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Percutaneous absorption of methyl nicotinate

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Abstract

The percutaneous absorption of methyl nicotinate was measured in vitro across hairless rat skin. The methyl nicotinate was applied in vehicles containing propylene glycol dipelargonate, Labrafac Hydrophile® and Transcutol®. In vitro experiments were analysed using solutions to Fick's laws of diffusion in order to determine permeation parameters.

Keywords: Skin absorption; Methyl nicotinate; Penetration enhancer

1. Introduction

Many topical formulations have poor bioavailability with only a few percent of the applied dose reaching the target site. Significant improvements can be made by optimising the thermodynamic activity of the drug in the formulation and with the judicial use of permeation enhancers (Hadgraft et al., 1973). However, in practice, the selection of an appropriate enhancer or mixture of enhancers is often arbitrary. When mixtures of enhancers are used it is often difficult to predict their precise effect and often synergism between them can exist. In this paper three potential penetration enhancers, Labrafac Hydrophile® (LH), Transcutol® (T) and propylene glycol dipelargonate (DPPG), have been studied. The way in which they affect the percutaneous penetration of the potent vasodilator, methyl nicotinate, has been studied. Their influence has been studied in vitro using hairless rat skin With a knowledge of the physicochemical parameters of methyl nicotinate in the different vehicles it is possible to put a mechanistic interpretation on their influence on the skin barrier function.

2. Material and methods

Methyl nicotinate was used as received from Sigma. The formulation vehicles were kindly supplied by Gattefossé. Transcutol® is diethylene glycol monoethyl ether, whilst Labrafac Hydrophile® is a mixture of C_8–C_{10} ethoxylated glycerides. These in combination with propylene glycol dipelargonate were used either singly or as a ternary mixture (TDL) with equal volumes of the three components.

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2.1. Solubility determinations

Methyl nicotinate was added sequentially to the different vehicles until saturation. Saturation was achieved when excess solid persisted for more than 12 h with constant shaking at 30° C.

2.2. Permeability determinations

Skin was obtained from the abdomen of 8-week-old hairless rats (Iffa Credo). It was mounted into all-glass static diffusion cells with an effective skin surface area of 2.54 cm^2 and thermostated such that the skin surface temperature was 30° C. The receptor phase was 0.9% sodium chloride and was stirred continuously. The donor phase was 2 g of the vehicle which contained excess methyl nicotinate (120% of the determined solubility). Samples were regularly extracted from the receptor phase and analysed using HPLC. The HPLC was a Hewlett Packard HP 1050 fitted with a Lichrospher 100-RP 18 5 μm, 4 × 125 mm column with a Lichrospher 100-RP 18 pre-column. UV detection was at 218 nm with a mobile phase of methanol/water (60:40) and a flow rate of 1 ml/min. The methyl nicotinate retention time under these conditions was 2.7 min.

3. Results

The solubilities of methyl nicotinate in the various vehicles are given in Table 1.

The amount of methyl nicotinate penetrating the hairless rat skin was monitored over a 6 h period. At least five replicates were conducted. The results for four vehicles LH, DPPG, T and TDL are given in Fig. 1. No data were excluded; the exclusion criteria adopted were any points which were outside the mean ± 2SD.

Table 1
Solubility of methyl nicotinate in the vehicle

Vehicle	Solubility (mg/g)
LH	723
DPPG	537
T	869
TDL	858
Water	925

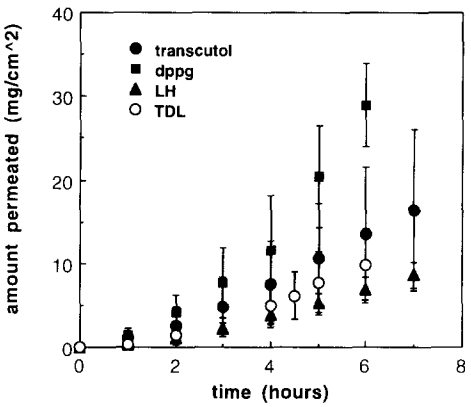

Fig. 1. Penetration of methyl nicotinate through hairless rat skin from the different vehicles. At least five replicates were conducted and the error bars show the standard deviation.

