International Journal of Pharmaceutics 396 (2010) 134–139

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Thermodynamic considerations of solvent/enhancer uptake into a model membrane

W.J. McAuley[1], G. Oliveira, D. Mohammed, A.E. Beezer, J. Hadgraft, M.E. Lane*

Department of Pharmaceutics, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom

ARTICLE INFO

Article history:
Received 19 April 2010
Received in revised form 7 June 2010
Accepted 19 June 2010
Available online 25 June 2010

Keywords:
Solvent uptake
Membrane partitioning
Temperature effects
Thermodynamics
Polydimethylsiloxane

ABSTRACT

The aim of this study was to conduct a thermodynamic analysis of the uptake of solvents into a model membrane as a precursor to skin transport studies. The investigation was designed so that the methodology may be applied to analyse data produced from measurement of the uptake of enhancers into skin. The uptake of a series of alcohols into polydimethylsiloxane (silicone) membranes in the temperature range 5–45 °C was examined. A thermodynamic analysis of the data was performed to provide fundamental insight into the uptake process. A simple structure activity relationship was found to exist for the uptake of alcohols with a carbon chain length greater than four, with additional methylene groups exponentially decreasing the equilibrium uptake. Two separate straight lines were observed in the van't Hoff plot for the equilibrium solvent uptake above and below 16 °C.

The two separate straight lines in the van't Hoff plot suggest a change in the mechanism of solvent uptake and solvent structure in the membrane above and below 16 °C. This is likely to have implications for the effect of the solvents on the partitioning of drugs into the membrane and will be used to provide insight into dynamic measurements of the effect of temperature on the transport of drug molecules in the same vehicles, across the membrane. The analysis described here should provide a useful methodology for investigating the uptake of solvents into model membranes.

1. Introduction

Early work investigating the effect of temperature on solute permeation across skin was performed in the 1950s and 1960s (Mali, 1956; Piotrowski, 1957; Blank and MacFarlane, 1967; Fritsch and Stoughton, 1963). However the area has not been fully explored and more recently there has been a marked resurgence of interest. This interest is motivated by the potential of using temperature as a means to modify the delivery of drugs across the skin and to gain an understanding of the effects of environmental thermal stresses on skin absorption (Ogiso et al., 1998; Jones et al., 2003; Jain and Panchagnula, 2003; Burgess et al., 2005).

Previous studies have focussed mainly on the effect of temperature on the transport of the drug molecule itself. However the equilibrium uptake into the stratum corneum of any formulation components in which the drug molecule is contained would be expected to vary with temperature. The uptake and interaction of formulation components, notably penetration enhancers with skin is of considerable importance for the delivery of drugs from topical dosage forms. The effects of temperature on equilibrium uptake of these components such as solvents and its implications for penetration enhancement have not been addressed previously and are the focus of this paper.

The application of an equilibrium parameter (time independent) to aid understanding of the transport of molecules across skin (a dynamic process) is commonly used already. One form of Fick's law used to model diffusion across membranes under steady state conditions is shown in Eq. (1):

$$J = \frac{DKC}{h}. \quad (1)$$

J is the drug flux, D is the diffusion coefficient, K the partition coefficient, h the membrane thickness and C the concentration of drug applied to the membrane. A partition coefficient is an equilibrium parameter and is often introduced into Fick's law as use of the equation requires knowledge of the concentration of drug in the superficial layer of the membrane. Typically this is unknown and so the partition coefficient relates the concentration of the applied vehicle which is readily known to that of the superficial layer. The uptake of formulation components into a membrane may alter the partitioning of the drug into and diffusion across the membrane and the effect of temperature on this uptake is important for a complete understanding of the effect of temperature on drug transport. Burgess et al. (2005) have described a method, based upon Eq.

* Corresponding author. Tel.: +44 207 753 5821; fax: +44 870 165 0275.
E-mail address: majella.lane@btinternet.com (M.E. Lane).
[1] Current address: The School of Pharmacy, University of Hertfordshire, College Lane, Hatfield AL10 9AB, United Kingdom.

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.06.040

(1) to separate the dynamic and equilibrium aspects of diffusion across membranes. However before conducting such an analysis, an understanding of the true equilibrium process should inform interpretation of the data associated with dynamic measurements.

