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Surfactant effects in topical drug availability

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Summary

The effects of two surfactants, sodium lauryl sulphate (SLS) and Brij 36T on the thermodynamic activity of methyl nicotinate (MN) and hexyl nicotinate (HN) in aqueous gels have been investigated. In vivo, the permeability of the skin has been assessed by measuring the time of onset of the erythema which is induced by these nicotinate esters. Times of onset of erythema caused by gels containing SLS correlate with the in vitro release rates. This suggests that over this time interval (less than 15 min) SLS does not affect the barrier function of the skin. Results obtained for Brij 36T-containing gels, however, imply that this surfactant does increase skin permeability. That SLS is normally considered to be the more powerful penetration enhancer yet has no observable effect indicates that the two surfactants exert their effect in different ways.

Introduction

Surfactants are frequently used in the preparation of many topical formulations and their inclusion is normally based on the effects they have on its stability or appearance. Comparatively little attention is given to any effects they may have on the thermodynamic activity of a compound within a formulation, or on the permeability of the skin itself, despite a wealth of information indicating that many of the more frequently used surfactants exert a considerable influence on both (Attwood and Florence, 1984; Barry, 1983; Schaeffer et al., 1981).

The effect of two surfactants, sodium lauryl sulphate (SLS) and Brij 36T on the thermodynamic activity of two model compounds in aqueous gel vehicle was investigated. SLS is an anionic surfactant while Brij 36T is non-ionic consisting of a polyoxyethylene chain of 10 units linked to a linear alkyl chain of 12 units. Two esters of nicotinic acid, methyl nicotinate (MN) and hexyl nicotinate (HN) were chosen as model compounds; both are vasodilators and the time taken for them to produce erythema in volunteers is indicative of the speed at which they penetrate the skin (Barrett et al., 1964; Cronin and Stoughton, 1962). These compounds also have greatly differing lipophilicity; we have estimated the log of the MN octanol/water partition coefficient to be 0.81 and that of HN to be 3.46.

Carbopol 941 was used as a gelling agent. This is a synthetic polymer composed of polyacrylic

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acid linked to allyl sucrose (Saito and Taniguchi, 1973) and is widely used in the pharmaceutical and cosmetic industries (Barry and Meyer, 1979).

Materials and Methods

Materials

Gels were prepared using Carbopol 941 base (a gift from B.F. Goodrich Chemical Co.); Na_2SO_4 and specially pure SLS were obtained from B.D.H. Chemicals Ltd. Brij 36T was purchased from Sigma Chemical Co., as were MN and HN. Isopropyl myristate (IPM) was supplied by Croda and Celgard 2400 membrane was a gift from Celanese Corporation. The materials were used as received.

Preparation and characterisation of the gels

To 50 ml distilled water surfactant was added and when this had dissolved either MN or HN was added. After stirring for 30 min with a magnetic stirrer, 1 g Carbopol 941 was slowly added and stirred for 24 h. 50 ml 0.25 M NaOH was then stirred in using a spatula and the resulting gel, of pH 7.7 ($\pm$0.2) centrifuged at 3000 rpm for 4 min to remove bubbles. At this pH the viscosity of the gels is high and independent of small fluctuations in pH. Gels containing 0.5% MN and either 0.5%, 1.0%, 1.5% or no surfactant were formulated and where necessary the gels' ionic strength was maintained by the addition of Na_2SO_4. Similarly gels were prepared containing between 0.25% and 0.5% HN and up to 1.5% surfactant.

The microviscosity of each gel was determined by the use of photon correlation spectroscopy (PCS). This technique, generally used for particle sizing, measures the Brownian motion of the particles and hence their diffusion coefficient. This will be dependent on the viscosity of the medium in which they are dispersed and their size. To measure microviscosity, latex particles of a known standard size were dispersed within the gels and their diffusion coefficients were determined. The viscosity that the particles experienced from the suspending medium can be calculated using the Stokes–Einstein equation.

The thermodynamic activity of MN and HN within each formulation was determined by headspace analysis (Al-Khamis et al., 1982). Small samples of each gel were placed into glass vials which were then sealed with polytetrafluoroethylene caps. After being allowed to equilibrate for 30 days at 25°C, 100-μl samples of vapour were withdrawn and analysed by GLC on a Packard 437 with flame ionisation detection using a 2 m $\times$ 2 mm i.d. 2% OV17 on AWDMCS 80/100 Chromosorb W column and a LDC 301 computing integrator. The column was maintained at 150°C for HN and 120°C for MN. This allowed the thermodynamic activity of the nicotinate within the gels to be estimated (Achenberg and Schmidt, 1977).

