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Alcohol enhanced permeation in model membranes. Part II. Thermodynamic analysis of membrane partitioning

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ABSTRACT

The role of solvents in drug transport has not been properly addressed in the literature, despite its well known influence on drug permeation. Previously we have conducted thermodynamic and kinetic analyses to probe the molecular mechanisms of alcohol enhanced permeation. In the present study, the influence of temperature on the partitioning of methyl paraben into silicone membranes is investigated. In line with previous membrane transport studies of methyl paraben in silicone membranes, butanol and heptanol are used as representative alcohols. The results show higher amounts of methyl paraben extracted from the silicone membrane following equilibration with butanol, at all experimental temperatures. This was in line with alcohol uptake data. In fact, a linear correlation (r^2 ~0.97) was found between the amount of methyl paraben in the silicone membrane and the corresponding alcohol uptake. Calculated "specific" vehicle–membrane partition coefficients for both alcohols were approximately one, suggesting that the effective concentrations of methyl paraben inside and outside the membrane were the same. Thermodynamic analysis of the alcohol–membrane partition coefficients as a function of temperature showed no apparent trend for butanol, with an associated enthalpy change of approximately zero. Conversely, there was a positive trend in the van't Hoff plot for methyl paraben in heptanol, indicative of an exothermic process. Moreover, the partitioning trends of methyl paraben in silicone membranes obtained from membrane transport and equilibrium experiments were not the same. This reflects the fundamental differences between the calculated vehicle–membrane partition coefficients in the two studies. Finally, the findings from membrane transport and equilibrium experiments support a model of alcohol enhanced permeation where high solvent sorption promotes high solute concentrations in the overall volume of the membrane (i.e. *K*), thus leading to modified solute transport (i.e. increased flux). The same model also accounts for changes in membrane diffusivity (i.e. *D*) related to the properties of the imbibed alcohol.

1. Introduction

Despite the wide use of permeation enhancers in, for example, dermal delivery (Finnin and Morgan, 1999; Williams and Barry, 2004; Ahad et al., 2009), their mechanism of action is not yet completely understood. The uptake of formulation components is known to affect the partition and diffusion properties of the membrane, thus modulating drug permeation. However, the actual role of vehicle uptake on membrane transport has not been properly addressed in the literature.

In a previous investigation, McAuley et al. (2010) conducted a thermodynamic analysis of the uptake of a series of primary alcohols into silicone membranes, giving fundamental insight into the uptake process. The results showed two different mechanisms of alcohol sorption into silicone membranes, separated by a break point at ~16 °C. Below this transition temperature, the solvent uptake was relatively small and the process was entropy driven. Above 16 °C there was a marked increase in alcohol uptake with temperature and the process was mainly determined by the associated enthalpy (endothermic process). These findings suggest that, at temperatures below 16 °C, the alcohol molecules inside the membrane exist in a state similar to bulk solvent. Conversely, at higher temperatures the enthalpy associated with the uptake process implies that the structural organisation of the alcohol molecules inside the membrane differs from that in the bulk solvent. However, the implications of this for the partitioning of solutes into the membrane, and thus membrane transport, remain to be elucidated.

In the first paper of this series, we investigated the influence of temperature on the permeation of the model compound methyl paraben across silicone membranes from two representative alcohol vehicles (Oliveira et al., 2010). Building on the study by McAuley et al. (2010), butanol was selected because it showed the highest membrane uptake, whereas heptanol was selected as a model for alcohols with >4 carbon chain length. Thermodynamic and kinetic

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analyses of the permeation data obtained at different temperatures were conducted using the methodology reported by Burgess et al. (2005). Unlike solvent uptake or solute partitioning, membrane transport is a time-dependent (i.e. dynamic) process. Fick's first law of diffusion is commonly used in the mathematical treatment of permeation data, and incorporates both dynamic and equilibrium (i.e. time-independent) parameters to model diffusion across membranes under steady-state conditions, as described in Eq. (1).