In this study the effect of temperature on the uptake of formulation components (solvent) is investigated to gain an understanding of the role that temperature has on the vehicle–membrane interaction and to give insight into possible temperature effects on the membrane itself. Silicone has been selected as a model membrane as it should allow a mechanistic understanding of membrane behaviour to be elucidated more simply than could be achieved using more complex heterogeneous skin tissue. A series of n-alcohols was used as model vehicles to explore any structure activity relationships as their effects on drug transport across silicone membranes have been investigated previously, though not at different temperatures (Twist and Zatz, 1988). They should, therefore, provide a convenient starting point for this study. By performing the experiments over a range of temperatures thermodynamic analysis will allow insight into the interaction of vehicles with membranes through investigation of the enthalpy (ΔH) and entropy (ΔS) of the uptake process. The importance of ΔH in the uptake process has been highlighted previously (Burgess et al., 2005). For example in situations where the solvent, enhancer or drug uptake is enthalpically driven, if ΔH is negative then uptake will be increased at lower temperatures. Transport of a drug across model membranes and skin depends on the rate of diffusion, which increases with temperature. Therefore careful consideration of what the temperature effects are on both the diffusion of any drug or solvent and its partition/uptake into skin/membrane are required if maximum drug permeation is to be obtained in response to temperature modulation.

2. Materials and methods

2.1. Materials

Silicone membrane of 250 μm thickness was obtained from Samco (Nuneaton, UK). Of the alcohols (all >98% purity) ethanol and butanol were supplied by VWR (Lutterworth, UK) whilst propanol, pentanol, hexanol, heptanol, octanol, nonanol and decanol were supplied by Sigma–Aldrich (Poole, UK).

2.2. Membrane solvent uptake studies

The uptake of different alcohols into the silicone membrane was determined using a gravimetric method. The light dusting of talc present on the silicone membrane was removed by blotting with wet tissue paper and the membrane was allowed to air dry before use. Discs of membrane of approximately 0.25 g were accurately weighed and then soaked in an excess of alcohol (2 ml) in sealed glass vials which were placed in a temperature controlled water bath for 24 h. A number of experimental temperatures were used 5, 7.5, 10, 15, 17, 20, 25, 30, 35, 40 and 45 °C and these were controlled to within 0.5 °C. The membranes were removed from the solvent, blotted dry and reweighed. Control experiments, performed using a rotary evaporator (Buchi, Rotavapor, Oldham, UK) to remove the solvent from the membrane following solvent uptake, indicated that any weight change as a result of extractables being removed from the membrane was negligible. A similar protocol has been used previously to examine solvent uptake by silicone membrane (Cross et al., 2001; Dias et al., 2007). A 24-h time period for the experiment was selected as initial experiments indicated that no further mass uptake occurred after 48 h indicating that the system had reached equilibrium. Five replicates using separate pieces of membrane were performed for each solvent at each experimental temperature. Membrane volume change following the sorption of butanol and heptanol was assessed by measuring the dimensions of accurately cut pieces of silicone of approximately 5 cm × 3 cm with Vernier calipers and use of digital micrometer (both obtained from RS Components, Corby, UK).

2.3. Statistical analyses

Statistical analysis of the effects of temperature and alcohol hydrocarbon chain length on uptake of alcohol into the silicone membrane was performed using a two-way ANOVA. Post hoc comparisons were made using the Bonferroni method. Confirmation of the normality of the data was made with the Shapiro–Wilks test. Comparisons of the Gibbs free energy (ΔG) of the uptake process were made similarly.

Least squares linear regression analysis of each of the van't Hoff plots was performed and comparisons of the gradients (slopes) of the best fits were made using an unpaired t test, enabling determination of statistical differences in the ΔH of the uptake process (ΔH is calculated directly from the gradient of the van't Hoff plot). In addition comparisons of whether the gradients of each of the lines were significantly different from zero were performed.

Comparisons of the membrane volume change following the uptake process were made using the Kruskal–Wallis test with post hoc comparison using Dunn's test. Comparison between the experimentally measured membrane volume change and that calculated from the solvent mass uptake and the alcohol's bulk density was made with the Mann–Whitney test. These tests were selected because the volume change data were found to be not normally distributed with the Shapiro–Wilks test.

All statistical analyses were performed using GraphPad Prism version 5, GraphPad Software, San Diego, USA. In all cases five replicate measurements of experimental data were taken and used for the statistical analyses. Statistical significance was accepted at the $p < 0.05$ level.

2.4. McGowan's characteristic volume calculation

ADME Boxes 3.5 software by Pharma Algorithms (Toronto, Canada) was used to calculate the McGowan's characteristic volume for each alcohol.

