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Research paper

ATR-FTIR spectroscopy and spectroscopic imaging of solvent and permeant diffusion across model membranes

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ABSTRACT

The uptake and diffusion of solvents across polymer membranes is important in controlled drug delivery, effects on drug uptake into, for example, infusion bags and containers, as well as transport across protective clothing. Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) spectroscopy has been used to monitor the effects of different solvents on the diffusion of a model compound, 4-cyanophenol (CNP) across silicone membrane and on the equilibrium concentration of CNP obtained in the membrane following diffusion. ATR-FTIR spectroscopic imaging of membrane diffusion was used to gain an understanding of when the boundary conditions applied to Fick's second law, used to model the diffusion of permeants across the silicone membrane do not hold. The imaging experiments indicated that when the solvent was not taken up appreciably into the membrane, the presence of discrete solvent pools between the ATR crystal and the silicone membrane can affect the diffusion profile of the permeant. This effect is more significant if the permeant has a high solubility in the solvent. In contrast, solvents that are taken up into the membrane to a greater extent, or those where the solubility of the permeant in the vehicle is relatively low, were found to show a good fit to the diffusion model. As such these systems allow the ATR-FTIR spectroscopic approach to give mechanistic insight into how the particular solvents enhance permeation. The solubility of CNP in the solvent and the uptake of the solvent into the membrane were found to be important influences on the equilibrium concentration of the permeant obtained in the membrane following diffusion. In general, solvents which were taken up to a significant extent into the membrane and which caused the membrane to swell increased the diffusion coefficient of the permeant in the membrane though other factors such as solvent viscosity may also be important.

1. Introduction

The ATR-FTIR spectroscopic technique to study the diffusion of permeants is well established in the pharmaceutical field [1–4]. It allows the separation of the diffusion and partition coefficient of permeants into the membrane, and the effect of penetration enhancers on these properties to be achieved more easily than can be obtained using conventional diffusion cell experiments. Chemometric analysis allows the diffusion of several different components to be followed simultaneously and physical changes in the membrane itself can also be monitored. A typical Fickian diffusion plot obtained from this type of experiment will be sigmoidal and includes a lag phase and an exponential phase related to a permeant's diffusion and a plateau related to its partitioning. Harrison et al. [5] used this technique to show that Transcutol® works mainly through increasing the solubility of a permeant in the stratum corneum, whereas Azone® exerts its actions through increasing its diffusivity. Dias et al. [3] have used ATR-FTIR spectroscopy on model silicone membranes to demonstrate the importance of the solubility of a permeant in a vehicle to the plateau absorbance and Moser et al. [6] were able to demonstrate the effect of supersaturation on the membrane concentration of permeant using this technique.

However, incidences of ATR-FTIR spectroscopic diffusion data not fitting the applied boundary conditions used for the diffusion model have been reported, where the observed profile showed a continual rise rather than a plateau [4]. In this study, ATR-FTIR spectroscopic imaging has been used to gain an understanding of such situations and an account of when the boundary conditions applied to the diffusion model are not met has been given. Furthermore, for solvent systems where the data could be modelled using Fick's second law of diffusion, the effects of solvent (enhancer) uptake into the membrane on the diffusion coefficient of a permeant

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and the equilibrium concentration of the permeant in the membrane have been investigated.

These factors are important in considerations of drug delivery across membranes in controlled delivery devices, for the uptake of drugs into containers, where the solvent may simply be water, e.g. infusion bags, and the transport of materials across protective clothing, e.g. gloves. It is also important to determine the significance of the different processes in the interpretation of data generated in more complex systems such as bio-membranes.

Various studies have reported the use of polydimethylsiloxane (PDMS) membrane to study the influence of topical and transdermal formulation components on solute transport [7–10]. Although synthetic polymer membranes cannot fully replicate in vivo conditions, they have also been shown to be useful in identifying general trends for solute transport in skin [11,12]. These model membranes are therefore employed to give insight into the general mechanisms through which solvents modify the membrane transport process. Such experiments are performed in the expectation that an understanding of the general principles underpinning transport across the model membrane will also be relevant to transport across biological membranes.

Novel chemometric and imaging techniques have been applied to understand these phenomena and to aid the interpretation of extant data in the literature, e.g. the continual rise in signal where a plateau is expected in the diffusion data presented by McCarley and Bunge [4].