$$J_{ss} = \frac{DKC_v}{h} \quad (1)$$

J_{ss} is the steady-state flux per unit area, D the diffusion coefficient, K the vehicle–membrane partition coefficient, C_v is the concentration of the drug in the vehicle and h represents the length of the path of drug diffusion across the membrane. The equilibrium parameter K is used in Eq. (1) as a measure of the concentration of the drug in the superficial layer of the membrane where the formulation is applied, which is not readily known experimentally. The approach developed by Burgess et al. (2005) distinguishes between the two composites of the flux activation energy: the diffusion activation energy and the enthalpy change associated with the partitioning of the solute with the membrane; thus allowing a mechanistic understanding of the processes involved in solute transport across the membrane. Oliveira et al. (2010) noted that higher fluxes of methyl paraben were obtained using butanol at all experimental temperatures studied, in line with the uptake data. For butanol, it was possible to discern two different mechanisms for methyl paraben diffusion and partition with the silicone membrane at temperatures above and below ~20 °C. This was not observed for the kinetic analysis of methyl paraben flux from butanol vehicles because of the compensatory trends in diffusion and partition observed at high and low temperatures. No break point was observed in the same analysis of partition and diffusion data for methyl paraben in heptanol. Based on these findings, the authors proposed that high solvent uptake by the silicone membrane impacts on both the partition (K) and the diffusion of the solute (D): (1) by increasing the concentration of the solute inside the membrane and (2) by decreasing the diffusional resistance of the rate-limiting barrier. However, it must be noted that the K values used in the analysis by Oliveira et al. (2010) were obtained indirectly from the permeation data by non-linear modelling, using an analytical solution to Fick's second law of diffusion. As for Eq. (1), the model equation assumes that the membrane is an inert, homogeneous slab with established dimensions for cross sectional (diffusional) area and thickness (Crank, 1975; Watkinson and Brain, 2002). These are known experimental parameters, which are introduced in the model equation prior to fitting. Hence, in the context of the membrane transport experiments, the calculated K represents the concentration of methyl paraben at the donor–membrane interface with respect to the volume of the silicone membrane. In this case, no specific information regarding the solvent uptake into the membrane is taken into consideration for the calculation of K.

Following on from the membrane uptake and transport experiments reported by McAuley et al. (2010) and Oliveira et al. (2010), this paper examines the influence of temperature on the partitioning of methyl paraben into silicone membranes from butanol and heptanol vehicles. Subsequent thermodynamic analysis of the results is conducted to allow the elucidation of the mechanisms of solute partitioning with the silicone membrane. Most importantly, the analysis of the partitioning data described in this paper takes into account the specific information regarding the alcohol uptake into the silicone membrane, which was not considered in the analysis by Oliveira et al. (2010). For this purpose, the calculation of a "specific" membrane concentration of methyl paraben, based upon the mass (not volume) of alcohol inside the membrane, is proposed. This serves to overcome the fact that calculating the concentration of methyl paraben in the solvent fraction inside the membrane is not possible at temperatures above ~16 °C since the alcohol inside the membrane no longer retains its bulk density (McAuley et al., 2010). The underlying assumptions of this equilibrium analysis are that: (1) this investigation is representative of the equilibrium established during passive membrane transport at the superficial layer of the membrane, where the donor solution is applied (Eq. (1)); (2) the volume occupied inside the membrane by the alcohol molecules is not significantly affected by the presence of methyl paraben; and (3) the methyl paraben inside the membrane exists only in the solvent fraction inside the membrane. Both the methyl paraben and the alcohol uptake were also normalised to a specified amount of membrane to allow comparison with previous experiments (McAuley et al., 2010).

Finally, a model of alcohol enhanced permeation in silicone membranes is proposed in this paper, based on the findings of both the membrane transport (Oliveira et al., 2010) and equilibrium studies.

2. Materials and methods

2.1. Materials

Methyl paraben (Methyl-4-hydroxybenzoate, puriss. ≥99%, Fluka) was supplied by Sigma–Aldrich, UK. Butan-1-ol (AnalaR® grade, BDH) and ethanol (99.7–100% (v/v), AnalaR® grade, BDH) were supplied by VWR UK, and 1-heptanol (98%, Aldrich) was supplied by Sigma–Aldrich, UK. Silicone membranes (250 μm thickness were obtained from Samco, Nuneaton, UK). All solvents used in the HPLC analysis were HPLC grade and supplied by Fisher Scientific, UK.