3. Results

The mass uptake of alcohol into the silicone membrane can be converted to the molar uptake using each alcohol's relative molecular mass. Fig. 1 shows the uptake of the series of alcohols as millimoles of solvent per kilogram of membrane at five experimental temperatures. The results show that there is an increase in the uptake from ethanol to butanol, subsequently followed by a decrease in molar uptake, with increasing chain length. The uptake of propanol and butanol are similar and only significantly different at 45 °C. The uptake of subsequent alcohols was significantly different from each other. This trend is the same regardless of whether the results are presented as mass, volume uptake calculated from each alcohol's bulk density or McGowan volume uptake. The McGowan volume uses group contributions to estimate the volume of a molecule and therefore can give an account of the volume of alcohol taken up into the membrane without making the assumption that the packing of the molecules inside the membrane is the same as that in bulk solvent (Abraham and McGowan, 1987). This is inherent if density is used to calculate volume uptake. In response to temperature there was no significant difference in alcohol uptake between 5 and 17 °C. At 20 °C and above significant differences were observed for propanol through to hexanol with significant differences observed for heptanol and octanol at 30 °C.

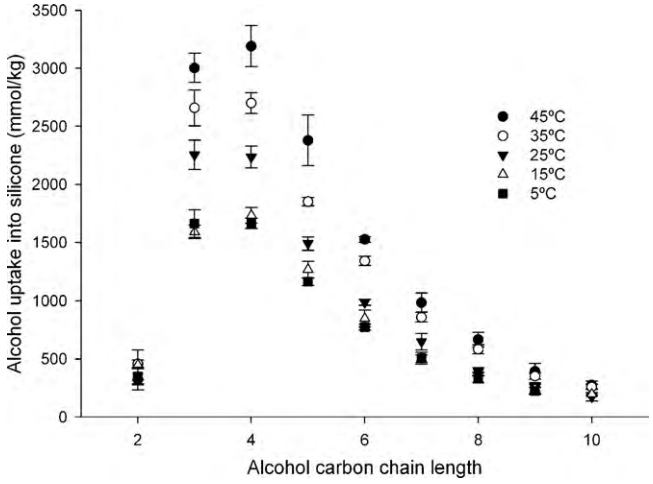

Fig. 1. Solvent uptake into silicone membrane (millimoles of solvent per kilogram of membrane) as a function of carbon number at five experimental temperatures. Error bars show the standard deviation ($n = 5$). The data from only five temperatures are shown for clarity.

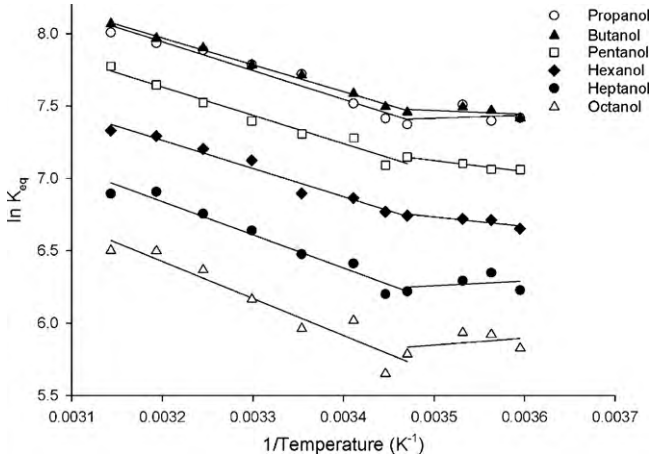

Fig. 3. Plot of the natural logarithm of K_{eq} against the reciprocal of the absolute temperature for the uptake of each of the alcohols from propanol through to octanol into silicone membrane ($n = 5$). The solid lines show the linear best fits of the data in the low and high temperature regions.

Significant differences of nonanol and decanol uptake were only observed at higher temperatures. Fig. 2 shows plots of the natural log of the uptake versus carbon chain length of the alcohols after butanol at five different temperatures. All best fit lines have correlation coefficients in excess of 0.99 demonstrating that the decrease in the uptake of the alcohols after butanol is exponential.

