The Influence of Volatile Solvents on Skin Permeation

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Introduction

Overcoming the excellent barrier properties of the human skin represents the major challenge and limitation to (trans)dermal drug delivery. An informed choice of excipients is therefore the key to construct elegant yet efficient transdermal formulations. Topical formulations which include volatile components, such as gels or sprays, are user-friendly and attractive from a cosmetic perspective. The present study aims to examine the influence of the volatile solvent ethanol (EtOH) in combination with Transcutol P® (TC), dimethyl isosorbide (DMI) and isopropyl myristate (IPM), on methyl paraben (MP) skin permeation.

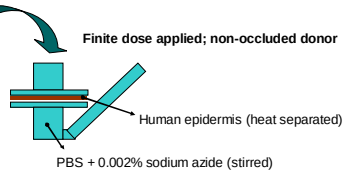
Materials and Methods

Methyl paraben (puriss. ≥99%, Fluka) and IPM (98%, Aldrich) were supplied by Sigma-Aldrich, UK. Dimethyl isosorbide (Arlasolve®) and TC were supplied by Uniqema and Gattefossé, respectively. Ethanol (99.7 - 100% v/v AnalaR® grade, BDH) was supplied by VWR UK. The receptor phase 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). 1ml of a 2% w/v sodium azide solution was also added to the receptor phase.

In vitro diffusion experiments were conducted in human epidermis obtained by the heat separation method (female Caucasian abdominal skin). Finite dose studies were conducted at 32 (±1)°C using Franz-type diffusion cells and PBS + 0.002% sodium azide as the receptor solution. Two types of formulations were tested: saturated solutions of methyl paraben in each vehicle alone and incorporating the volatile solvent in 50:50 % v/v proportion. Mass balance studies of both drug and vehicle were conducted at the end of each experiment. Methyl paraben was quantified using HPLC. TC, IPM and DMI were quantified using GC-MS.

Formulations tested:

- **Saturated solutions of methyl paraben**
  1. MP in IPM sat.
  2. MP in DMI sat.
  3. MP in TC sat.
  4. MP in EtOH sat.
- **Formulations incorporating ethanol (volatile solvent)**
  1. MP in IPM sat. + EtOH (50:50) formulation
  2. MP in DMI sat. + EtOH (50:50) formulation
  3. MP in TC sat. + EtOH (50:50) formulation



Results and Discussion

Amount of methyl paraben applied for finite dose studies

Formulations tested	Dose applied (µmol/cm²)
MP in IPM sat.	2.0
MP in DMI sat.	19.1
MP in TC sat.	25.2
MP in EtOH sat.	20.9
MP in IPM sat. + EtOH (50:50)	1.0
MP in DMI sat. + EtOH (50:50)	8.9
MP in TC sat. + EtOH (50:50)	11.4

Volatile vs. non-volatile formulations

IPM

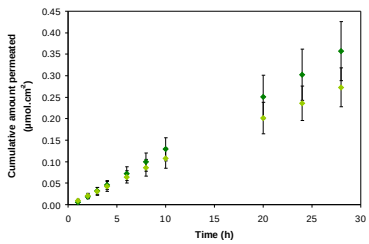


Figure 1. Cumulative amount of methyl paraben permeated across skin (finite dose) from ♦ IPM sat. and ♦ IPM sat. + EtOH (50:50) formulations at 32°C. Error bars represent ±SD (n=5).

DMI

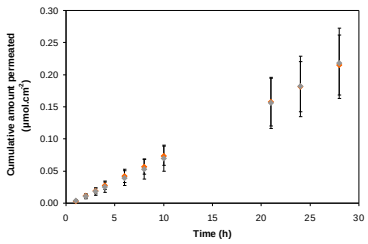


Figure 2. Cumulative amount of methyl paraben permeated across skin (finite dose) from ♦ DMI sat. and ♦ DMI sat. + EtOH (50:50) formulations at 32°C. Error bars represent ±SD (4≤n≤5).

TC

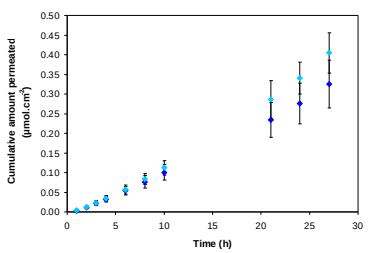


Figure 3. Cumulative amount of methyl paraben permeated across skin (finite dose) from ♦ TC sat. and ♦ TC sat. + EtOH (50:50) formulations at 32°C. Error bars represent ±SD (4≤n≤5).

✓ Figures 1 – 3 confirm that the presence of EtOH had little effect on the absolute skin flux of methyl paraben compared with the corresponding saturated solutions.

