death and the zero time sample (preliminary experiments indicated that hydration linked effects were not evident for at least 1h following immersion). Samples were taken from the receptor compartment at preset times for up to 8 h and analysed spectrophotometrically, against a suitable blank, for methyl nicotinate concentration. Hydration effects were determined by prior bathing of the stratum corneum in saline for up to 72 h. Surfactant effects were determined by exposing the epidermis to 0·5% (w/v) methyl nicotinate in varying concentrations (usually 0·1%w/v) of surfactant solution in saline and sampling as described above. The presence of surfactants was found to have no effect on the analytical procedure. All experiments were carried out at 37°C.

Individual cell data were plotted as concentration of permeant in the receptor chamber as a function of time. Correction was made for sampling which, in all cases, was done with replacement using saline. The permeability coefficient (P) for a given run was calculated from:

$$J = PA\Delta C = VdC/dt \qquad (1)$$

Here J is the total flux, ΔC is the permeant concentration difference across the membrane of area A. V is the volume of the half-cell into which the permeant was collected.

Partition coefficient determination

Saline and isopropyl myristate, representing the aqueous and organic phases, respectively, were mutually saturated at 37°C before use. The partitioning of methyl nicotinate (0·005%w/v) from the saline into isopropyl myristate in the presence of selected surfactants (0·05%w/v) was determined after 12 h equilibration at 37°C. After separating the two phases, each was analysed spectrophotometrically for methyl nicotinate concentration. The partition coefficient (K) was calculated from:

$$K = C_o/C_w$$

Here C_o and C_w represent the concentrations in the organic and aqueous phases after equilibration.

Results and Discussion

It is generally assumed that flux across skin is directly proportional to concentration when the permeant is in solution in the vehicle. This relationship, which can be predicted from equation 1, is limited by drug solubility characteristics and linearity is normally only observed at low permeant concentrations. Given the high aqueous solubility of methyl nicotinate (>50%; Stoughton et al 1960) it is not surprising that the flux of this permeant across hairless mouse skin from aqueous solutions was linearly dependent on concentration within the range 0·1–1·0%w/v (Fig. 1). Thus, for a given vehicle, the permeability coefficient will remain constant throughout the permeant concentration range used in this study provided no vehicle induced membrane alteration occurs. Methyl nicotinate appears to penetrate the skin very rapidly (0·03 cm h^{-1}) compared with, for example, water (0·003 cm h^{-1}; Behl et al 1984). This is not without precedent, the skin of the hairless mouse presenting little resistance to the permeation of molecules such as phenol, 2-chlorophenol (Huq et al 1986), hexanol and octanol (Behl et al 1984a). Hairless mouse skin contains about 30% lipid and it seems reasonable to assume that this is a significant barrier to water penetration but not to permeants that preferentially partition into the stratum corneum lipid or whose solubility characteristics are such that they have equal affinities for either aqueous or lipid phases.

Surfactant-mediated effects on methyl nicotinate permeation are shown in Fig. 2 and Table 2. At a concentration of 0·1%w/v all the surfactants, with the exception of polyoxyethylene (10) alphanol (C.M.C. = 0·5%) were in excess of their critical micelle concentration. However, the non-equilibrium dialysis experiments indicated no permeant-micelle interaction suggesting that solubilization of methyl nicotinate did not occur (Table 2). This was true for all the surfactants used in this study. All surfactants having a linear alkyl chain length greater than C8 and an ethylene oxide chain length of between E6–E14 caused significant increases in the flux of methyl nicotinate across hairless mouse skin. In Fig. 2a the influence of surfactant alkyl chain length (at a constant ethylene oxide chain length of E10) on methyl nicotinate flux is expressed as a percentage increase in the permeability coefficient. Similarly, in Fig. 2b the influence of surfactant ethylene oxide chain length (at a constant alkyl