In order to conduct a thermodynamic analysis of the data, the uptake of the alcohols into silicone membrane must first be expressed in the form of an equilibrium-based equation:

$$\text{membrane} + \text{bulk solvent} \leftrightarrow \text{membrane solvent complex} \quad (2)$$

In Eq. (2) the dry membrane and solvent can be regarded as a solid and pure liquid respectively and therefore both have an activity of 1. An equilibrium constant for the alcohol uptake (K_{eq}) can then be calculated from the molar uptake of each alcohol as follows:

$$K_{eq} = \frac{[\text{membrane} + \text{solvent}]}{[\text{membrane}][\text{solvent}]} \approx \text{molar solvent uptake} \quad (3)$$

The temperature dependence of any equilibrium constant can be explored through a van't Hoff plot, using Eq. (4), the slope of which, if linear, is proportional to the enthalpy change involved in the process:

$$\ln Keq = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} \quad (4)$$

ΔH is the enthalpy, ΔS is the entropy, R is the gas constant and T is the temperature in Kelvin. An equilibrium constant similar to that in Eqs. (2) and (3) has been described by Pinkrah et al. (2004) for hydrogel swelling. These authors used photon correlation spectroscopy to measure hydrogel volume at a range of temperatures. They were able to set their standard reference state as the volume occupied by the microgel at 333 K, as at this temperature each of the different microgels tested occupied the same volume; assumed to be the microgel volume in its most collapsed state. That is, the microgel volume without swelling or solvent uptake.

It is not as clear how best to define a standard reference state for the uptake of the different alcohols in this study. The solvent uptake must be normalised to a specified amount of membrane to allow comparison between experiments and we have set the reference state of the millimolar solvent uptake per kilogram of silicone. This is analogous to the concept of molality and similarly is independent of temperature. Using this reference state allows comparisons to be made between the different alcohols and by setting the reference state as one millimole per kilogram represents a suitably low alcohol uptake, similar to the reference state used by Pinkrah et al. (2004). The van't Hoff analysis of the alcohols with higher solvent uptake (propanol, butanol, pentanol, hexanol, heptanol and octanol) revealed a very similar trend seen in Fig. 3. The remaining alcohols (ethanol, nonanol and decanol) produced scattered plots with no defined trend because of the small degree of uptake and limited sensitivity of the gravimetric method used (analytical balance of ±0.0001 g), and hence were not considered for the same analysis.

The van't Hoff plots shown in Fig. 3 are not linear over the entire temperature range. Instead there appears to be two separate linear regions at low and high temperatures, indicated by the two separate best fit lines for each of the alcohols. For each of the plots the slopes of the two different best fit lines were found to be significantly different. In all cases for the low temperature region with the exception of pentanol, the gradients of the best fit lines were not found to be significantly different from zero. In the case of pentanol, the gradient in this temperature range is small. The ΔH of the process is calculated from the gradient of the line as from Eq. (4) the gradient of the plot of $\ln K_{eq}$ against $1/T$ is equal to $\Delta H/R$.

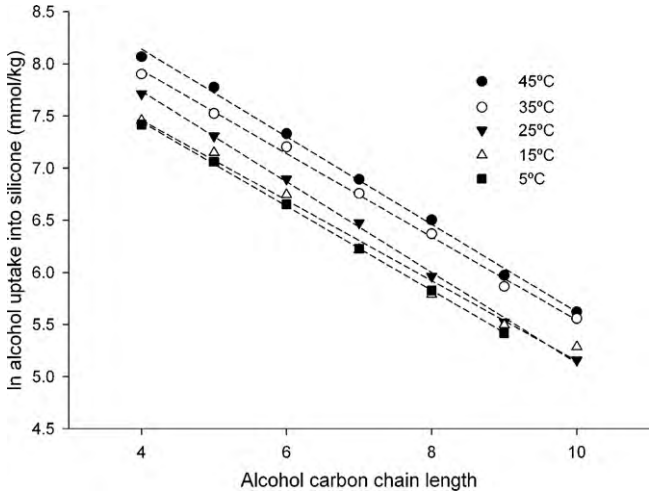

Fig. 2. Best fits (dashed lines) of the natural log of the uptake of the alcohols as a function of carbon number at five experimental temperatures. The best fit lines were calculated using linear regression analysis and all r^2 values are greater than 0.98.

Table 1
Van't Hoff enthalpy (ΔH), entropy (ΔS) and Gibbs free energy (ΔG) calculated for the membrane uptake of each alcohol below the transition temperature (T_{tr}). T_{tr} values were calculated from the intersection of the linear regression lines. Values in parentheses are the standard error ($n = 5$).