2. Materials and methods

2.1. Materials

4-Cyanophenol (CNP), hexanol, octanol, decanol, propylene glycol and polyethylene glycol (PEG) 400 were obtained from Fisher Scientific (Loughborough, UK). 2-Ethyl hexyl salicylate (OSAL) and isopropyl myristate (IPM) were obtained from Sigma–Aldrich (Poole, UK), isostearyl isostearate (ISIS), isopropyl isostearate (IPIS) and isopropyl palmitate (IPP) were received as gifts from Uniqema (Gouda, The Netherlands) and propylene glycol laurate (PGL) was received as a gift from Gatteffosse (Binfield, UK). Silicone membrane of 80 μm thickness was also received as a gift from Dow Corning (Seneffe, Belgium). CNP was chosen as a model permeant because it possesses a CN group which absorbs in a spectrally silent region of the silicone membrane which also does not overlap with the spectra of any of the solvents used. The solvents were chosen to allow structure activity relationships to be elucidated between the effect of the solvent on the membrane, the diffusion coefficient of the penetrant in the membrane and the concentration of the penetrant in the membrane.

2.2. Methods

2.2.1. Diffusion experiments

Diffusion experiments were conducted at ambient temperature (21 ± 2 °C) using a Bruker Tensor 27 FTIR spectrometer fitted with a Specac multibounce ATR accessory with a Zinc Selenide (ZnSe) crystal. Ten scans were taken every 40 s with resolution of 2 cm^{-1} and an average spectrum was produced at each time point. All experiments were repeated five times. Spectral analysis was performed using Opus® 5.5 software (Bruker Optics).

Silicone membranes were pre-soaked for 24 h in the solvent of interest at ambient temperature (21 ± 2 °C). This prevents any effects of solvent permeation into the membrane affecting the solute diffusion profile as described previously by Dias et al. [3]. Pre-soaked membranes were blotted dry and placed on the ZnSe crystal and intimate contact between the membrane and crystal was assessed visually. An aluminium trough constructed specifically for this purpose was placed on top of the membrane and was sealed with silicone grease. A saturated drug solution was applied to the membrane and an aluminium lid was placed on top, again sealed with silicone grease. The diffusion of CNP was followed through integration of the CN peak at 2230 cm^{-1}. Saturated solutions of CNP were used to control the activity of CNP in the vehicle. This experimental design is similar to that described by Pellett et al. [2].

2.2.2. Spectroscopic imaging

ATR-FTIR imaging experiments were performed using a Varian imaging system (Bio-Rad 60A) coupled with a 64 × 64 focal plane array (FPA) detector. The arrangement of this approach is described in more detail elsewhere [2]. The FTIR spectrometer was fitted with a single-reflection ATR accessory (Oil Analyser Specac Ltd.) with a ZnSe crystal. The FTIR images were obtained by co-adding 256 scans at 8 cm^{-1} resolution with a spectral range from 4000 to 900 cm^{-1}. The experimental protocol was the same as that described in the diffusion studies section mentioned earlier. The spectral images were then obtained by plotting the distribution of the integrated absorbance of the CN band of CNP (CN peak at 2230 cm^{-1}). In the images presented, the colour red represents high absorbance which equates to a higher concentration of CNP having passed through the membrane.

2.2.3. Modelling of diffusion data

Assuming that the Beer–Lambert law applies, the increase in IR absorbance associated with either the drug or solvent molecule with time is directly related to the concentration of the species in the membrane. The increase in absorbance can therefore be modelled by fitting appropriate boundary conditions to Fick's second law,

$$\frac{\partial C}{\partial t} = -D\frac{\partial^2 C}{\partial x^2} \tag{1}$$

where C is the concentration of the diffusing species in the membrane, D is the diffusion coefficient of the diffusing species, x is the diffusional pathlength, and t is time. Previous studies using the ATR-FTIR spectroscopic technique have used the method of separation of variables to solve Eq. (1) to obtain diffusion coefficients for permeant molecules in model membranes and human skin [4,13,14]. In this study, the method of Laplace transformation was used. The diffusion coefficients were obtained by fitting the normalised data (obtained by dividing the absorbance by the plateau absorbance) with Micromath Scientist® 3.0 for Windows, using the following Laplace transformation:

$$\frac{A}{A_\infty} = \frac{\overline{C}}{\overline{C}_\infty} = \frac{\cosh\left(h \cdot \sqrt{\frac{s}{D}}\right)}{S} \tag{2}$$

where A is the absorbance, A_∞ is the absorbance at infinite time, $\overline{C}$ is the concentration in the Laplace domain, $\overline{C}_\infty$ is the concentration in the Laplace domain at infinite time, s is the Laplace variable and h is the diffusional pathlength. The diffusional pathlength was taken as the pre-soaked membrane thickness.

