Solvent Enhancement Effect From Finite Dose Application

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Introduction and Aim

The use of penetration enhancers is a well-known strategy to improve delivery across human skin. In spite of extensive literature on permeation enhancers and their mechanisms of action, little has been published on the effect of the enhancer when applied at clinically relevant doses (typically less than a few mg/cm^2). A recent study (Trottet et al., 2004) has shown evidence that the depletion of propylene glycol from the formulation can limit its enhancing effect, especially when relatively small doses are used. The authors also suggested that the penetration enhancement of solvents may be overestimated in *in vitro* studies because most studies are performed under infinite dose conditions.

The aim of the present investigation was to study the enhancement effect of Transcutol P® (TC), dimethyl isosorbide (DMI) and isopropyl myristate (IPM) on the permeation of methyl paraben using finite doses across silicone membranes. A number of formulations incorporating ethanol were also tested to examine the influence of volatile solvent on permeation.

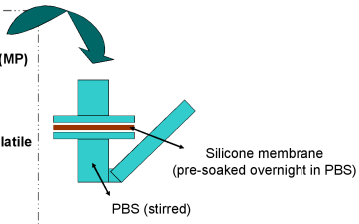
Materials and Methods

Methyl paraben (Methyl-4-hydroxybenzoate puriss. ≥99%, Fluka) and IPM (Isopropyl Myristate 98%, Aldrich) were supplied by Sigma-Aldrich, UK. Dimethyl isosorbide (Arlasolve® DMI) and Transcutol P® were supplied by Uniqema and Gattefossé, respectively. Ethanol (99.7 - 100% v/v AnalaR® grade, BDH) was supplied by VWR UK. PBS was prepared *in situ* by dissolving 10 Phosphate Buffered Saline (Dulbecco A) tablets (pH 7.3±0.2 at 25oC, Oxoid) supplied by Fisher Scientific UK in 1 litre of deionised water (diH_2O). The silicone membranes (aprox. 250 µm thickness) were supplied by Samco, UK.

Saturated solutions were produced by adding excess amount of solute to each solvent with stirring for at least 24 hours at 32 (±0.5)°C, after which the suspended drug crystals were removed by filtration. The permeation experiments were conducted at 32 (±0.5)°C using Franz-type diffusion cells (~0.801 cm^2 diffusion area) placed in a temperature controlled water bath. A small volume of the donor solutions (10 µl) was evenly spread at the membrane surface using a micropipette (finite dose study). An infinite dose study was also performed, using 1ml of a saturated suspension of methyl paraben in water (containing undissolved drug to ensure maintenance of saturation during the experiment) as donor. Sampling of the receptor occurred at designated time points with volume replacement using fresh PBS. Sink conditions were maintained throughout the experiment. Methyl paraben was quantified using HPLC. The permeation of methyl paraben was evaluated by plotting the cumulative amount permeated per unit surface area of the membrane (µg/cm^2) against collection time in minutes.

Formulations tested:

- **Saturated solutions of methyl paraben (MP)**
  - MP in IPM sat.
  - MP in DMI sat.
  - MP in Transcutol P® (TC) sat.
- **Formulations incorporating ethanol (volatile solvent)**
  1. MP in IPM sat. (50%) + EtOH (50%)
  2. MP in DMI sat. (50%) + EtOH (50%)
  3. MP in TC sat. (50%) + EtOH (50%)



Results

• Quantification of methyl paraben in the formulations

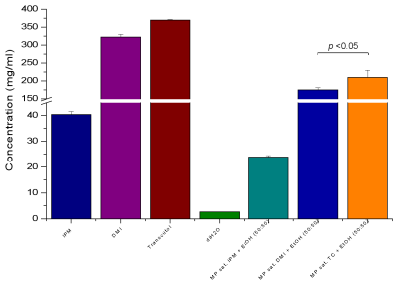


Figure 1. Solubility of methyl paraben in ▪ IPM, ▪ DMI, ▪ TC, and ▪ deionised water (diH_2O) at 32°C, and its concentration in the corresponding formulations incorporating ethanol. Error bars represent ±SD (n=3).

• Amount of methyl paraben applied for a 10µl dose

Formulations tested	Dose applied (mg)
MP in IPM sat.	0.40
MP in DMI sat.	3.22
MP in TC sat.	3.70
MP sat. IPM + EtOH (50:50)	0.24
MP sat. DMI + EtOH (50:50)	1.75
MP sat. TC + EtOH (50:50)	2.10

• Permeation of methyl paraben from saturated solutions

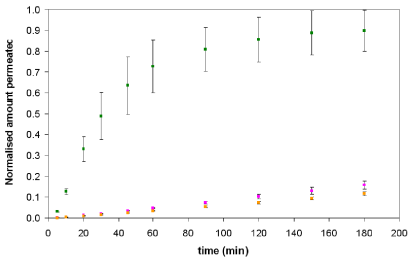


Figure 2. Normalised amount of methyl paraben permeated from saturated solutions in ▪ IPM, ▪ DMI and ▪ TC at 32°C, estimated by dividing the cumulative amount permeated (in µg/cm^2 versus time in minutes) by the dose applied (µg). Error bars represent ±SD (n=5).