	Propanol	Butanol	Pentanol	Hexanol	Heptanol	Octanol
ΔH (kJ mol^{-1})	−0.80 (±1.56)	2.22 (±3.12)	3.35 (±1.97)	5.47 (±1.93)	−4.36 (±4.03)	−3.98 (±7.54)
ΔG at 10 °C (kJ mol^{-1})	−17.68 (±0.01)	−17.64 (±0.02)	−16.72 (±0.01)	−15.82 (±0.03)	−14.81 (±0.05)	−13.97 (±0.04)
ΔS at 10 °C (J K^{-1} mol^{-1})	63 (±92)	77 (±185)	77 (±117)	81 (±114)	48 (±240)	40 (±448)
T_{tr} (°C)	14.6	15.2	16.7	16.0	16.1	18.4

Table 2
Van't Hoff enthalpy (ΔH), entropy (ΔS) and Gibbs free energy (ΔG) estimated for the membrane uptake of each alcohol above the transition temperature (T_{tr}). T_{tr} values were calculated from the intersection of the linear regression lines. Values in parentheses are the standard error ($n = 5$).

	Propanol	Butanol	Pentanol	Hexanol	Heptanol	Octanol
ΔH (kJ mol^{-1})	16.51 (±1.56)	15.43 (±0.45)	17.04 (±1.33)	16.15 (±1.10)	19.04 (±1.84)	22.20 (±3.13)
ΔG at 40 °C (kJ mol^{-1})	−20.66 (±0.02)	−20.75 (±0.003)	−19.91 (0.01)	−18.99 (±0.01)	−17.98 (±0.02)	−16.92 (±0.01)
ΔS at 40 °C (J K^{-1} mol^{-1})	119 (±5)	116 (±1)	118 (±4)	112 (±4)	118 (±6)	125 (±10)
T_{tr} (°C)	14.6	15.2	16.7	16.0	16.1	18.4

Table 3
The observed membrane volume change following the uptake of butanol and heptanol at 40 and 10 °C and the solvent volume uptake of the same solvents at the same temperatures calculated using the solvent bulk density. Values in parentheses are the standard deviation of the mean ($n = 5$).

Solvent	Temperature (°C)	Membrane volume change per gram of silicone (cm^3)	Solvent volume uptake calculated using bulk density (cm^3)
Butanol	40	1.82 (±0.19)	0.270 (±0.002)
Butanol	10	1.31 (±0.09)	0.163 (±0.006)
Heptanol	40	0.71 (±0.26)	0.144 (±0.006)
Heptanol	10	0.46 (±0.11)	0.076 (±0.007)

The difference in gradient indicates a significant change in the ΔH of the process.

The Gibbs' free energy (ΔG) and entropy (ΔS) associated with the solvent uptake may be calculated using the following fundamental equations:

$$\Delta G = -RT \ln K_{eq} \quad (5)$$

$$\Delta G = \Delta H - T\,\Delta S \quad (6)$$

Calculated values for ΔG and ΔS at two experimental temperatures, 10 and 40 °C, chosen to represent the low and high temperature regions of the van't Hoff plot, together with the calculated enthalpies for the two regions of the plots and the transition temperatures (T_{tr}) are shown in Tables 1 and 2. ΔG values at the two temperatures are significantly different. As the enthalpy associated with the uptake process in the low temperature region is approximately zero, the process is entropically driven. Table 1 shows calculated positive entropies for the uptake of the different alcohols at 10 °C. The relatively large error associated with this calculation is produced from the linear regression analysis. Nonetheless as the enthalpy of the process at this temperature is approximately zero, positive entropy must drive the process. The enthalpy at higher temperatures which opposes the uptake of the solvent into the membrane is overcome by an increase in the entropy of the process.

In order to gain further understanding of the uptake process, the change in membrane volume associated with the uptake of two of the alcohols, butanol and heptanol were performed at 10 and 40 °C, the low and high temperature regions respectively. These were compared to the expected membrane volume changes if the volume increases were only what was required to accommodate the alcohols at their bulk densities. The bulk densities of the alcohols at the different temperatures were taken from Wilhoit and Zwolinski (1973). Butanol was selected as it showed the highest uptake into the membrane and heptanol was chosen to be representative of the higher alcohols. The data are shown in Table 3. It can be seen that the increase in membrane volume considerably (and significantly) exceeds what is required to accommodate the inclusion of either alcohol if the solvent taken up into the membrane retains its bulk density. This is true both at high and low temperatures.