2.2.4. Chemometric data analysis

Chemometric data analysis was used to separate changes in the spectral profile of the solvent from that of CNP and silicone membrane. The multivariate, target factor analysis approach was used to deconvolute the solvent profile. This method is based on the numerical decomposition method Factor Analysis and has the advantages of being able to be used without requiring any external calibration, which is difficult to perform using the diffusion experimental set-up. The analysis was conducted using InSight software

(DiKnow Ltd., Kent, UK). The algorithms and methods used by this programme are described in more detail elsewhere [15]. For extraction of the solvent profiles, the 2865–2770 cm^{-1} spectral region was used for both IPM and octanol, and the 945–898 cm^{-1} region was used for propylene glycol.

2.2.5. Solvent uptake studies

Solvent uptake by the silicone membrane was determined gravimetrically at ambient temperature. Approximately 0.25 g of silicone membrane was weighed and the thickness measured. Following soaking in the appropriate solvent for 24 h, the silicone was blotted dry, reweighed and any change in membrane thickness was recorded using an external digital micrometer, 0–25 mm (RS Components, Corby, UK).

2.2.6. Solubility studies

The solubilities of CNP at ambient temperature in the different solvents except for OSAL were measured by UV absorbance at 249 nm. The solubility of CNP in OSAL was performed by HPLC using a UV detector (249 nm). A Hewlett Packard 1050 series instrument was used with a flow rate of 1 ml/min (Symmetry shield ODS 5 μm (15 cm × 4.6 mm) column (Waters, Elstree, UK) and mobile phase 25% acetonitrile 75% water, adjusted to pH 3.0 with acetic acid). Saturated solutions of CNP were prepared using constant agitation for 24 h. An aliquot of this was then centrifuged to separate any solid material and the supernatant was sampled, diluted as necessary and analysed.

3. Results

Fig. 1 shows IR spectra taken at several time points of the diffusion of CNP in octanol across pre-soaked silicone membrane. The increase of the CN absorbance band can clearly be seen and the change in absorbance of this band can be used to follow the diffusion of CNP across the membrane. Typical examples of sigmoidal diffusion profiles of CNP in several solvents are shown in Fig. 2. Short lag times were observed because of the rapid diffusion of the CNP and the relatively thin silicone membrane. The data show that for CNP in IPM, the diffusion of CNP across the silicone membrane appears to be faster than for that of CNP in decanol, suggesting that IPM lowers the membrane's diffusional resistance. Significant differences are observed in the plateau levels of the diffusion plots, indicating different equilibrium concentrations of CNP in the membrane. The plots shown in Fig. 2 can be modelled using Eq. (2) to obtain diffusion coefficients for CNP. Fig. 3 shows a typical normalised plot of CNP in IPM along with the Scientist generated model fitting, from which the diffusion coefficient is obtained.

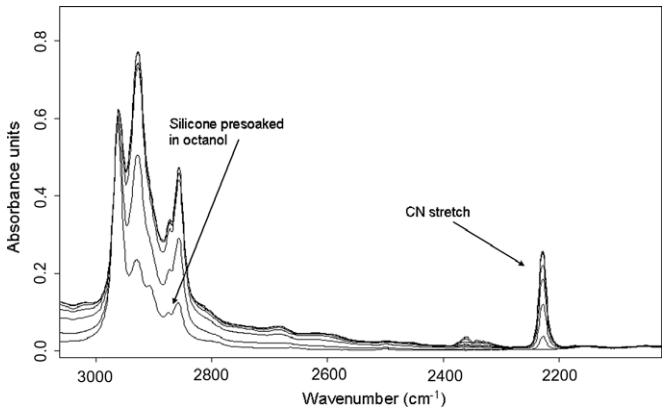

Fig. 1. ATR-FTIR spectra, taken as a function of time of a CNP in octanol experiment. The CN absorbance can be seen to increase with time.

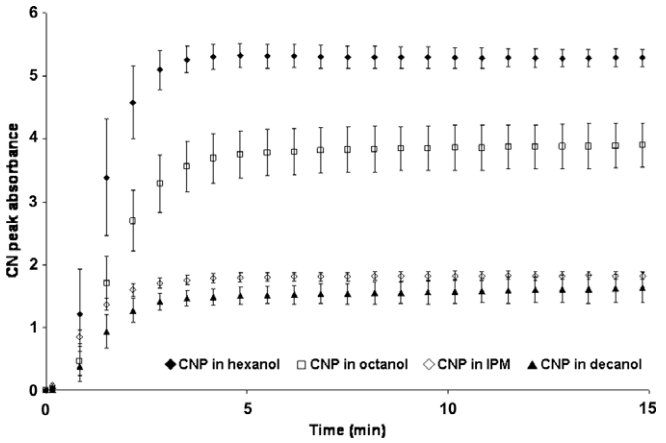

Fig. 2. Increase in CN peak absorbance with time of CNP in hexanol, octanol, decanol and IPM across silicone membrane. Error bars show the standard deviation ($n = 5$).

