Vehicle effects on dermal delivery

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Introduction and Aim

ATR-FTIR spectroscopy and membrane diffusion studies are established techniques to study the effects of penetration enhancers and can be used to estimate the diffusion and partitioning parameters in permeation studies.

ATR-FTIR spectroscopy and conventional Franz-type diffusion cells are used to study the effects of selected chemical enhancers; isostearyl isostearate (ISIS), isopropyl isostearate (IPIS), isopropyl myristate (IPM), hexanol, octanol and decanol, on the permeation of methylparaben (MP) and butylparaben (BP) through polydimethylsiloxane (silicone) membrane.

MP and BP were chosen to understand of the effects of vehicles on penetrants with different lipophilicities. The vehicles were chosen to allow structure-activity relationships to be explored. Dow corning silicone membrane (80 microns, type 7-4107) was used as a model membrane to avoid the heterogeneity and complexity associated with skin tissue simplifying data interpretation.

Materials and Methods

ATR- FTIR spectroscopic diffusion experiments were performed using a Nicolet Avatar 360 spectrophotometer (Figure 1) fitted with an ATR accessory ZnSe crystal (Figure 2).

Figure 1. Nicolet Avatar 360 spectrometer

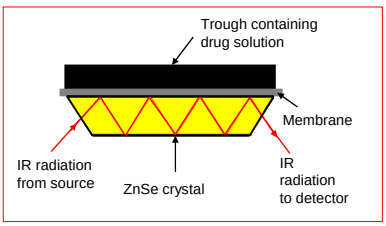

Figure 2. Illustration of the bulk diffusion ATR-FTIR setup to investigate the diffusion of MP and BP across membranes.

Permeation experiments were conducted using Franz-type diffusion cells (~1cm^2 diffusional area) (Figure 3).

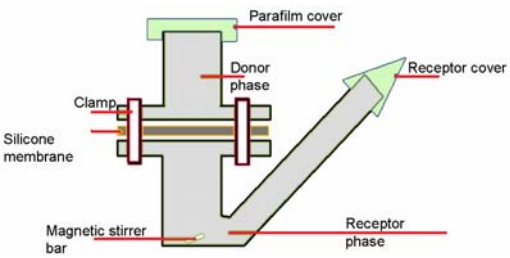

Figure 3. Franz cell setup

Both ATR-FTIR and Franz diffusion cell experiments were performed using saturated solutions at infinite dose. The silicone membranes were pre-soaked in each solvent for 24 hours at ambient temperature (21°C ± 2°C).

Sink conditions were used throughout the experiment. The amount of MP and BP permeated was quantified using HPLC. MP and BP saturated solubilities in the different solvents were determined by UV spectroscopy. Solvent uptake was determined gravimetrically. Data analyses were performed using OPUS and Scientist® software.

The diffusion of the permeants across the membrane was followed using the aromatic ring stretching of MP and BP at around 1625-1575 cm^{-1}.

Results and Discussion

Typical Fickian diffusion profiles were obtained for MP and BP in the 6 different solvents using ATR-FTIR spectroscopy. These data were successfully modelled using the Laplace transform method in Scientist® to obtain diffusion coefficients for MP and BP (Figure 5).

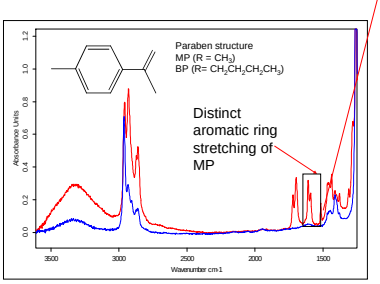

Figure 4. ATR-FTIR spectra of MP in hexanol (Red) through pre-soaked silicone membrane (Blue)

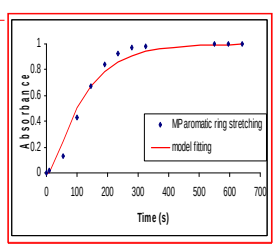

Figure 5. Typical normalised absorbance plot of MP in hexanol across silicone membrane and model fitting by Scientist ®

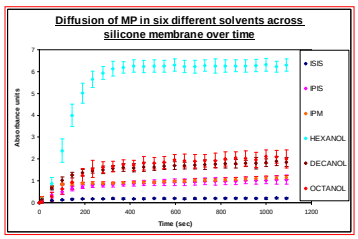

Figure 6. Diffusion profiles of MP in the 6 solvents

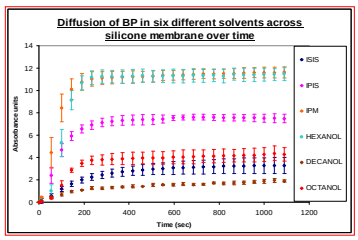

Figure 7. Diffusion profiles of BP in the 6 solvents

- Plateau value is proportional to the concentration of the drug in the membrane, so an increase in plateau value should lead to an increase in flux. These values are related to the concentration of MP and BP in the membrane and were thus strongly influenced by the solubility of the permeant in the vehicle and the uptake of vehicle into the membrane.