4. Discussion

Twist and Zatz (1988) have previously studied the uptake of alcohols into silicone membrane and they observed a similar trend to that obtained in this work for the molar uptake of alcohols from methanol through to octanol at a single temperature (37 °C). However they found propanol to show the greatest uptake into the membrane rather than butanol and did not note that the decrease in uptake in alcohols higher than butanol is exponential. The explanation of the shape of Fig. 1 provided by Twist and Zatz (1988), was that the increase of uptake with increasing carbon number up to a length of three carbons is a result of decreased associative tendencies of the individual alcohols (Anderson et al., 1978), and the decrease in uptake after a carbon chain length of four is because of a decrease in the entropy of dilution (Mulder et al., 1985). Other studies of pharmaceutical relevance investigating structure activity relationships have observed a change in the properties of homologs above a four carbon chain length (Yalkowsky et al., 1972; Forster et al., 1991). These observations may be explained through intramolecular interaction of the methylene groups on the carbon chain with an adjacent moiety on the molecule. The methylene groups of carbons 1–4 in the chain are able to form 'RING' structures with the adjacent moiety, in this study the alcohol's hydroxyl group (Nisbet, 1977). Additional methylene groups above the fourth carbon have a greater degree of rotational freedom about the carbon–carbon bond (Forster et al., 1991). The conformity of the data above a carbon chain length of four to a simple structure activity relationship allows calculation of the effect of the addition of a methylene group to the uptake of solvent. In addition by extrapolation of the line to a carbon chain length of zero a calculation can be made of the molar uptake of the hydroxyl group. Such an approach should allow comparison of the uptake between the func-

tional groups of different classes of solvents including for example carboxylic acids or esters.

Non-linearity in a van't Hoff plot indicates that either the enthalpy of the process is temperature dependent or that there is a change in the mechanism of the process. In Fig. 3 the two separate linear regions suggest that it is a change in mechanism rather than a temperature dependence of the enthalpy of the process which causes the non-linear behaviour. All of the alcohols treated with this analysis, propanol through to octanol, showed plots similar to that in Fig. 3 suggesting that the change in mechanism is associated with the membrane behaviour rather than that of the alcohols. It would not be expected that each of the alcohols would exhibit the same transition at the same temperature. At low temperatures the gradients of the plots and therefore the enthalpy associated with the uptake in this temperature range are effectively zero within experimental error. This implies that the net solvent–solvent interactions, inside and outside the membrane are the same and that there is no enthalpic contribution from any alcohol–membrane interaction.

Conversely at higher temperatures there is a significant gradient in the plot and the alcohol uptake has a corresponding, significant associated enthalpy. However as the gradient of the plot is negative, ΔH is positive, indicating that the enthalpy change opposes the uptake process. A detailed investigation of the molecular mechanism behind the change in membrane properties at 16 °C has not been performed, however the data help to illustrate the importance of temperature in experiments using silicone as a model membrane. Temperature variation has been suggested to be one reason why a multicentre study attempting to validate inter- and intra-laboratory flux measurements across silicone membrane produced a large variation in the measurement of drug flux (Chilcott et al., 2005).

The analysis suggests that at lower temperatures the alcohols taken up into the membrane exist in a state similar to the bulk alcohol, that is, as there is no measurable enthalpy of the process, the net interactions are the same both sides of the equilibrium. It is unlikely that different net interactions could lead to the same enthalpy for the process being calculated. At higher temperatures the significant enthalpy indicates that the net interactions are different and that the solvent taken up into the membrane is not structurally the same as the bulk solvent. The Flory–Huggins theory suggests that the free energy of mixing polymers with solvents is related to the volume fractions of the solvent and polymer and an interaction parameter. However the theory has been found to describe the sorption of polar solvents such as the alcohols into cross-linked silicone membrane inadequately (Favre et al., 1993; Chandak et al., 1998). Modified models based on the Flory–Huggins theory provide better fits of the data, though they are more complex and semi-empirical (Favre et al., 1993). The simpler approach used in this study allows the alcohol equilibrium uptake data to be structured in order to give an account of the uptake process.