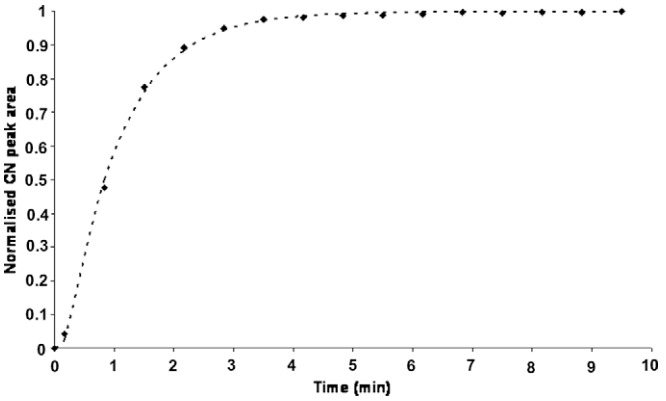

Fig. 3. Typical normalised diffusion profile of CNP in IPM across silicone membrane with model fitting. Data from each individual experiment was individually modelled to obtain a diffusion coefficient and the values averaged.

The plots obtained for CNP in some other solvents did not follow the expected profiles observed in Fig. 2. For example, Fig. 4 shows diffusion of CNP in IPIS, PEG 400 and propylene glycol. In contrast to the CNP in IPIS, CNP in PEG 400 shows the exponential phase but also a continual rise rather than a plateau. The CNP in PEG 400 experiment was, additionally, conducted for 24 h (data

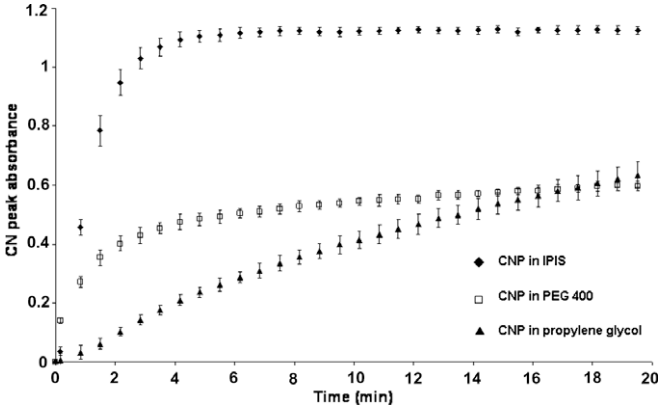

Fig. 4. Increase in CN peak absorbance with time of CNP in IPIS, PEG 400, and propylene glycol across silicone membrane. Error bars show the standard deviation ($n = 5$).

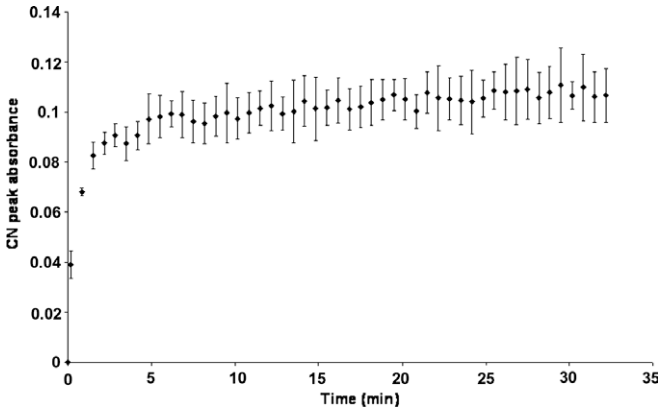

Fig. 5. Increase in CN peak absorbance with time of CNP in water across silicone membrane. Error bars show the standard deviation ($n = 5$).

not shown) to monitor the observed gradual increase in absorbance. Over 24 h, there was a continual but small increase in absorbance with time. The rate of this increase decreased over the 24 h. The change in the plateau absorbance is not related to a time dependent change in the diffusion coefficient. A similar result is also observed for CNP in water (Fig. 5). The CNP in propylene glycol experiment shows a continual rise which is not consistent with Fickian diffusion using the selected boundary conditions. In order to quantify the data in which the maximum change in absorbance with time was observed, an initial 20-min period was selected to provide an approximation of the diffusion coefficient of CNP for the different solvents.