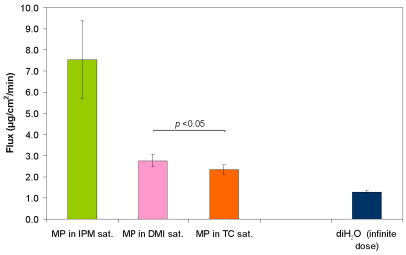
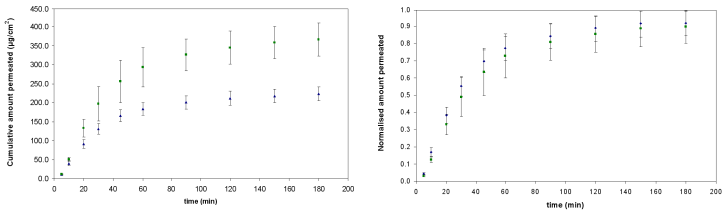
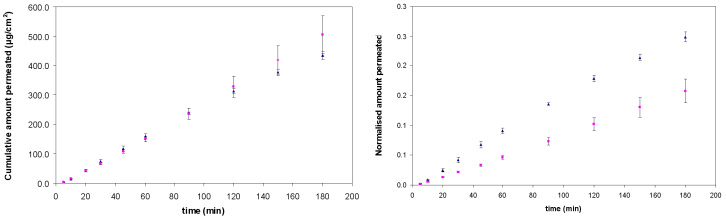


Figure 3. Estimated flux in µg/cm^2/min for the permeation of methyl paraben from saturated solutions in IPM, DMI and TC at 32°C, compared with an infinite dose study using water as solvent. The flux was estimated from the slope of the pseudo steady-state portion of the plot of cumulative amount permeated (in µg/cm^2 versus time in minutes). Error bars represent ±SD (n=5).

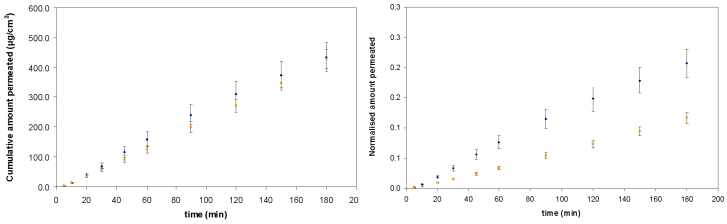
• Permeation of methyl paraben from formulations incorporating ethanol



Figures 4 and 5. Cumulative amount in µg/cm^2 (*left*) and normalised amount (*right*) of methyl paraben permeated from ▪ saturated solution in IPM and from ▲ MP in IPM sat + EtOH (50:50) formulation. Error bars represent ±SD (n=5).



Figures 6 and 7. Cumulative amount in µg/cm^2 (*left*) and normalised amount (*right*) of methyl paraben permeated from ▪ saturated solution in DMI and from ▲ MP in DMI sat + EtOH (50:50) formulation. Error bars represent ±SD (n=5).



Figures 8 and 9. Cumulative amount in µg/cm^2 (*left*) and normalised amount (*right*) of methyl paraben permeated from ▪ saturated solution in TC and from ▲ MP in TC sat + EtOH (50:50) formulation. Error bars represent ±SD (n=5).

Results and conclusions

- ✓ The flux of MP from saturated solutions in IPM, DMI and TC (finite dose) across silicone membranes was higher than flux from aqueous solutions (infinite dose), suggesting solvent interaction with the membrane.
- ✓ The greatest permeation of MP was observed from IPM, ~80% permeation after 1.5 hours. For DMI and TC the fluxes were similar and comparatively low. In addition, crystals of MP could be observed on the surface of the silicone membrane at the end of the experiment with these solvents, suggesting donor depletion. This suggests that solvents with high affinity for the membrane (IPM) have greater enhancement effects than those which permeate into and out of the membrane (TC and DMI).
- ✓ The presence of a volatile solvent (ethanol) had little effect on drug flux when compared with the saturated solutions (Figures 4, 6 and 8), although for DMI and TC the presence of ethanol increased the efficiency of the formulations (Figures 7 and 9).
- ✓ Future work will be extended to human skin, the results ultimately improving optimal selection of excipients for dermal drug delivery.

References

Trottet, L., Merly, C., Mirza, M., Hadgraft, J. and Davis, A. F. (2004). "Effect of finite doses of propylene glycol on enhancement of in vitro percutaneous permeation of loperamide hydrochloride." International Journal of Pharmaceutics **274**: 213-219.

Acknowledgments

Gabriela Oliveira would like to thank The School of Pharmacy, University of London for funding, and Uniqema and Gattefossé for supplying the chemicals.