At both the high and low temperature regions the increase in membrane volume considerably exceeds what is required to accommodate the inclusion of either alcohol if the solvent taken up into the membrane retains its bulk density. Two extreme possibilities are that either both the butanol and heptanol retain their bulk densities and there is a large increase in free volume, or that the alcohols occupy the entire increase in volume and therefore no longer possess the same density as they do in the bulk. At low temperatures the thermodynamic analysis supports the theory that the butanol and heptanol taken up into the membrane retain their bulk density, and therefore there must be a large increase in free volume. In contrast at higher temperatures where there is a significant enthalpy the alcohols are organised differently to the bulk and the density of the alcohol taken up into the membrane would therefore be expected to be altered. This would be expected to alter the partitioning of any drug into the membrane. The insight gained through this study will be used to inform interpretation of dynamic experiments following drug diffusion across the same membrane in the same alcoholic vehicles.

Model membranes such as silicone membrane are useful for providing an understanding of membrane transport processes (Flynn et al., 1974). However this can only be a precursor to investigations of the membrane of interest, in this case the stratum corneum. Analysing and interpreting the uptake of solvents and penetration enhancers into stratum corneum rather than silicone must be performed with great care, as extraction of skin lipids by the enhancer may affect the results. However a number of studies have investigated this at a single temperature using a similar protocol to that described here (Cornwell et al., 1996; Mackay et al., 2001; Chantasart et al., 2004). The analysis presented in this study should prove a useful basis for analysing such data produced over a range of temperatures and should give fundamental insight into the enhancer mechanism as well as improving our understanding of the effect of temperature on drug transport across skin.

5. Conclusions

The uptake of several alcohols into silicone membranes has been performed as a function of temperature. Increased uptake was observed with increasing chain length from two to four carbons, followed by an exponential decrease with subsequent increases in chain length. A thermodynamic analysis of the data was performed which showed two separate trends above and below 16.4 ± 2 °C. At low temperatures the enthalpy associated with the uptake process was zero within experimental error, whereas above the transition temperature there was a significant positive enthalpy. Each of the alcohols analysed exhibited this same transition at approximately 16 °C and therefore it is likely to reflect a change in membrane properties and suggests that there is a change in the uptake mechanism in the two temperature regions. Moreover the data indicate a difference in the net interactions above and below the transition temperature suggesting that the alcohols inside the membrane are structurally different in the two temperature ranges. The implications of the change in equilibrium uptake mechanisms for the transport of drugs across the membrane are currently unclear however it is likely that if the solvent exists in different environments within the membrane this will affect the partitioning of any solute into the membrane. Studies are ongoing to investigate this. Overall it is hoped that this study will be useful in providing a methodology and system of analysis which may be used to examine the uptake of solvents into model membranes and an appreciation of how temperature can be used to maximise penetration enhancement.

Acknowledgement

This work was funded by EPSRC Grant Number EP/D50273X/1.

References

Abraham, M.H., McGowan, J.C., 1987. The use of characteristic volumes to measure cavity terms in reversed phase liquid chromatography. Chromatographia 23, 243–246.
Anderson, B.D., et al., 1978. Vapor-pressure studies of self-association of alcohols in isooctane. 1. Effect of chain length. Int. J. Pharm. 1, 15–31.
Blank, I.H., MacFarlane, D.J., 1967. The effect of temperature on the transport of non-electrolytes across skin. J. Invest. Dermatol. 49, 582–589.
Burgess, S.E., O'Neill, M.A.A., Beezer, A.E., Hadgraft, J., Gaisford, S., 2005. Thermodynamics of membrane transport and implications for dermal delivery. J. Drug Deliv. Sci. Technol. 15, 325–327.
Chandak, M.V., Lin, Y.S., Ji, W., Higgins, R.J., 1998. Sorption and diffusion of volatile organic compounds in polydimethylsiloxane membranes. J. Appl. Polym. Sci. 67, 165–175.
Chantasart, D., Li, S.K., He, N., Warner, K.S., Prakongpan, S., Higuchi, W.I., 2004. Mechanistic studies of branched chain alkanols as skin permeation enhancers. J. Pharm. Sci. 93, 762–779.

Chilcott, R.P., Barai, N., Beezer, A.E., Brain, S.I., Brown, M.B., Bunge, A.L., Burgess, S.E., Cross, S., Dalton, C.H., Dias, M., Farinha, A., Finnin, B.C., Gallagher, S.J., Green, D.M., Gunt, H., Gwyther, R.L., Heard, C.M., Jarvis, C.A., Kamiyama, F., Kasting, G.B., Ley, E.E., Lim, S.T., Mcnaughton, G.S., Morris, A., Nazemi, M.H., Pellett, M.A., DU Plessis, J., Quan, Y.S., Raghavan, S.L., Roberts, M., Romonchuk, W., Roper, C.S., Schenk, D., Simonsen, L., Simpson, A., Traversa, B.D., Trottet, L., Watkinson, A., Wilkinson, S.C., Williams, F.M., Yamamoto, A., Hadgraft, J., 2005. Inter- and intralaboratory variation of in vitro diffusion cell measurements: an international multicenter study using quasi-standardized methods and materials. J. Pharm. Sci. 94, 632–638.