In an attempt to understand this, chemometric data analysis was used to extract the evolution profile of the solvents. Fig. 6 shows normalised extracted spectral profiles for propylene glycol, octanol and isopropyl myristate. The profiles were normalised by setting the evolution concentration of each solvent after 20 min to 1 h. This allows the profiles to be compared on the same scale. As the membranes were pre-soaked, little change in the solvent profile would be anticipated. A small decrease in the IPM and octanol profiles is observed following the initial rise. It is likely that this is a result transient change in the solvent levels in the membrane following application of a solution containing CNP. The IPM and octanol profiles show rapid increases and then are relatively constant, whereas the propylene glycol profile shows a continuous rise similar to that of the CNP. In order to investigate this further, ATR-FTIR spectroscopic imaging was applied to spatially resolve different components in the sample and with the experimental design used in this study the spatial resolution was approximately 40 μm. The images show that for CNP in IPM after approximately 15 min the concentration of CNP across the membrane is fairly homogeneous (Fig. 7b). For CNP in propylene glycol, the image (Fig. 7d) shows very little CNP after 5 h. With the CNP in propylene glycol system, the imaging experiment was allowed to run for a longer period of time than was performed for the multiple bounce ATR-FTIR spectroscopic measurements. This was done to see if there was an increase in the CNP concentration with time. At this point, it has to be noted that the imaging system has only one reflection compared to several reflections in the multiple bounce ATR-FTIR system, and low CN absorbances cannot be detected. After 5 and 24 h, the CN absorbance is observed only in discrete pools rather than throughout the membrane.

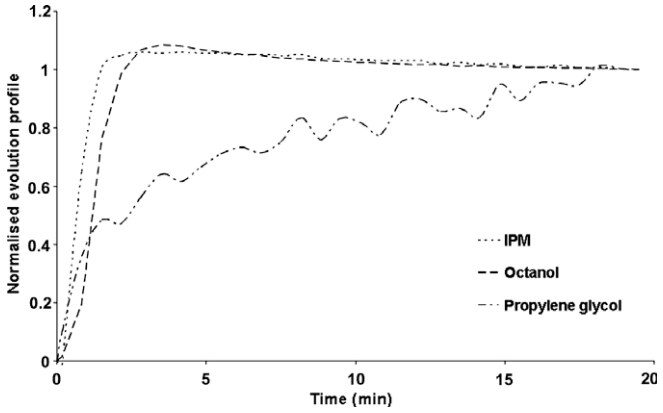

Fig. 6. Typical normalised evolution profiles of IPM, octanol and propylene glycol in pre-soaked silicone membranes.