The transmittance of each HN-containing gel was measured at 360 nm using an LKB Ultraspec II spectrophotometer. This was found to be proportional to the concentration of solubilised HN present in the gels and enabled the concentration of solubilised HN to be estimated.

In vitro assessment

The in vitro release of nicotinate from the gels was measured using the apparatus shown in Fig. 1 (Billups and Patel, 1970).

Of each gel, 25 g was loaded into the donor compartment and the apperance of nicotinate in the receptor was monitored using a Cecil U.V. spectrophotometer at 264 nm. The two compartments were separated by a synthetic porous membrane (Celgard 2400) which was impregnated with

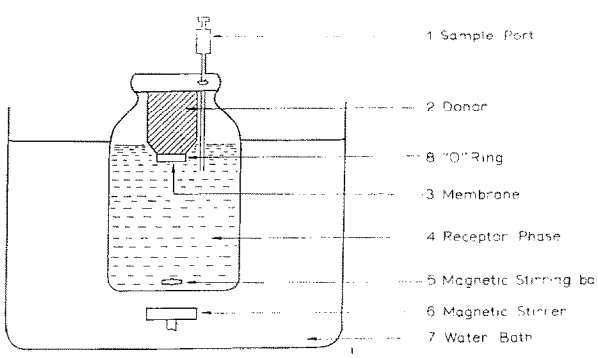

Fig. 1. Apparatus for the measurement of nicotinate release from the gels.

IPM to prevent osmotic flow of water from the receiver into the gel. The barrier presented by this membrane to the diffusion of nicotinate from the gels was not rate-limiting. A graph of concentration in the receptor phase against the square root of time allowed the apparent diffusion constants to be calculated (see Theoretical section).

In vivo assessment

The capacity of each formulation to induce local erythema when applied to the skin of healthy volunteers was determined. A measured dose of each formulation, ca. 10 mg, was applied to the forearms of up to 20 subjects and the time taken for the local blood flow to increase by a factor of 3 was measured by laser Doppler velocimetry (LDV). In this technique laser light is directed into the skin via an optical fibre and the frequency of the reflected light is detected (Tenland, 1983). Light reflected from moving red blood cells is subject to a Doppler shift and it is this change in frequency which is converted to a D.C. signal enabling changes in blood flow to be measured quantitatively (Fig. 2). Using this technique many aspects of cutaneous microcirculation have been studied (Nilsson et al, 1980; Guy et al., 1985).

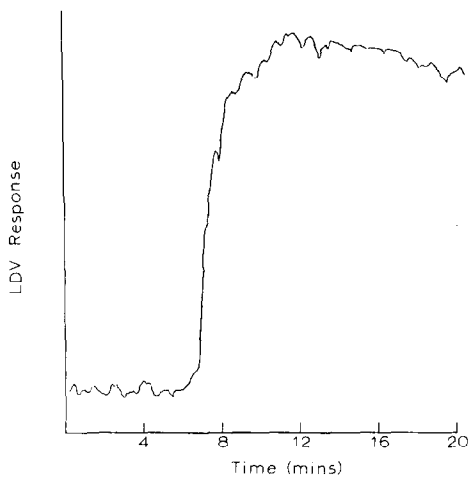

Fig. 2. LDV response following the application of 10 μl of 0.04% MN in acetone to the forearm.

Theoretical

Diffusion from gels

The diffusion of a fully dissolved drug from a vehicle is given by Eqn. 1.

$$Q = hC_0\left[1 - \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)} \times \exp\frac{-D(2m+1)^2\pi^2 t}{4h^2}\right] \quad (1)$$

where Q is the quantity released per unit area, h is the thickness of the vehicle, t the time of application, C_0 is the initial concentration of the diffusing species and D its diffusion coefficient in the vehicle. It is assumed that D is independent of time and position in the vehicle. The bulk composition of the vehicle is assumed to be constant with only the drug diffusing out. It is further assumed that drug reaching the receptor is quickly removed from the surface, i.e. there are sink conditions (Higuchi, 1960).