Cornwell, P.A., Barry, B.W., Bouwstra, J.A., Gooris, G.S., 1996. Modes of action of terpene penetration enhancers in human skin; differential scanning calorimetry, small-angle X-ray diffraction and enhancer uptake studies. Int. J. Pharm. 127, 9–26.

Cross, S.E., Pugh, W.J., Roberts, M.S., Hadgraft, J., 2001. Probing the effect of vehicles on topical delivery: understanding the basic relationship between solvent and solute penetration using silicone membranes. Pharm. Res. 18, 999–1005.

Dias, M., Hadgraft, J., Lane, M.E., 2007. Influence of membrane–solvent–solute interactions on solute permeation in model membranes. Int. J. Pharm. 336, 108–114.

Favre, E., Nguyen, Q.T., Schaetzel, P., Clément, R., Néel, J., 1993. Sorption of organic-solvents into dense silicone membranes. 1. Validity and limitations of Flory–Huggins and related theories. J. Chem. Soc. Faraday Trans. 89, 4339–4346.

Flynn, G.L., Yalkowsky, S.H., Roseman, T.J., 1974. Mass transport phenomena and models: theoretical concepts. J. Pharm. Sci. 63, 479–509.

Forster, S., Buckton, G., Beezer, A.E., 1991. The importance of chain length on the wettability and solubility of organic homologs. Int. J. Pharm. 72, 29–34.

Fritsch, W.C., Stoughton, R.B., 1963. The effect of temperature and humidity on the penetration of C^{14} acetylsalicylic acid in excised human skin. J. Invest. Dermatol. 41, 307–311.

Jain, A.K., Panchagnula, R., 2003. Effect of temperature on imipramine hydrochloride permeation: role of lipid bilayer arrangement and chemical composition of rat skin. Int. J. Pharm. 250, 287–293.

Jones, K., Cocker, J., Dodd, L.J., Fraser, I., 2003. Factors affecting the extent of dermal absorption of solvent vapours: a human volunteer study. Ann. Occup. Hyg. 47, 145–150.

Mackay, K.M.B., Williams, A.C., Barry, B.W., 2001. Effect of melting point of chiral terpenes on human stratum corneum uptake. Int. J. Pharm. 228, 89–97.

Mali, J.W.H., 1956. The transport of water through the human epidermis. J. Invest. Dermatol. 27, 451–469.

Mulder, M.H.V., Franken, T., Smolders, C.A., 1985. Preferential sorption versus preferential permeability in pervaporation. J. Membr. Sci. 22, 155–173.

Nisbet, K., 1977. Structure–solubility parameter relationships in alcohols. In: Harris, F., Seymour, R. (Eds.), Structure–Solubility Relationships in Polymers. Academic Press, London.

Ogiso, T., Hirota, T., Iwaki, M., Hino, T., Tanino, T., 1998. Effect of temperature on percutaneous absorption of terodiline, and relationship between penetration and fluidity of the stratum corneum lipids. Int. J. Pharm. 176, 63–72.

Pinkrah, V.T., Beezer, A.E., Chowdhry, B.Z., Gracia, L.H., Mitchell, J.C., Snowden, M.C., 2004. Thermodynamic considerations of microgel swelling behavior. Langmuir 20, 8531–8536.

Piotrowski, J., 1957. Quantitative estimation of aniline absorption through the skin in man. J. Hyg. Epidem. 1, 23–31.

Twist, J.N., Zatz, J.L., 1988. Membrane–solvent–solute interaction in a model permeation system. J. Pharm. Sci. 77, 536–540.

Wilhoit, R., Zwolinski, B., 1973. Physical and thermodynamic properties of aliphatic alcohols. J. Phys. Chem. Ref. Data 2, 1–420.

Yalkowsky, S.H., Flynn, G.L., Slunick, T.L., 1972. Importance of chain length on physicochemical and crystalline properties of organic homologs. J. Pharm. Sci. 61, 852–857.