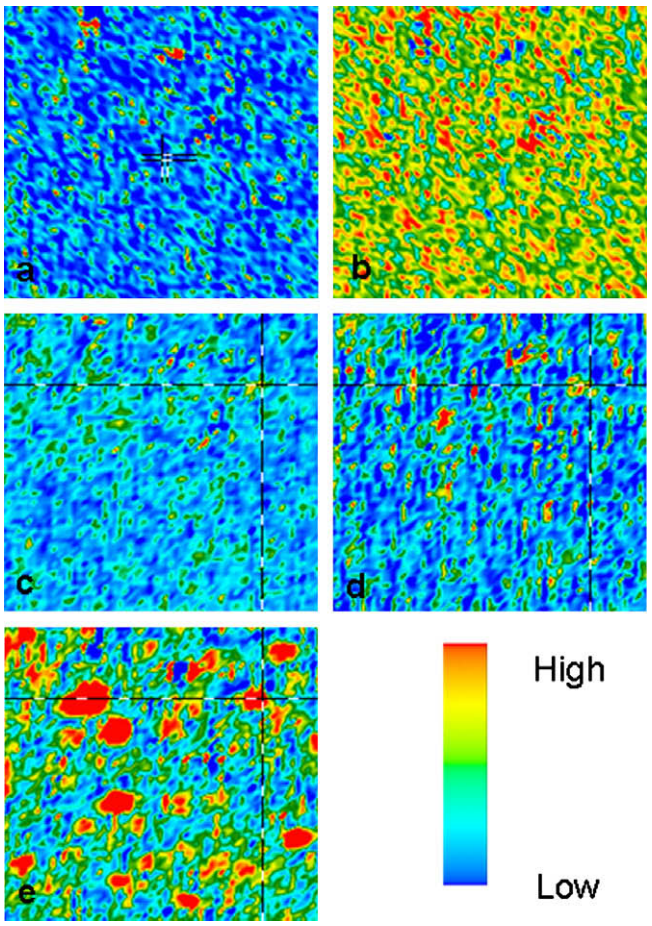

Fig. 7. ATR-FTIR spectroscopic images of diffusion experiments of CNP in propylene glycol and IPM. Image colour indicates intensity of CN stretching, with blue being the lowest and red the highest. The scale bar shows colours corresponding to high and low concentrations. Picture (a) IPM soaked silicone membrane, (b) CNP in IPM experiment after 15 min, (c) propylene glycol soaked membrane, (d) CNP in propylene glycol experiment after 5 h, (e) CNP in propylene glycol experiment after 24 h. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Solvent uptake experiments were performed to elucidate the mechanisms and understand why some solvents fitted the Fickian model while others did not. The results are shown in Table 1 which also describes the change in membrane thickness on soaking in the particular solvent, the solubility of CNP in the solvent, the plateau value of the diffusion plot and the calculated CNP diffusion coefficient. In general, the solvents for which the diffusion of CNP across silicone membrane could be fitted to a Fickian model, such as IPM and octanol were also those that were taken up by the membrane to a larger extent.

Table 1
The solubility of CNP in each solvent, the solvent uptake into silicone membrane and the associated change in membrane thickness, the plateau absorbance of CNP in the membrane pre-soaked with each solvent and the calculated diffusion coefficient for CNP across the pre-soaked membrane (mean values ± the standard deviation, $n = 5$).

Solvent	CNP solubility (mol/dm^3)	Silicone solvent uptake (cm^3/g)	Average change in membrane thickness (μm)	Plateau absorbance	Diffusion coefficient ($\times 10^{-7}$ cm^2/s)
Hexanol	2.882	0.1274 ± 0.0061	5.0 ± 1.1	5.27 ± 0.178	4.3 ± 0.9
Octanol	2.193	0.0755 ± 0.0036	0.0 ± 1.2	3.82 ± 0.36	3.6 ± 0.4
Decanol	1.672	0.0474 ± 0.0047	−1.0 ± 2.7	1.53 ± 0.161	3.4 ± 0.6
Isopropyl myristate	0.496	0.6603 ± 0.0124	9.4 ± 1.7	1.82 ± 0.067	4.6 ± 0.4
Isopropyl isostearate	0.496	0.4183 ± 0.0033	10.8 ± 1.8	1.12 ± 0.013	5.2 ± 0.4
Isostearyl isostearate	0.387	0.0506 ± 0.0052	4.6 ± 1.1	0.29 ± 0.026	3.9 ± 0.4
Octyl salicylate	0.126	0.2121 ± 0.0254	2.8 ± 1.5	0.31 ± 0.018	5.6 ± 0.9
Propylene glycol laurate	1.286	0.0635 ± 0.0096	0.6 ± 2.1	1.68 ± 0.28	2.3 ± 0.1
Polyethylene glycol 400	3.151	0.0103 ± 0.0089	0.0 ± 1.0	0.49 ± 0.03	5.6 ± 0.3
Water	0.123	0.0022 ± 0.0009	0.2 ± 1.1	0.095 ± 0.008	6.3 ± 0.6
Isopropyl palmitate	0.462	0.4658 ± 0.0352	9.6 ± 2.3	1.41 ± 0.016	6.2 ± 0.2
Propylene glycol	3.252	0.0013 ± 0.0005	−0.5 ± 0.6	[a]	[a]

[a] No plateau observed and not possible to calculate a diffusion coefficient.

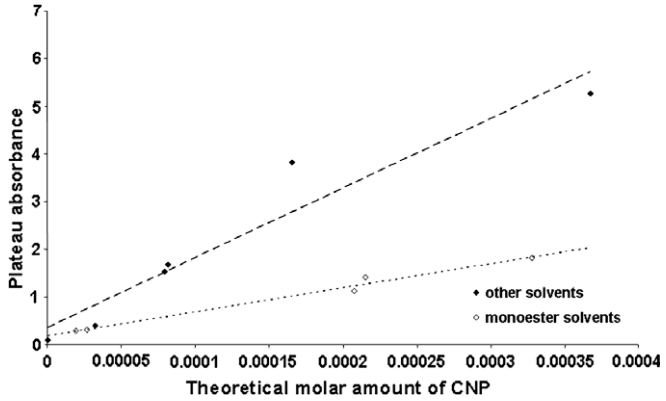

Fig. 8. Plot of plateau absorbance against the specific theoretical uptake of CNP into the silicone membrane.