A statistical analysis of the 6 h data points using analysis of variance shows that the only significant difference ($p < 0.05$) was between DPPG and the other vehicles. There was no significant difference between Transcutol, Labrafac Hydrophile and the ternary mixture TDL.

The flux of methyl nicotinate from the latter three vehicles is directly proportional to its thermodynamic activity (unity) in those vehicles. For this permeant either these vehicles have an equal enhancing effect or, more likely, they do not influence the barrier function of the skin. It is possible that they may enhance the permeation of other diffusants.

On the other hand, DPPG does not behave ideally as enhanced fluxes were obtained. The data were therefore examined in more detail using an analysis based on a solution to Fick's second law of diffusion (Diez-Sales et al., 1991).

The experimental data were fitted to the equation:

$$Q(t) = AKhc\left[\frac{Dt}{h^2} - \frac{1}{6} - \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2} \times \exp\left(-\frac{Dn^2\pi^2 t}{h^2}\right)\right] \quad (1)$$

Table 2
P_1 and P_2 values obtained from fitting the experimental data to Eq. 1

Vehicle	From individual data (±SD)		From mean data (±95% CI)	
q	P_1	P_2	P_1	P_2
T	0.027 (0.017)	0.14 (0.09)	0.02 (0.008)	0.13 (0.03)
DPPG	0.38 (0.3)	0.08 (0.08)	0.22 (0.19)	0.06 (0.03)
LH	0.03 (0.03)	0.09 (0.03)	0.02 (0.003)	0.10 (0.01)
TDL	0.03 (0.02)	0.11 (0.06)	0.03 (0.014)	0.096 (0.03)
DPPG (4 h)			0.03 (0.02)	0.21 (0.10)

where $Q(t)$ is the amount permeating the skin of area A at time t, K denotes the partition coefficient between the vehicle and the skin, c is the applied concentration, D represents the diffusion coefficient of the permeant in the skin and h is the diffusional path length.

In this equation K, D and h are unknown. The thickness of the skin can be used as an estimate of h but then an apparent diffusion coefficient (D_{app}) will be obtained. Any tortuosity factor for hairless rat skin has yet to be determined.

In order to solve the equation, the parameters P_1 and P_2 were substituted for Kh and D/h^2, respectively. P_1 and P_2 were then calculated by fitting the experimental data to the theoretical equation using a computerised non-linear least-squares method (Ultrafit, Biosoft). The product P_1P_2 then provides a measure of the permeability coefficient (KD/h) which does not require a precise knowledge of the diffusional path length.

There are two ways of analysing the data. The theoretical equation can be fitted to the data from the individual experiments to give a series of P_1 and P_2 values or the mean data values from all the experiments can be chosen and P_1 and P_2 values calculated from the means. Both approaches were adopted and the results are given in Table 2.

Ultrafit gives an indication of goodness of fit (GOF) (0, worst; 1, perfect). For Transcutol, LH and TDL, however, the GOF values were (with the exception of one individual experiment for TDL) greater than 0.95. For DPPG the GOF values were very poor. This indicates that the data for DPPG cannot be interpreted using straightforward solutions to Fick's second law of diffusion. It may indicate that the barrier function is compromised by high concentrations of DPPG. If the data points for the first 4 h application of DPPG are examined the data can be fitted with a GOF = 0.97. It appears that normal diffusion occurs for a 4 h period after which time there is breakdown of the barrier function.

The P_1 and P_2 values can be used to estimate K_p and steady-state flux, J_{ss}.

$$J_{ss} = K_p S \tag{2}$$

where S is the solubility (given in Table 1). Estimates of the lag time (τ) can also be calculated.

$$\tau = \frac{h^2}{6D} = \frac{1}{6P_2} \tag{3}$$

Table 3
Transport parameters of methyl nicotinate calculated from P_1 and P_2 values determined from the mean data points

Vehicle	K_p (cm h^{-1})	τ (h)	D_{app} (cm^2 h^{-1})	K	J_{ss} (mg/cm^2 per h)
T	3.25×10^{-3}	1.25	0.048	0.03	2.82
LH	2.22×10^{-3}	1.25	0.048	0.03	1.61
TDL	2.78×10^{-3}	1.67	0.036	0.05	2.28
DPPG (4 h)	6.63×10^{-3}	0.78	0.077	0.05	3.56

If a value of h for hairless rat skin is taken as the observed thickness of 600 μm a value of D_{app} can be calculated together with K. These parameters are listed in Table 3.