2.2. Membrane uptake studies

The alcohol uptake was determined by a gravimetric method (weight difference) using a Sartorius balance (±0.0001 g accuracy). The silicone membrane (approx. 250 μm thickness) was wiped to remove dust. The dry membrane was carefully cut into circular discs with a stainless steel borer (R and L Enterprises, i.d. 1.9 cm, Fisher Scientific, UK), accurately weighed and placed into labelled glass sample vials. 2 mL of the appropriate alcohol were added and the sealed vials placed inside a temperature controlled water bath, equipped with a refrigerated bath circulator (Julabo VC, JWS Ltd., Dublin, Ireland). The vials were allowed to equilibrate for 24 h at each experimental temperature, after which the membranes were removed, blotted dry on absorbent paper and carefully weighed. A minimum of five replicates was tested for each alcohol. The relative mass uptake of each alcohol per gram of membrane (m_{upt}) was derived by the difference between the weight of the membrane before (m_b) and after (m_a) soaking, as described by Eq. (2). The molar (mol_{upt}) uptake (Eq. (3)) was calculated using the molecular weight (M) of each alcohol.

$$m_{upt} = \frac{m_a - m_b}{m_b} \quad (2)$$

$$mol_{upt} = \frac{m_{upt}}{M} \quad (3)$$

2.3. Membrane partition experiments

Stock solutions of methyl paraben in butanol and heptanol were prepared with a concentration of 1.52 mg/mL (0.01 M). The silicone membranes (approx. 250 μm thickness) were cut into discs using the stainless steel borer described in Section 2.2 weighed and placed in labelled sample vials. 2 mL of each stock solution were

added (5 replicates for each alcohol), the vials were sealed and the system was allowed to equilibrate for 24 h at the experimental temperature inside the temperature controlled water bath equipped with a refrigerated bath circulator (Section 2.2). The experimental temperatures were 40, 30, 20, 15, 10 and 5 °C (±0.5). After equilibration, the membranes were removed, carefully blotted with absorbent tissue to remove excess solvent and weighed (Sartorius Balance, ±0.0001 g accuracy; Sartorius, U.K.). The drug inside the membranes was extracted twice with 2 mL of ethanol, first for 17 h and then 5 h, at room temperature. Both extractions were combined and the methyl paraben was quantified by HPLC. The extraction procedure was validated for the butanol and heptanol systems by extracting the drug inside the membranes three times with 2 mL of ethanol, first for 16 h and then for 5 and 2 h. The extractions were quantified separately by HPLC. The amount extracted in the second extraction was less than 5% of the total, and in the third extraction quantification was below the detection limit of the method. Therefore, two extractions with 2 mL of ethanol for 17 and 5 h were considered sufficient for the purpose of the present investigation. The external solvent phase was also sampled and quantified by HPLC, after diluting with ethanol. The thickness of each membrane was measured before and after equilibration (Digital micrometer ±0.001 mm accuracy; RS Components, Corby, UK).

2.4. HPLC analysis

Methyl paraben in the samples was quantified using a Phenomenex Luna 5μ C_8 (2) 150 mm × 4.60 mm column with UV detection at 254 nm. 10 μL of the sample was injected into the system and eluted at room temperature (flow rate 1.0 mL/min) using a mobile phase composed of 30% acetonitrile, 70% water and 0.1% trifluoroacetic acid (pH 1.6). The analysis was carried out on an 1100 Series Hewlett Packard HPLC system equipped with a diode array detector. The data were acquired and analysed using ChemStation for LC 3D software by Agilent Technologies (Waldbronn, Germany). This method was suitable for the quantification of methyl paraben between 0.078 and 100 μg/mL. Method validation showed good linearity and accuracy within the quantification range (coefficient of variance ≤ 10–20%; $r^2 \geq 0.999$). The method also showed good injection reproducibility (coefficient of variance < 5%, $n = 5$).

2.5. Data analysis

The data treatment and statistical analysis were performed using Microsoft® Office Excel 2003. The linear regression of the data by least-mean-squares was carried out in Origin® 7.0PRO, v7.0220. The standard error of the slope was provided by this software and converted to thermodynamic units by multiplying by the gas constant ($R = 8.314\ J\ K^{-1}\ mol^{-1}$).