If less than 60% of the diffusant is released from the vehicle (Higuchi, 1962) Eqn. 1 can be simplified to

$$Q = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \quad (2)$$

Similarly an equation has been proposed to describe release from an emulsion or suspension in which the diffusion from the vehicle is rate limiting (Higuchi, 1961).

$$Q = (2C_0 - C_s)\left(\frac{DtC_s}{1 + 2(C_0 - C_s)}\right)^{1/2} \quad (3)$$

Where C_0 is the initial concentration of diffusant in the vehicle and C_s is the solubility limit of the diffusant in the vehicle. If $C_s \ll C_0$ this equation can be simplified to

$$Q = (2C_0 DtC_s)^{1/2} \quad (4)$$

The diffusion constant D may be defined by the Stokes–Einstein equation (Atkins, 1978):

$$D = \frac{RT}{6\pi\eta r} \tag{5}$$

where η is the viscosity, R the Boltzman constant, T the absolute temperature and r the hydrodynamic radius of the diffusing species.

Concentration of colloid in the gel

The fractional decrease in the intensity of light passing through 1 cm of a colloidal solution (the turbidity) is defined as (Commarata et al., 1969)

$$\frac{HC}{T} = \frac{1}{M} + 2BC \tag{6}$$

This can be rearranged to

$$T = \frac{HMC}{1 + 2BCM} \tag{7}$$

where T is the turbidity, C the concentration of the colloid, B the colloid/media interaction constant and M the molecular mass average of the colloid. H is a complex variable defined as

$$H = \frac{32\pi^3 n^2 (\mathrm{d}n/\mathrm{d}C)^2}{3N\lambda^4} \tag{8}$$

Where n is the refractive index of the media, λ the wavelength and N is Avogadro's number.

For a given colloid in constant media the constants B and $\mathrm{d}n/\mathrm{d}C$ can be assumed to be constant. Colloids of constant size can therefore be described by a reduced form of Eqn. 7

$$T = \frac{aC}{1 + bC} \tag{9}$$

Measurement of turbidity therefore allows the concentration of particles to be estimated.

Results

Using PCS the size of HN droplets in gels containing Brij 36T was found to be independent of surfactant concentration provided HN was present in excess. The results for each emulsion are presented in Table 1 and show a mean particle size of 96.9 nm with a S.D. of 11 nm. The size of Brij 36T micelles in fully solubilised gels (containing 0.25% HN and more than 0.9% Brij 36T) was found to be 10.3 nm with a S.D. of 0.3 nm and again no significant dependence on concentration was found (Table 1).

TABLE 1

The effect of surfactant type and concentration (w/v) on the size of HN droplet

Surfactant	Concentration (%)	Colloid size (nm)
SLS	0.3	102 (7)
SLS	0.4	93 (2)
SLS	0.5	87 (3)
SLS	0.6	97 (4)
Brij 36T	0.3	131 (10)
Brij 36T	0.4	94 (2)
Brij 36T	0.5	97 (7)
Brij 36T	0.6	114 (5)
Brij 36T	0.7	124 (10)
Brij 36T	0.9	114 (2)
Brij 36T	1.2	10.1 (0.3)
Brij 36T	1.5	10.6 (0.3)

These results are the means of 20 individual determinations using PCS with S.D. shown in brackets.

The size of hexyl nicotinate droplets in saturated micellar solutions containing SLS and Na_2SO_4 was found to be 95 nm (the mean of 10 determinations on each formulation) with a S.D. of 7 nm and independent of both SLS and Na_2SO_4 concentrations over the range encountered in the gels (Table 1). In addition the transmittance of these systems at 360 nm was found to be proportional to the degree of solubilisation of HN, determined by centrifugation and subsequent analysis of the aqueous phase (see theoretical section). Measurement of the transmittance of the gels therefore allowed the amount of solubilised drug present to be estimated (Fig. 3).

Neither Brij 36T nor SLS had a significant effect on the thermodynamic activity of MN as determined by head space analysis or its release rate from the gels measured in vitro (Table 2). Similarly the time of onset of the erythema produced by MN-containing gels was not significantly affected by SLS concentration, but an in-

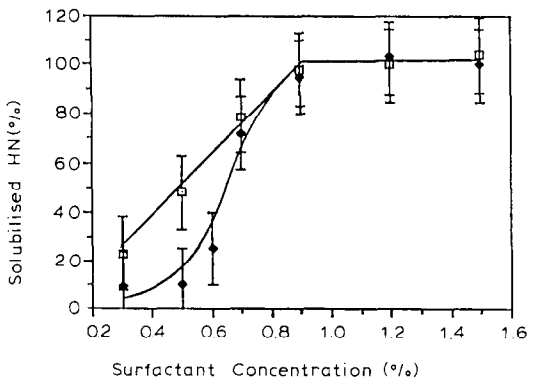

Fig. 3. The percentage of solubilised HN within gels containing (□), Brij 36T or (◆), SLS. Each point is the mean of 5 determinations ± S.E.M.

