Understanding vehicle effects on penetration enhancement using attenuated total reflectance - Fourier transform infrared (ATR-FTIR) spectroscopy

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Introduction

One of the major challenges in topical drug delivery is to improve the bioavailability of the active ingredient. A frequently used approach is to include chemical penetration enhancers in the formulation. Penetration enhancers are believed to work via different mechanisms though little is known of how they exert their action. Studying diffusion using ATR-FTIR spectroscopy is advantageous in that it allows separation of the diffusion coefficient (D) and partition coefficient (K) of the drug in the membrane more easily than can be achieved with conventional Franz cell analysis. A typical diffusion profile includes a lag and exponential phase related to the diffusion of the permeant and a plateau related to the partitioning of the permeant into the membrane.

Aims

This aim of this study is to evaluate the effect of 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 gain an understanding of the effects of vehicles on penetrants with different lipophilicities. The vehicles were chosen to allow structure-activity relationships to be explored. Silicone membrane 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 fitted with an ATR accessory zinc selenide crystal (Figure 2). The silicone membranes were received as a gift from Dow Corning. IPIS and ISIS were also received as gifts from Uniqema. All other materials were obtained from Sigma.

Silicone membranes were pre-soaked in each solvent for 24 hours and mounted on the ATR crystal ensuring close contact. A specially designed aluminium trough was placed on top of the membrane and sealed with silicone grease. Saturated solutions of MP and BP in the 6 solvents were performed at ambient temperature. The saturated solution was then added to a trough on top of the membrane. An aluminium lid was placed on top sealed with silicone grease. The ATR-FTIR imaging experiments were performed at ten scans every 40 seconds with a resolution of $2cm^{-1}$ and an average spectrum was produced at each time point.

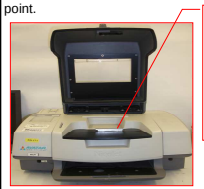


Figure 1. Nicolet Avatar 360 spectrometer

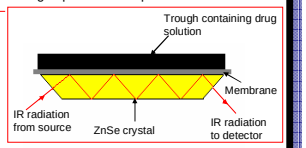


Figure 2. Illustration of the bulk diffusion ATR-FTIR setup to investigate the diffusion of MP and BP across membranes.

Solvent uptake was determined gravimetrically. MP and BP saturated solubilities in the different solvents were determined by UV spectroscopy. Data analyses were performed using OPUS 5.5 and Scientist® software.

Results and Discussion

Typical Fickian diffusion profiles were obtained for MP and BP in the 6 different solvents. These data were successfully modelled using Scientist® to obtain diffusion coefficients for MP and BP. Scientist® uses solutions to Fick's second law of diffusion obtained by the Laplace transform method to model the experimental data (Figure 4).

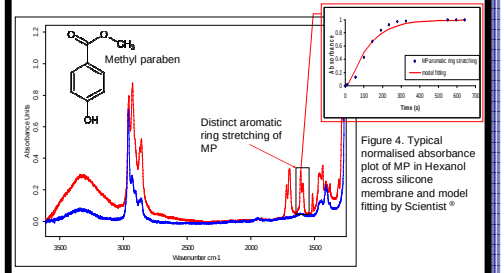


Figure 4. Typical normalised absorbance plot of MP in Hexanol across silicone membrane and model fitting by Scientist ®

Figure 3. ATR-FTIR spectra of MP in Hexanol (Red) through pre-soaked Silicone membrane (Blue)

It was found that in general, vehicles which were highly sorbed by the membrane altered its properties increasing the diffusion coefficient of the permeant.

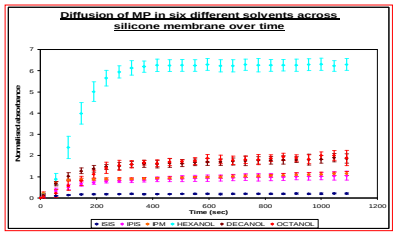
Differences in the plateau absorbance values of MP and BP in the different vehicles were observed. These values are related to the concentration of MP and BP in the membrane and were thus strongly influenced by the solubility of the permeant in the vehicle and the uptake of vehicle into the membrane.

Solvents	Solubility		FTIR DATA				SVU* (ml)		
	MP	BP	MP		BP			MP	BP
	Conc. (mg/ml)		P	D	P	D		SVU* x Solubility (mg)	
ISIS	9.85	62.49	0.19	4.18E-07	3.15	1.86E-07	0.05	0.50	3.16
IPIS	17.77	108.55	0.88	2.87E-07	7.59	3.43E-07	0.42	7.43	45.40
IPM	22.24	144.63	0.90	9.18E-07	11.22	5.02E-07	0.66	14.68	95.50
HEXANOL	129.98	385.60	6.25	2.62E-07	11.26	3.10E-07	0.13	16.56	49.13
OCTANOL	148.36	303.74	1.56	1.90E-07	3.86	2.41E-07	0.08	11.21	22.94
DECANOL	78.47	293.66	1.61	2.94E-07	1.24	1.89E-07	0.05	3.72	13.93

*Specific volume uptake

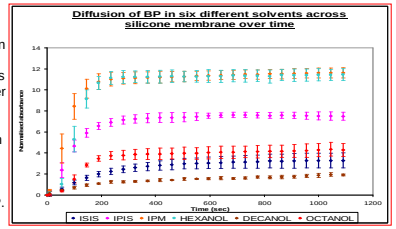
Table 1. The measured solubility, calculated diffusion coefficients (D), plateau (P), and specific volume uptake (SVU) of MP and BP in the 6 solvents

Normalised diffusion profiles obtained for MP and BP in the 6 different solvents using the aromatic ring stretching frequencies are shown in Figure 5 and Figure 6 respectively.



← Figure 5. Diffusion profiles of MP in the 6 solvents across silicone membrane.

↓Figure 6. Diffusion profiles of BP in the 6 solvents across silicone membrane



BP (log *P* 2.71) is more lipophillic than MP (log *P* 1.96). MP has a much higher solubility in more polar solvents such as Hexanol, Octanol and Decanol relative to BP. 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. The 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. The results highlight the importance of selecting individual enhancers to match the physiochemical nature of the penetrant in order to maximise penetration enhancement.

Conclusion

The data suggested that to maximise penetration, different vehicles should be chosen for different penetrants based on the penetrants lipophilicity. ATR-FTIR is an effective technique in understanding the mechanistic role by which different penetration enhancers affect diffusion across membranes.

Future work will examine the correlation of the ATR-FTIR data with that of Franz diffusion cells to improve our understanding of the effects of penetration enhancers on the membrane transport process.

Acknowledgements

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