3. Results and discussion

3.1. Methyl paraben partitioning into silicone membranes

Figs. 1 and 2 show the amount of methyl paraben extracted from the silicone membrane after equilibration with butanol and heptanol as a function of temperature. The results were normalised to a specified amount of membrane to allow comparison with previous experiments. Fig. 1 shows a non-linear increase with temperature in the amount of methyl paraben extracted using butanol. At temperatures below 20 °C there is a relatively small gradient ($p < 0.05$), whereas above this temperature the amount extracted from the membrane increases sharply with temperature ($p < 0.05$). A similar trend is observed using heptanol (Fig. 2). At temperatures below 20 °C the amount of methyl paraben extracted after equilibration with heptanol is the same within experimental

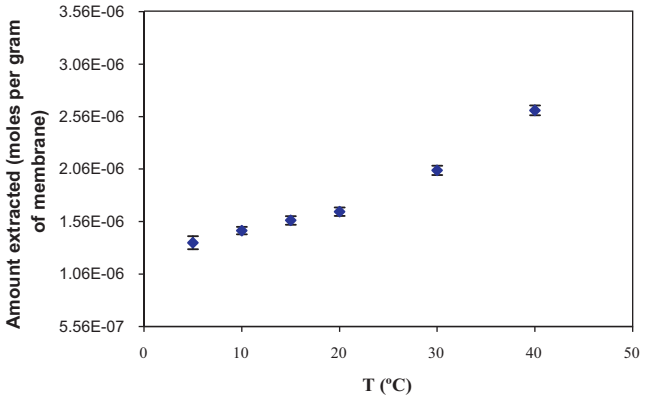

Fig. 1. Amount of methyl paraben extracted from silicone membrane after equilibration with butanol at each experimental temperature (Mean ± SD; $n = 5$).

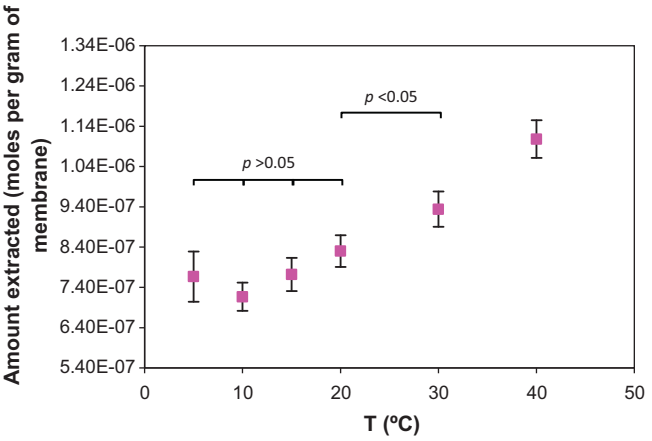

Fig. 2. Amount of methyl paraben extracted from the silicone membrane after equilibration with heptanol at each experimental temperature (Mean ± SD; $n = 5$).

error ($p > 0.05$), whereas above 20 °C it increases significantly with temperature ($p < 0.05$). In previous solvent uptake experiments using the same grade of silicone membrane, McAuley et al. (2010) demonstrated that alcohol sorption was temperature-dependent and followed two different mechanisms at temperatures above and below ~16 °C. At lower temperatures, the solvent uptake was relatively small and entropy driven, whereas at higher temperatures there was a marked increase in solvent uptake and the process was mainly determined by the associated positive enthalpy. The data in Figs. 1 and 2 are consistent with this temperature-dependent membrane sorption behaviour for both alcohols. Additionally, higher amounts of methyl paraben were extracted using butanol for each experimental temperature ($p < 0.05$), which is also the alcohol with highest uptake into the silicone membrane. This suggests a relationship between the quantity of solute which is taken up the silicone membrane and the degree of alcohol sorption. Fig. 3 shows a good correlation (r^2 ~0.97) between the amount of methyl paraben extracted from the silicone membrane after equilibration with butanol and heptanol at all the experimental temperatures, and the corresponding alcohol uptake.

A thermodynamic analysis of membrane partitioning requires that the system is at equilibrium, i.e. that its properties do not change over time. The following equilibrium-based equation was proposed by McAuley et al. (2010) to describe the uptake of alcohols into the silicone membrane:

$$\text{membrane} + \text{bulk solvent} \leftrightarrow \text{membrane} - \text{solvent complex}$$

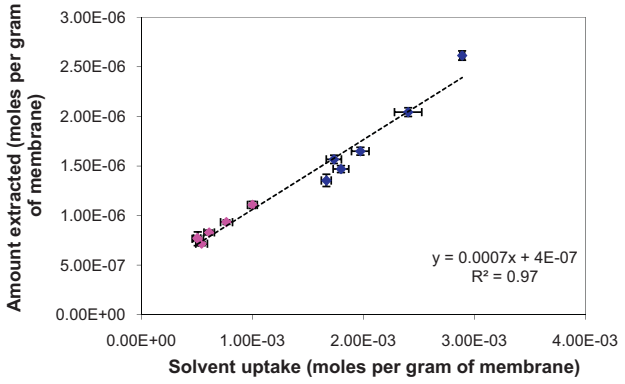

Fig. 3. Correlation between the amount of methyl paraben extracted from the silicone membrane and the corresponding uptake of ■ butanol and ■ heptanol. Data obtained at 5, 10, 15, 20, 30 and 40 °C (Mean ± SD; $n = 5$).