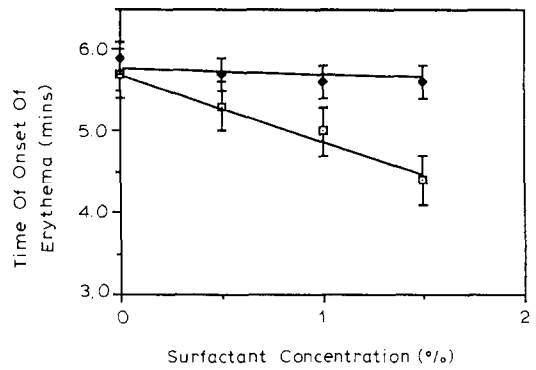

Fig. 4. Times of onset of erythema produced by gels containing 0.5% MN and varying amounts of (□), Brij 36T or (◆), SLS. Each point is the mean of 16 determinations ± S.E.M.

crease in concentration of Brij 36T resulted in a decrease in the time of onset of erythema (Fig. 4).

Brij 36T had no effect on the thermodynamic activity and in vitro release of gels containing 0.5% HN. At 0.5% HN the solute is not fully solubilised at any of the surfactant concentrations studied. However, the surfactant did affect the activity of 0.25% HN gels (Fig. 5). Between 0.3% to 0.7% surfactant, the HN was saturated in the gel and its in vitro release remained constant. At concentrations of 0.9% Brij 36T and above, HN was fully solubilised and as more surfactant was added the thermodynamic activity of HN decreased (Fig. 5) causing a decrease in release rate (Fig. 6). This was not matched by an increase in the time of onset of erythema which appeared to be independent of Brij concentration (Fig. 7). SLS influenced the behaviour of gels containing HN in a comparable manner. Increasing the SLS content from 0.3% caused an increase in the in vitro release rate with a maximum being reached at 0.7%, any further increase in surfactant concentration retarded release (Fig. 6). Times of onset of erythema were influenced by SLS with a minimum occurring between 0.6% and 0.9% SLS (Fig. 7) although the thermodynamic activity of HN in the gels did not follow the same trend. This was found

TABLE 2

The effect of surfactant type and concentration (w/v) on the release and thermodynamic activity on MN in Carbopol gels containing 0.5% MN

Compound (%)	Surfactant (%)	Release rate ($M\ min^{-1/2}m^{-2}$)	Thermodynamic activity
MN 0.5	None	1.78	0.1
MN 0.5	SLS 0.5	1.85	0.1
MN 0.5	SLS 1.0	1.88	0.1
MN 0.5	SLS 1.5	1.78	0.1
MN 0.5	B36T 0.5	1.69	0.1
MN 0.5	B36T 1.0	1.88	0.1
MN 0.5	B36T 1.5	1.78	0.1

The results are the means of 4 determinations and are subject to an error of ± 0.5 M $min^{-1/2}m^{-2}$. The standard error involved in the measurement of thermodynamic activity was ± 0.05.

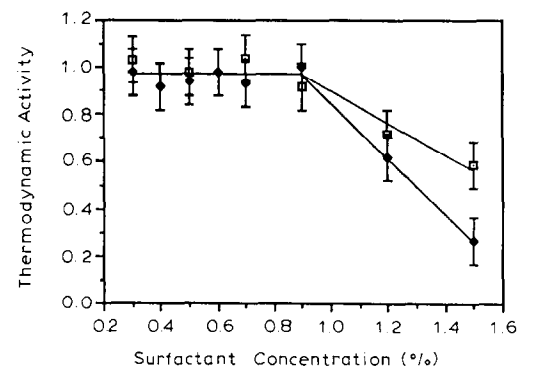

Fig. 5. The effect of concentration on the thermodynamic activity of HN in gels containing (□), Brij 36T or (◆), SLS. Each point is the mean of 5 determinations ± S.E.M.