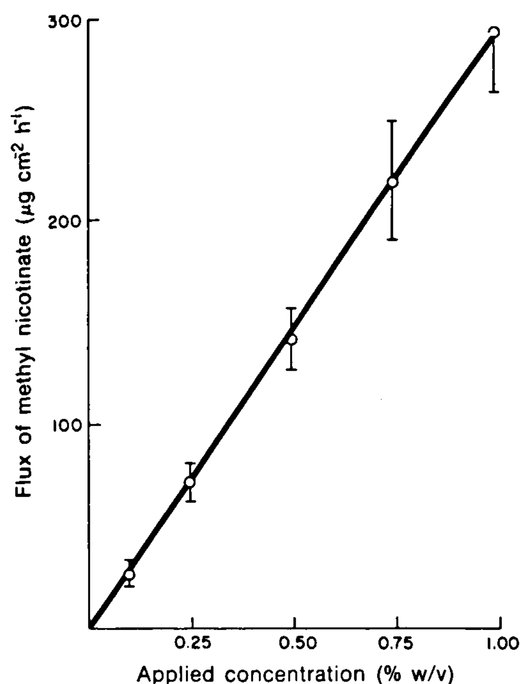

Fig. 1. Flux of methyl nicotinate across hairless mouse skin as a function of applied permeant concentration.

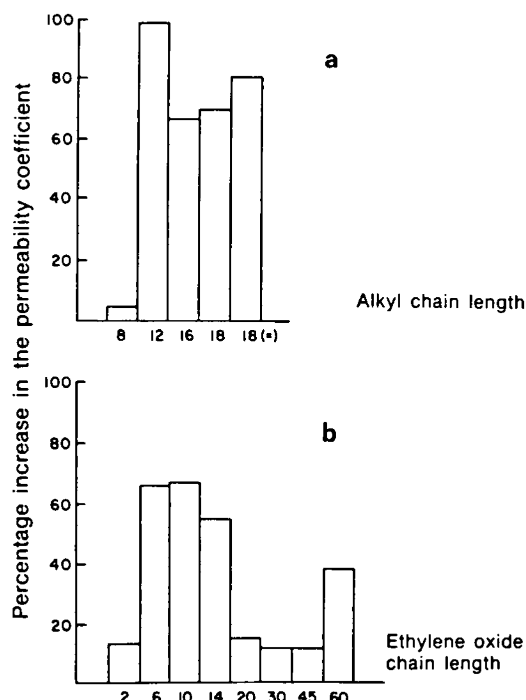

Fig. 2. Enhancement of methyl nicotinate permeation as a function of surfactant structure. (a) with a constant ethylene oxide chain length of 10. (b) with a constant alkyl chain length of 16.

chain length of C16) is shown. Those surfactants having a non-linear alkyl chain had little accelerant activity on the flux of methyl nicotinate (Table 2).

The presence of *cis*-double bonds in fatty acids and alcohols has been shown to increase considerably their enhancement potential when compared with their saturated or *trans*-double bond counterparts (Cooper 1984; Aungst et al 1986). In the latter study the permeation of naloxone was increased 22-fold in the presence of oleic acid but was unaffected by polyoxyethylene (20) oleyl ether. This is presumably a function of the relative ability of these compounds to partition into the lipid phases of the stratum corneum from the propylene glycol vehicle. Although these studies concerned the permeability of relatively lipophilic molecules, Goodman & Barry (1986) have also shown that oleic acid can considerably enhance the flux of a hydrophilic permeant (5-fluorouracil). The data presented here show that surfactants with *cis*-double bonds in the hydrophobic portion have little effect on the penetration rate of methyl nicotinate across hairless mouse skin. This could potentially reflect the importance of the vehicle used to apply the enhancer and this aspect is presently under investigation.

Basically there are two possible ways by which the rate of drug transfer from a solution across biological membranes may be altered. The first is a change in the physicochemical properties of a drug due to the presence of an additive which can result in a reduction or enhancement of the rate of transport. For example enhancement of permeation of an ionized drug can be achieved by the addition of a pH altering adjuvant or by the formation of an ion-pair. Reduction is usually the result of some form of complexation such as solubilization. Secondly an alteration of the barrier properties of the membrane may occur. Either an enhancement or

Table 2. Surfactant effects on methyl nicotinate permeation across hairless mouse skin.