There are a wide range of plateau absorbance values for CNP in different solvents given in Table 1. In an attempt to ascertain the main influences underlying this, Fig. 8 shows a plot of the plateau absorbance of the diffusion plots against the specific theoretical amount of drug taken up into the membrane. This is calculated from the solubility of the drug in the particular solvent and the solvent uptake into the membrane and assumes that the membrane itself has no effect on the CNP solubility. In addition, it is assumed that the swelling of the membrane has a negligible effect on the volume of (dry) membrane which is applied to the crystal. The data appear to lie broadly on two separate straight lines, with monoesters such as IPM and IPIS lying on a separate line to other solvents such as the alcohols. Two best fit straight lines have been constructed in Fig. 8, one through the monoesters (IPM, IPIS, IPP, ISIS and OSAL) and one through the other solvents.

4. Discussion

The diffusion of CNP in the majority of the solvents tested in this study across silicone membrane produce the expected sigmoidal diffusion profile. Fig. 3, which shows the model fitting of a typical dataset, indicates that the data are described well by the Fickian model. Similar results have been obtained by other authors for the diffusion of permeants across silicone membrane [2,14,15]. However, some CNP profiles such as that of CNP in propylene glycol could not be described by the Fickian model, whereas others, CNP in PEG 400 and CNP in water, exhibited the expected exponential phases, but then showed a continuous rise rather than a plateau. This effect has been reported previously for CNP in water across silicone membranes which were cured on the crystal surface [4]. To help explain why the CNP diffusion profiles, in some solvents, fitted the diffusion model and others did not, chemometric data analysis was used to separate the diffusion profiles of the solvents from the CNP and silicone membrane. As the silicone membranes were pre-soaked in the solvent prior to the diffusion experiment little change in the profile was expected. For solvents in which the CNP diffusion could be fitted with a Fickian model such as IPM and octanol, the solvent profile was observed to show a rapid rise and then to be relatively constant. The rapid increases observed are likely to be a result of restoration of the surface concentration following the blotting procedure prior to application of the membrane on the ATR crystal. In contrast, for propylene glycol in which the CNP diffusion profile did not fit the Fickian model, the solvent profile continually increased such that it mimicked that of CNP. McCarley and Bunge [4] also found that the continuous rise in the diffusion profile observed for CNP in water correlated with increased water absorption peaks. The diffusion model for the ATR-FTIR spectroscopy experiment assumes that there is zero flux at the membrane ATR crystal interface. If this assumption holds the solvent, diffusion profile cannot continue to increase but must reach a plateau. ATR-FTIR spectroscopic imaging was used to gain insight into the reasons why the assumptions used for the diffusion model did not hold. The data indicate for CNP in IPM that a reasonably homogeneous distribution of CNP is obtained throughout the membrane after 15 min. This correlates well with the results shown in Fig. 2 where equilibrium is achieved within 15 min. For CNP in propylene glycol, the low CN absorbances cannot be detected in the same time scale as the diffusion experiments using a multiple bounce ATR-FTIR accessory. However, as the CNP profile in propylene glycol was observed to continually rise, it was hypothesised that CNP would be observed over a longer timescale. After 5 and 24 h, the CNP is observed to exist predominantly in discrete pools rather than throughout the membrane. This suggests that the solvent is accumulating between the ZnSe crystal and the membrane surface and therefore the boundary conditions used in the diffusion model, which assume that the membrane is loaded with the permeant and there is no transport out of the membrane at the crystal interface, are not correct. Therefore, the data would not be expected to fit the diffusion model. The data indicate that solvents that are taken up to a larger extent by the membrane such as IPM and decanol (interactive solvents) give typical Fickian diffusion profiles. Propylene glycol which is taken up by the membrane to a much lesser extent (less interactive) and in which CNP has a

high solubility does not fit the Fickian model. Intermediate solvents such as PEG 400, where a small amount of solvent is taken up into the membrane and water, where the solubility of CNP is relatively low show continual rises, rather than plateaus. To interpret the effects of penetration enhancers on the transport of a permeant across a membrane, it is useful to fit the data to a Fickian model which allows separation of the partitioning and diffusion aspects of the transport process. The data obtained from the CNP in PEG 400 and water experiments are still useful however, as the plateau absorbance value can be estimated from where the exponential phase is observed to finish and the continuous rise starts. An approximate value for the diffusion coefficient can also be obtained by modelling the first part of the curve, using a non-normalised form of Eq. (2).