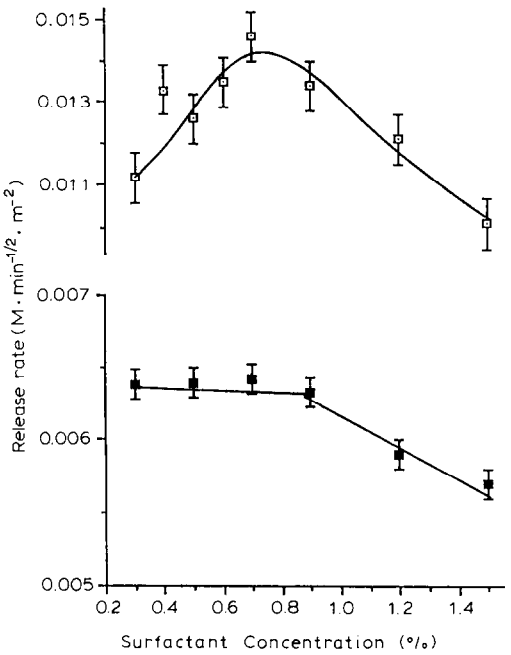

Fig. 6. The effect of concentration on the release rate of HN from gels containing (□), SLS and 0.5% HN or (■), Brij 36T and 0.25% HN. Each point is the mean of 8 determinations ± S.E.M.

to be constant between 0.3% and 0.9% at which point HN was just fully solubilised, and then decreasing as SLS content was increased (Fig. 5).

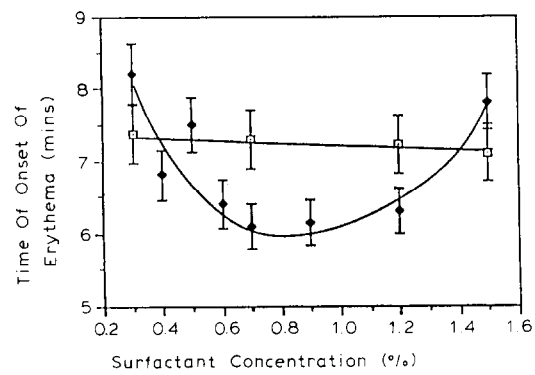

Fig. 7. The effect of surfactant concentration on the times of onset of erythema produced by gels containing (□), Brij 36T and 0.25% HN or (◆), SLS and 0.5% HN. Each point is the mean of 16 determinations ± S.E.M.

Discussion

MN is readily soluble in water and as the head space analysis results indicate, does not partition into surfactant micelles to an appreciable extent. Its release from the gels can therefore be adequately described by Eqn. 2. There are many reports that SLS decreases the barrier function of the skin (Chowhan and Pritchard, 1978; Gershbein, 1979). In this study, however, the time of onset of erythema produced by MN is not significantly affected by increasing concentrations of SLS indicating that over the time course of these experiments this surfactant has no significant effect on the barrier properties of the skin with respect to nicotinates.

HN is a comparatively non-polar molecule of low aqueous solubility and can therefore be expected to partition into surfactant micelles. At low concentrations of surfactant (below 0.9%) the solubilising capacity of SLS is saturated by HN which is present in 3 forms, free in solution, solubilised in micelles and emulsified droplets. Due to their size HN droplets can be expected to have a very small diffusion constant compared to free HN (Eqn. 5) and their contribution to diffusion through the gel can be ignored. As hexyl nicotinate is saturated in these gels its thermodynamic activity is constant over this range. When the concentration of surfactant is increased from 0.3%, more of the droplets are solubilised into micelles and at 0.9% SLS, HN is fully solubilised within micelles or else free in solution. The addition of more surfactant therefore causes a reduction in the thermodynamic activity (Fig. 5) and the release rate (Fig. 6) and hence an increase in the time for erythema (Fig. 7). As no evidence of a change in droplet size was detected the increase in release rate as surfactant concentration is increased from 0.3% to 0.7% can be explained in two ways. Either the diffusion of HN containing micelles through the gel is significant or the rate at which equilibrium is reached between HN droplets and free solution is rate-limiting and is influenced by the presence of SLS/HN micelles.

The time of onset of erythema caused by MN in Brij 36T-containing gels decreases as the surfactant concentration is increased, indicating

that the permeability barrier of the skin is reduced by this surfactant within the time course of these experiments. That SLS, usually considered to be the more powerful promoter (Aguiar and Weiner, 1969; Schaeffer, 1981) takes longer to exert its effect on the skin suggests that the two surfactants act on the skin in different ways.

HN partitions into Brij 36T micelles significantly reducing both its thermodynamic activity and its in vitro release rate. As no decrease in the time of onset of erythema is seen it appears that these effects cancel any increase in the skin's permeability.

Acknowledgements

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