Surfactant*	Methyl nicotinate** permeability Coefficient (cm h^{-1}) × 10^2 Skin	Dialysis membrane
	3·30±0·41***	17·7±3·4
Brij 96	3·13±0·70	18·9±2·6
Arosurf 66E10	3·26±0·47	16·5±0·9
Triton X100	3·08±0·20	18·8±3·4
Rewopal HV10	3·48±0·30	17·1±2·8

* Surfactant concentration: 0·5% (w/v).
** Methyl nicotinate concentration: 0·5% (w/v).
*** Data are given as means (n = 6) ± standard deviation.

reduction in permeation may result from a change in the thermodynamic properties of the system such that partitioning tendencies are altered. The importance of the skin-vehicle partition coefficient to skin permeability has been well established (Barry 1983). For a simple isotropic membrane, of thickness h, the permeability coefficient (P) is related to the membrane-vehicle partition coefficient (K) by:

$$P = DK/h$$

where D is the apparent diffusion constant of the permeant within the membrane (Flynn et al 1974). It is apparent, therefore, that one possible mechanism of action to explain the surfactant-induced enhancement of methyl nicotinate permeability through skin is by alteration of the partition coefficient. In the experiments described here, isopropyl myristate was selected as the oil phase because its blend of

polar and non-polar properties is supposed to approximate the complex nature of the stratum corneum (Barry 1983). The effects of selected surfactants on the oil-water partition coefficient of methyl nicotinate are given in Table 3. At a constant ethylene oxide chain length of E10, increasing the alkyl chain significantly increased the partitioning of methyl nicotinate in a linear fashion. By maintaining a constant alkyl chain length (C16) and varying the ethylene oxide chain length significant partitioning increases were also obtained. In this case a plateau effect was observed suggesting that the alkyl moiety was the dominant contributing factor in increasing the partition coefficient irrespective of ethylene oxide chain length.

The partitioning data suggest that one aspect of the penetration enhancement effects of the surfactants may be due to promotion of membrane-vehicle partitioning tendencies. These data do not explain, however, the variation in permeability as a function of ethylene oxide chain length (Fig. 2b) nor do they explain the maximum effect of the C12 alkyl moiety (Fig. 2a). C12 compounds have generally proved to be the most active in biological systems when a series of surfactants with similar hydrophilic portions are studied (Florence et al 1984). Evidence from studies on the penetration of cholesterol monolayers by polyoxyethylene alkyl ethers suggests that penetration can occur at very low concentrations (Walters et al 1982b), the C12 compounds interacting at a lower concentration than those with a C18 chain. The exact mode of action underlying the optimal effects of the C12 surfactants on biological membranes, however, remains elusive.

When the stratum corneum is considered, two possible mechanisms of surfactant activity may be discussed. The first possibility involves penetration of the surfactant into the intercellular lipid phase of the membrane. The incorporation of the surfactant into the lipid matrix would, presumably, increase the degree of fluidity in this phase resulting in a decreased resistance to permeation. Provided that no extraction of lipid components occurs this effect should be reversible upon removal of the surfactant. The second possible mode of action involves penetration of the surfactants into the intracellular matrix followed by interaction and binding with the keratin filaments (Dominguez et al 1977; Breuer 1979). A definite structural requirement is most likely necessary for this type of interaction and this may provide an explanation for the inactivity of those surfactants with branched or aromatic lipophilic moieties. This latter mechanism, which appears optimal at C12 alkyl chain length, should demonstrate some degree of reversibility depending on the extent of disruption of the long range order of the keratin filaments (preliminary studies have shown that the permeability enhancing effect of Brij 36T is partially reversible following 48 h exposure). Whatever the precise mode of action of individual surfactants it seems likely that the mechanisms discussed above are both operative to some degree.

Table 3. Surfactant effects on the isopropyl myristate/saline partition coefficient of methyl nicotinate.