In this case, both the dry membrane and the bulk solvent in the left hand side of the equation can be regarded as solid and pure liquid, thus having activity of 1. This allowed the calculation of equilibrium constants from the molar uptake of each alcohol and to conduct a thermodynamic analysis of the alcohol uptake data obtained at different temperatures. Similarly, the partitioning of methyl paraben into the silicone membrane requires a thermodynamic equilibrium between the two immiscible phases: bulk solvent and membrane. This can be expressed by the following equilibrium-based expression:

MP in bulk solvent ↔ MP in membrane

The traditional approach to calculate the vehicle–membrane partition coefficient would be to consider the membrane as a single phase, "solution medium". However, the van't Hoff analysis of alcohol uptake conducted by McAuley et al. (2010) shows that the enthalpies associated with alcohol uptake at temperatures below ~16 °C are effectively zero within experimental error. This indicates that within this temperature range the net solvent–solvent interactions inside and outside the membrane are the same. As it is unlikely that different net interactions would result in the same enthalpy for the process, this implies no significant enthalpic contribution from any membrane–alcohol interactions. These findings suggest that the alcohol molecules inside the membrane at low temperatures exist in a state similar to the bulk alcohol, i.e. that the structural organisation of the alcohol inside the membrane is the same as in bulk solvent. Hence it is possible to calculate the concentration of methyl paraben in the solvent fraction inside the membrane, and thus the vehicle–membrane partition coefficient. The assumptions underlying this calculation are that the methyl paraben inside the membrane exists only in the solvent fraction, and that the presence of the solute does not modify significantly the volume occupied by the alcohol inside the membrane.

Conversely, at temperatures above ~16 °C McAuley et al. (2010) observed a significant gradient in the van't Hoff plots. Within this temperature range, the authors reported a positive enthalpy associated with the uptake of alcohols into the silicone membrane. This indicates that at higher temperatures the net interactions are different for both sides of the equilibrium, and that the structure of the alcohol molecules inside the membrane differs from that in bulk solvent. As the alcohol inside the membrane no longer retains its bulk density, calculating the concentration of methyl paraben in the solvent fraction inside the membrane is not possible. To overcome this, the calculation of a "specific" membrane concentration of methyl paraben, based upon the mass (not volume) of alcohol inside the membrane, is proposed. Hence, the vehicle–membrane partition coefficients for methyl paraben were calculated using the following equations:

$$K_m = \frac{C_m}{C_v} \quad (4)$$

where

$$C_m = \frac{\text{amount of MP extracted per gram of membrane}}{\text{alcohol uptake per gram of membrane}}$$

A similar concept of a "specific" vehicle–membrane partition coefficient has already been reported in the literature. For instance in the work of Soulas et al., 2009; Soulas and Papadokostaki, 2011, for the analysis of membrane partitioning while probing the transport and release mechanisms of osmotically active solutes and a model hydrophilic compound in silicone rubber matrixes. However, volume – and not mass – based concentrations of the solute in the fraction of solvent imbibed in the membrane were used.

Table 1
Vehicle–membrane partition coefficient (K_m) estimated for methyl paraben in silicone membranes, after equilibration with butanol and heptanol at different temperatures. Mean ± SD ($n = 5$).

T (K)	Butanol	Heptanol
278.15	0.979 (±0.076)	1.005 (±0.107)
283.15	1.010 (±0.076)	0.913 (±0.092)
288.15	1.009 (±0.044)	0.931 (±0.064)
293.15	0.954 (±0.011)	0.929 (±0.044)
303.15	0.929 (±0.024)	0.859 (±0.044)
313.15	1.004 (±0.048)	0.830 (±0.039)

Table 2
Molar concentrations of methyl paraben (mol L^{-1}) in the solvent fraction inside the silicone membrane, calculated assuming that the alcohols retain their bulk density at low temperatures. Mean ± SD ($n = 5$).