Acknowledgments

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Permeation from the ethanol saturated solution

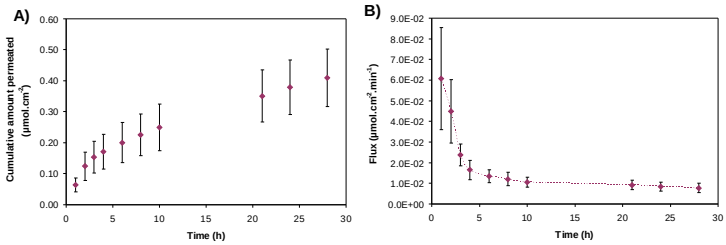

Figure 4. A) Cumulative amount of methyl paraben permeated across the skin from EtOH sat. formulation (finite dose) at 32°C. **B)** Flux profile of methyl paraben across the skin from EtOH sat. (finite dose) at 32°C. Error bars represent ±SD (n=4).

✓ The permeation of methyl paraben from the EtOH saturated solution showed an initial period of relatively fast permeation (i.e. 0–5 hours), followed by a marked decrease in the permeation rate (Figure 4A and 4B). This reflects significant EtOH depletion from the formulation, chiefly by evaporation; leaving a deposited film of crystallised methyl paraben at the surface of the skin.

Comparison between formulations

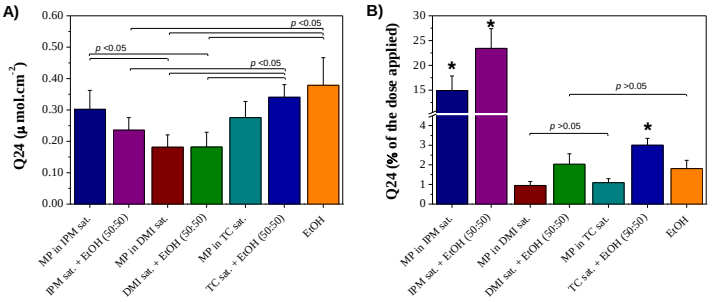

Figure 5. A) Cumulative amount of methyl paraben permeated across the skin after 24 hours (Q24) from each formulation at 32°C. **B)** Percent of the dose of methyl paraben applied in each formulation permeated through skin after 24 hours at 32°C. Error bars represent ±SD (4≤n≤5). Asterisk denotes significant differences between formulations (p <0.05).

✓ The skin permeation of methyl paraben was highest from the pure EtOH, IPM and TC based formulations, followed by the DMI based formulations (Figure 5A).

✓ The formulations incorporating the volatile solvent were clearly more efficient than the corresponding saturated solutions (Figure 5B).

Mass balance studies

Table 1. Recovery (% of applied dose) of both methyl paraben (MP) and vehicle at each compartment of the Franz cell, obtained at the end of finite dose studies using each formulation. Mean ± SD (4≤n≤5).

		Skin surface	Skin	Receptor phase	Total recovery
IPM sat	**MP**	71 (±3)	4 (±1)	18 (±3)	**92 (±3)**
	IPM	84 (±4)	3 (±1)	--- (*)	**87 (±3)**
IPM sat. + EtOH (50:50)	**MP**	46 (±7)	6 (±1)	27 (±4)	**79 (±6)**
	IPM	47 (±14)	4 (±1)	--- (*)	**51 (±14)**
DMI sat	**MP**	88 (±3)	5 (±1)	2 (±1)	**95 (±3)**
	DMI	79 (±7)	4 (±0)	12 (±5) (**)	
DMI sat. + EtOH (50:50)	**MP**	74 (±10)	9 (±4)	4 (±1)	**87 (±8)**
	DMI	53 (±8)	6 (±3)	27 (±3) (**)	
TC sat	**MP**	84 (±4)	7 (±0)	2 (±1)	**93 (±3)**
	TC	52 (±7)	4 (±0)	37 (±5) (**)	
TC sat. + EtOH (50:50)	**MP**	79 (±4)	12 (±2)	6 (±1)	**97 (±1)**
	TC	28 (±2)	5 (±1)	65 (±2) (**)	
EtOH	**MP**	84 (±4)	7 (±0)	2 (±1)	**93 (±3)**

(*) immiscible with the receptor phase, therefore the amounts of IPM expected in this compartment are effectively zero.
(**) Calculated by subtracting the amounts quantified in both donor and skin from the dose applied.

✓ Overall total recoveries were good (Table 1), except that of IPM in the study using the IPM sat + EtOH (50:50) formulation. The reasons for this are not completely understood, however losses of material may have occurred during the extraction procedure.

✓ At the end of the experiment using the pure EtOH, solution, most of the MP was crystallised on the skin surface. This is consistent with significant depletion of EtOH from the formulation.

✓ The results also show significant depletion of DMI and TC from the donor, although this did not noticeably affect the kinetics of the permeation (Figures 2 and 3).

Conclusions

The findings suggest that rapid evaporation of EtOH takes place from the formulations applied at the surface of the skin, leaving a saturated residue of the drug in the vehicle. The presence of EtOH clearly influenced the efficiency of the formulation, underlining the application of volatile components in optimal dermal delivery. In particular, such excipients have the potential to decrease drug loading in topical formulation, with obvious advantages from pharmaceutical, regulatory and environmental perspectives.