Surfactant*	Oil-water partition coefficient
—	2·06 ± 0·04**
Alphanol 10	2·67 ± 0·07
Brij 36T	3·04 ± 0·08
Brij 56	3·11 ± 0·09
Brij 76	3·28 ± 0·07
Brij 96	2·96 ± 0·04
Brij 52	2·97 ± 0·02
Texofor A6	2·61 ± 0·05
Texofor A14	2·93 ± 0·10
Brij 58	3·12 ± 0·13
Texofor A30	3·06 ± 0·01
Texofor A45	3·06 ± 0·03
Texofor A60	3·07 ± 0·01

* Surfactant concentration: 0·05% (w/v).
** Data are given as means (n = 3) ± standard deviation.

There is little doubt that surfactants of the type used here can penetrate into and diffuse across skin (Black & Howes 1979; Nishiyama et al 1983). In addition the use of such techniques as differential scanning calorimetry and Fourier Transform infrared spectroscopy have demonstrated that several penetration enhancing compounds are capable of disrupting stratum corneum lipid structure (Goodman & Barry 1986; Golden et al 1986). Further support for an effect on the lipid phase is offered by the hydration data (Table 4).

As a vehicle water is by no means inert and it has been shown that hydration can enhance, retard or have no effect on skin penetration depending on the physicochemical nature of the permeant. For example the permeability of hairless mouse skin to water, methanol and ethanol is unaffected by hydration whereas its permeability to butanol, hexanol and heptanol is doubled as a consequence of tissue hydration (Behl et al 1980). Likewise the permeation of caffeine, aspirin and ibuprofen across isolated human skin increases when the system is occluded (Southwell & Barry 1984; Akhter & Barry 1985) whereas a two-fold reduction in the permeation rate of propranolol following hydration has been observed (Behl et al 1984b). In the experiments reported here, significant increases in the permeability rate of methyl nicotinate was observed following 17 h hydration of the skin in saline (Table 4). Following hydration, however, the enhancing effect of the surfactant is diminished such that at 24 h no surfactant induced acceleration is evident. These data suggest that the mode of action of the surfactant and that of hydration is similar and primarily on the lipid phase of the membrane.

The surfactants used herein were the same as those used in previous studies including the gastric mucosal transport of paraquat (Walters et al 1981) and barbiturate transport in goldfish gill epithelium (Walters et al 1982a). For the type of experiments carried out, the use of nominal concentrations of surfactants is essential, although an average molecular

Table 4. Influence of tissue hydration on the permeability rate of methyl nicotinate across hairless mouse skin. Data are means (n = 6) and standard deviations.

Hydration time (h)	Permeability coefficient ($cm\ h^{-1} \times 100$)	
	From surfactant	From saline
0	5·61 ± 0·55	2·79 ± 0·34
17	4·69 ± 0·08	3·80 ± 0·06
24	6·85 ± 1·68	5·99 ± 1·08
72	7·73 ± 0·87	7·76 ± 0·73

weight can be calculated for each surfactant, the degree of purity of these commercially available agents means that there will be a wide molecular weight distribution making any accurate calculation of molar concentrations virtually impossible. Despite the difference in test penetrants and membrane systems similar surfactant structure-activity profiles were observed. The magnitude of effects, however, are greatly decreased in skin, suggesting that the cornified epithelium has a greater resistance to surfactants than mucosal tissues. In the system used here, a compound that permeates skin relatively rapidly was selected. It is well known that the effect of enhancers is more evident with slower permeants but this does not preclude their usefulness in systems where a two-or three-fold acceleration is required. Although the small magnitude of enhancement may raise questions concerning the validity of the results the fact that the observed trends show similarities to other membrane systems must, to some extent, support the presented data. In addition, preliminary data has shown that polyoxyethylene (10) lauryl ether has a much greater effect on the skin permeation of nicotinic acid in the ionized form, where enhancement factors of 19-fold were obtained, than the free acid (Walters et al 1984).

There is little doubt that skin penetration can be enhanced by surfactants. The magnitude of enhancement is dependent, to a large extent, on the physicochemical properties of the permeant and the nature of the vehicle used. This type of study may prove useful in the development of dermal and transdermal therapeutic systems.

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