T (K)	Butanol	Heptanol
278.15	0.0092 (±0.0005)	0.0093 (±0.0008)
283.15	0.0091 (±0.0003)	0.0081 (±0.0008)
288.15	0.0093 (±0.0002)	0.0087 (±0.0003)

The results obtained for butanol and heptanol at each experimental temperature are summarised in Table 1. The data show that the vehicle–membrane partition coefficients calculated for both alcohols at temperatures below 20 °C were the same within experimental error ($p > 0.05$). There also appears to be a decrease in the K_m for heptanol at higher temperatures, whereas no apparent trend is observed for butanol. Moreover, all the calculated K_m values listed in Table 1 are approximately one. A vehicle–membrane partition coefficient of one indicates that the concentrations of the solute inside and outside the membrane are the same. Considering that the alcohol molecules inside the membrane retain the bulk density at temperatures below ~16 °C (McAuley et al., 2010), it is also possible to calculate the molar concentration of methyl paraben in the alcohol fraction inside the membrane for this range of temperatures. The results, shown in Table 2, are very similar for both butanol and heptanol, and are the same within experimental error to the concentration of methyl paraben in the outside bulk solvent (i.e. 0.01 M). These findings indicate that, both alcohols have the same effective concentration of methyl paraben inside the membrane. In other words, if the assumptions discussed above are true, in the low temperature range the partitioning of methyl paraben into the silicone membrane is independent of the vehicle used. The differences between butanol and heptanol reflect the actual volume fraction occupied by the alcohols inside the silicone membrane. The great similarity between K_m calculated at low and high temperatures for both alcohols (Table 1) suggests that this is also true above ~16 °C, even though at high temperatures there is a change in the structure (i.e. density) of the alcohol molecules inside the

silicone membrane (McAuley et al., 2010). The implications of this for membrane partitioning are that vehicles which are greatly taken up by the silicone membrane will occupy a larger "accessible" volume inside the membrane. Since the concentration of the solute in the volume fraction inside the membrane remains the same as in the bulk phase, this will result in a higher total amount of methyl paraben inside the silicone membrane.

3.2. Comparison between membrane transport and equilibrium experiments

The passive transport of compounds across a given membrane involves an initial partitioning step at the superficial layer of the membrane, where the formulation is applied. Here, the compound will distribute between the two phases depending on its relative affinity between the vehicle and the membrane. When steady-state flux is achieved, the ratio of the concentrations of the permeant in the vehicle and the membrane will be a constant, i.e. the vehicle–membrane partition coefficient (K). This is an equilibrium (i.e. thermodynamic) property, which is used in Fick's law as a measure of the concentration of the compound at the vehicle–membrane interface (Eq. (1)).

In previous membrane transport experiments, Oliveira et al. (2010) obtained vehicle–membrane partition coefficients (K) of methyl paraben for silicone membranes by fitting the permeation data to a mathematical model derived from Fick's second law of diffusion. Both the membrane transport (Oliveira et al., 2010) and equilibrium experiments were conducted under similar experimental conditions. Assuming that the latter are representative of the thermodynamic equilibrium established at the donor–membrane interface when steady-state is achieved, a comparative analysis of both partition coefficients may thus be performed. The results show that the equilibrium K_m reported in the present paper for both butanol and heptanol (Table 1) differ significantly from the K obtained from the permeation studies at all experimental temperatures (Oliveira et al., 2010). Whereas K_m is similar for both vehicles and does not change significantly with temperature, K was significantly higher using butanol compared with heptanol ($p < 0.05$). Moreover, the vehicle–membrane partition coefficients obtained in membrane equilibrium experiments (i.e. K_m) were approximately one and of a much higher magnitude than those obtained in the membrane transport experiments (i.e. K). The significance of this lies in the different meaning of the two partition coefficients, as follows.

The partition coefficient K is obtained indirectly from the permeation data by non-linear modelling using an analytical solution to Fick's second law of diffusion. The model equation uses the assumption that the membrane is an inert, homogeneous slab with finite dimensions. Hence, in the context of the membrane transport experiments, the calculated K represents the concentration of methyl paraben at the donor–membrane interface with respect to the overall volume of the silicone membrane. This is possibly why the temperature-dependent behaviour of K obtained from the permeation data (Oliveira et al., 2010) showed a similar trend to that observed with the methyl paraben extraction data normalised per gram of membrane using butanol (Fig. 1), but not heptanol, as vehicle.