	Solubility		FTIR DATA				SVU* (ml)		
	MP	BP	MP		BP			MP	BP
Solvents	Conc. (mg/ml)		P	D	P	D		SVU* x Solubility (mg)	
ISIS	9.85	62.45	0.19	4.18E-07	3.15	1.86E-07	0.05	0.49	3.12
IPIS	17.55	108.57	0.88	2.87E-07	7.59	3.43E-07	0.42	7.37	45.60
IPM	22.03	142.97	0.90	9.18E-07	11.22	5.02E-07	0.66	14.54	94.36
HEXANOL	129.79	384.55	6.25	2.62E-07	11.26	3.10E-07	0.13	16.87	49.99
OCTANOL	146.11	302.48	1.56	1.90E-07	3.86	2.41E-07	0.08	11.69	24.20
DECANOL	78.15	292.38	1.61	2.94E-07	1.24	1.89E-07	0.05	3.91	14.62

Table 1. The measured solubility, calculated diffusion coefficients (D), plateau (P), and *Specific Volume Uptake (SVU) of MP and BP in the 6 solvents

- The higher solubility of BP in the more lipophillic ester vehicles gives rise to an increase in the plateau absorbance values relative to that of the alcohols in comparison with MP. MP has a much higher solubility in more polar solvents such as hexanol, octanol and decanol relative to BP.

- In general, vehicles which were highly sorbed by the membrane altered its properties increasing the diffusion coefficient of the permeant. BP (log *P* 3.57) is more lipophillic than MP (log *P* 1.96).

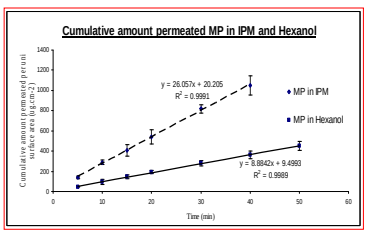

Figure 8. Franz diffusion cell permeation of the cumulative amount permeated over time for MP in IPM and hexanol

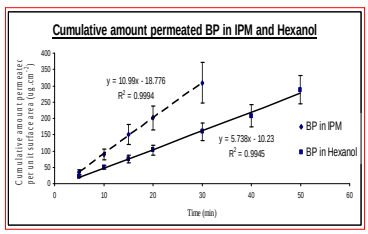

Figure 9. Franz diffusion cell permeation of the cumulative amount permeated over time for BP in IPM and hexanol

- Comparison of the permeability co-efficient, k_p (KD/h), for ATR-FTIR to Franz diffusion cell data do not follow similar trends.

- One possible hypothesis for the discrepancies in k_p values, based on preliminary observations, is the hydrogen bonding ability of the solvents.

Table 2. Comparison of the permeability coefficient (k_p) with the two techniques

k_p (cm/s)	ATR-FTIR	Franz cell
MP/IPM	7.40 x 10^{-05} ± 4.6 x 10^{-05}	1.97 x 10^{-05} ± 1.7 x 10^{-06}
MP/Hexanol	1.93 x 10^{-04} ± 2.5 x 10^{-05}	1.14 x 10^{-06} ± 1.2 x 10^{-07}
BP/IPM	6.30 x 10^{-04} ± 1.5 x 10^{-04}	1.28 x 10^{-06} ± 2.7 x 10^{-07}
BP/Hexanol	4.12 x 10^{-04} ± 5.2 x 10^{-05}	2.48 x 10^{-07} ± 4.4 x 10^{-08}

Conclusion

- Changes in partition and diffusion coefficients are attributed to interactions of the solute/ solvent with the membrane.

- The results highlight the importance of selecting individual permeants to match the physicochemical nature of the penetrants in order to maximise penetration enhancement.

- Further studies will investigate the influence of hydrogen bonding of solvents on permeability coefficients to probe the underlying reason for the discrepancies between the two techniques.

Acknowledgements

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