The plateau absorbance level obtained in a diffusion experiment is related to the concentration of CNP in the membrane, and is related to the solubility of CNP in the membrane. Dias et al. [3] have previously highlighted the significance of saturated solubility for the observed plateau absorbance. In the current work, the importance of uptake of the vehicle into the membrane on the plateau absorbance has also been demonstrated. For example CNP in IPM shows a similar CN stretch plateau absorbance to CNP in decanol, whereas the solubilities of CNP in the two vehicles are 0.50 and 1.67 mol/dm^3 respectively (Table 1). The uptake of IPM into the membrane is significantly larger than that of decanol, however, and this is likely to lead to the similar plateau absorbances. Fig. 8 attempts to correlate the plateau absorbance of the diffusion plots of CNP in the different solvents with CNP solubility in the solvent and the solvent uptake by the membrane. If a simple correlation existed all of the data points would be expected to lie on a single straight line. Instead the data lie on two separate lines with monoesters such as IPM and IPIS showing a separate trend to the other solvents. Nonetheless, the positive correlations in Fig. 8 suggest that both solvent uptake and the solubility of permeant in the membrane affect the concentration of the permeant in the membrane at equilibrium. There are at least two likely reasons why the data appear to lie on two separate lines, with the monoester solvents typically exhibiting a lower CNP plateau absorbance for a given specific molar uptake of solvent. Firstly, it is likely that the assumption that any swelling of the membrane caused by the solvent is negligible is not valid. IPM for example, increased the membrane thickness by approximately 12%. Assuming the swelling is equivalent in all directions, this will result in a significant increase in membrane volume, hence, the plateau absorbance would be lower than if the membrane swelling did not occur. In addition, monoesters such as IPM have been shown to interact strongly with silicone membrane [10] and this interaction may lower the solubility of the drug in the solvent, relative to that in the absence of silicone membrane. Previously Pellett et al. [2] were able to use the plateau absorbance from a CNP in water experiment across silicone membrane to obtain a reasonable correlation between the CNP permeability coefficient calculated with ATR-FTIR spectroscopy and that calculated from conventional Franz diffusion cells. It is thought therefore that a higher plateau absorbance will result in higher fluxes being obtained in conventional Franz cells for situations when the diffusion coefficients of the permeants are similar. However, the relationship between permeant concentrations in the membrane observed with ATR-FTIR spectroscopy using more interactive solvents and the concentration or activity of the permeant in the membrane as assessed by a Fickian analysis of data generated by conventional diffusion cells remains unclear. This will be assessed in future studies.

No clear trends are evident in the diffusion coefficient of CNP in the different solvents across pre-soaked membranes. It is generally true that for those solvents which are taken up into the membrane to a significant extent such as IPM, IPIS and IPP, higher CNP diffusion coefficients are obtained than for solvents which are less well taken up such as decanol. This is anticipated as solvents which cause the membrane to swell should lower its diffusional resistance. However, this is not exclusively the case. The diffusion coefficient for CNP in water which does not swell the membrane appreciably is high and the lowest value was obtained in PGL. It is likely that other factors which also influence the diffusion coefficient such as the viscosity of the solvent and possibly the presence of any solvation shell around the CNP molecule which may alter the effective radius of the diffusing species have a significant effect on the calculated diffusion coefficient.

5. Conclusions

The effects of a range of solvents on the diffusion of CNP across silicone membrane and on the equilibrium concentration of CNP obtained in the membrane were investigated using ATR-FTIR spectroscopy. ATR-FTIR spectroscopic imaging experiments were subsequently conducted to follow diffusion across silicone membrane to give insight into situations when the diffusion model used with a conventional ATR-FTIR spectroscopic approach did not fit the experimental data. The imaging experiments indicated that the presence of small discrete solvent pools between the membrane and the crystal may have a significant effect on the diffusion profile of the permeant. This is particularly the case when the drug has a high solubility in the solvent and the solvent is not taken up well into the membrane. A Fickian model could be used to fit the majority of systems used in this study and the influence of different solvents on the equilibrium concentration of CNP in silicone membrane and the diffusion coefficient of CNP in the membrane has been investigated. A large membrane CNP concentration was obtained by solvents which show good uptake into the membrane and in which the permeant has a high solubility. Such solvents should show considerable penetration enhancement. Evaluation of the effect of different solvents on the diffusion coefficient of CNP in the membrane was performed by fitting the data with a solution to Fick's second law using appropriate boundary conditions. In general, solvents which caused the membrane to swell showed faster diffusion coefficients, though other factors also appear to be important. The approaches used in this paper are also important in the interpretation of similar studies conducted in more complex biological membranes.

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