The values for D_{app} and K are nominal, since they assume that the route of penetration is straight through the skin and the permeant will distribute freely through the entire skin, i.e., not take an intercellular pathway.

From these data analyses it is apparent that the different vehicles do not have very large effects on either the partitioning or diffusional characteristics of methyl nicotinate in the skin. The maximum effect observed in Table 3 is less than 2-fold. Small changes in the partition behaviour can have significant effects on the onset of erythema induced by the nicotinates.

It should also be remembered, however, that the effects are multiplicative and that the overall flux is a function of the product of D_{app} and K.

From the values of P_1 and P_2 it is possible to reconstruct the anticipated amount of drug permeating the skin using Eq. 1. This has been achieved using Mathematica software (Appendix). The theoretical curves for T, LH, TDL are shown in Fig. 2 and demonstrate very good agreement with the experimental data.

Fig. 3 shows the experimental data for DPPG and the theoretical curve based on the parameters from the 4 h analysis.

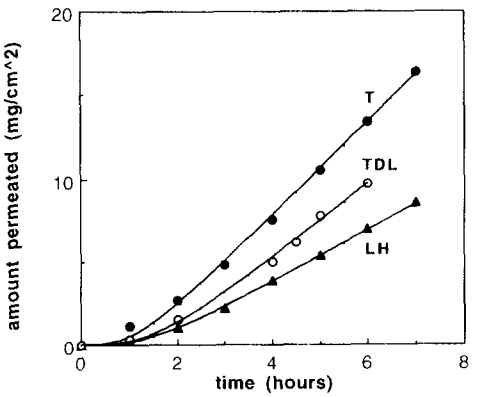

Fig. 2. Penetration of methyl nicotinate through hairless rat skin from T, LH and TDL showing the experimental data and the reconstructed theoretical profiles (solid lines) using Eq. 1.

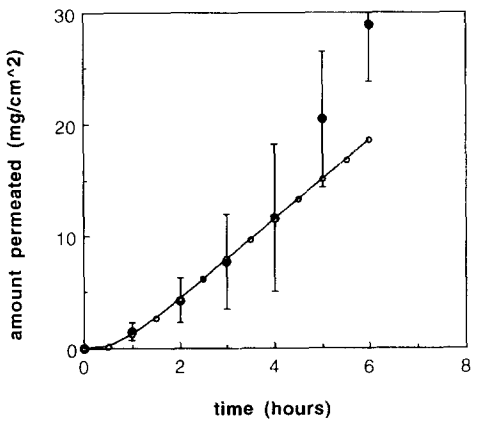

Fig. 3. Penetration of methyl nicotinate through hairless rat skin from DPPG showing the experimental data and the reconstructed profile (solid line) using Eq. 1 from the first 4 h data points.

There is a clear deviation from ideal behaviour after 4 h showing that DPPG probably compromises the barrier function. This occurs at high DPPG concentrations and may not be the case for human skin.

These problems and data analyses highlight the difficulties in interpreting skin permeation data. It is common practice to use the last few data points from an experimental run, assume steady state has been achieved and extrapolate to determine lag time. Considerable errors can be made using this simplistic approach. Data fitting using solutions to Fick's second law is also problematic as has been experienced with DPPG. Barrier function properties which alter with time are difficult to model and interpret.

4. Appendix

The Mathematica software (Wolfram Research Inc.) has a very high level programming language of its own. The following commands were used to generate theoretical diffusion curves

where $a = P_1$, $b = P_2$, m = donor concentration, t = time and ? = fitted or relevant value.

```
a = ?
b = ?
m = ?
Q = Flatten[Table[{t,a * m * (((t * b))-(1/6)-
((2/(Pi ^2)) * Sum[(((-1) ^n)/(n ^2)) * Exp[-(n ^2)
*(Pi ^2) * (t * a)],{n,1,20}]))},{t,0,8,0.5}],1]
Partition [u,2]
q = N[%]
b = ListPlot[q,PlotJoined → True]
```

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