In the present paper, the vehicle–membrane partition coefficients from the equilibrium experiments are calculated taking into account the specific information of the alcohol uptake into the membrane and assuming that the drug exists solely within the alcohol fraction inside the silicone membrane. The structure of the silicone membrane will likely comprise areas that are accessible and others that are not to the molecules of a given vehicle taken up by the membrane. The "accessible" volume inside the membrane will be thus occupied by the vehicle depending on its molecular characteristics. Also, silica filler (typically 20–30%, w/w) is often included during the casting of silicone, where it behaves like an inert dispersed phase (Twist and Zatz, 1986). The interplay between these factors will cause the volume available for partitioning to be drastically reduced compared with the total volume of the membrane. In the case of butanol and heptanol, the respective solvent fractions occupied inside the silicone membrane range only from about 12–21 (smaller molecule) and 7–11% (w/w). This restricted volume of the membrane occupied by the solvent and available for partitioning is taken into account in the calculation of the K_m from the equilibrium experiment, but not in the membrane transport experiments. The K values derived from Fick's laws of diffusion (Eq. (1)) will fit the data assuming all the volume of the membrane is available for permeation and in order to express the concentration of the methyl paraben at the donor–membrane interface, the magnitude of K will be less than that of K_m.

Another important point to consider is the relevance of the findings of the equilibrium experiments for membrane transport. The findings from the membrane partition experiment indicate that the concentrations of methyl paraben in the solvent fraction inside the membrane are the same for butanol and heptanol, and thus the vehicle–membrane partition coefficients. Accordingly, the differences observed in the fluxes of methyl paraben in the two alcohols (Oliveira et al., 2010) will necessarily be attributed to the dynamic part of the equilibrium (i.e. diffusion coefficient, D). In this case, the diffusion of the solute will be ultimately affected by the properties of the alcohol phase in the membrane. The self diffusion coefficients of butanol and heptanol are reported in the literature at 25 °C as $0.43(\pm0.03)\text{E}{-09}\ \text{m}^2\ \text{s}^{-1}$ and $0.18(\pm0.01)\text{E}{-09}\ \text{m}^2\ \text{s}^{-1}$ (Stilbs et al., 1983), respectively. These values suggest that the diffusion of methyl paraben across the silicone membrane should be faster in butanol compared with heptanol, which is in line with our previous experimental observations (Oliveira et al., 2010). Further support is given by the results from the kinetic analysis of diffusion coefficients of methyl paraben in butanol through silicone membranes reported by Oliveira et al. (2010). The authors showed a great similarity between the diffusion activation energy calculated above 20 °C and that reported in the literature for the viscous flow of butanol. This indicates a dominant effect of the properties of the imbibed alcohol on the diffusional characteristics of the silicone membrane. However, this was not observed for heptanol, possibly owing to the relatively smaller volume fraction occupied by this alcohol in the silicone membrane.

3.3. Thermodynamic analysis of K_m

The van't Hoff plots constructed with the vehicle–membrane partition coefficients obtained from the equilibrium experiments (Table 1) are shown in Figs. 4 and 5 for butanol and heptanol, respectively. The data show no apparent trend in the partitioning behaviour of methyl paraben into the silicone membrane using butanol as vehicle. The enthalpy change (ΔH) for the process, calculated from the slope of the line in Fig. 4, was $-0.4\ \text{kJ mol}^{-1}$ (±0.9). This value may be considered negligible in terms of the thermal energy of the system. Conversely, the van't Hoff plot obtained using heptanol as vehicle (Fig. 5) shows a definite positive trend for the membrane partitioning behaviour of methyl paraben. This corresponds to a small but meaningful enthalpy, ΔH of $-3.5\ \text{kJ mol}^{-1}$ (±0.7), which is indicative of an exothermic process. The analysis by Burgess et al. (2005) suggests that an exothermic process such as that reported in Fig. 6 favours partitioning of methyl paraben at lower temperatures from heptanol vehicles. Since the activation energy for drug diffusion is necessarily positive, and assuming that diffusion is faster than the partitioning process, cycling between low and high temperatures could thus be used in this case to promote membrane transport.

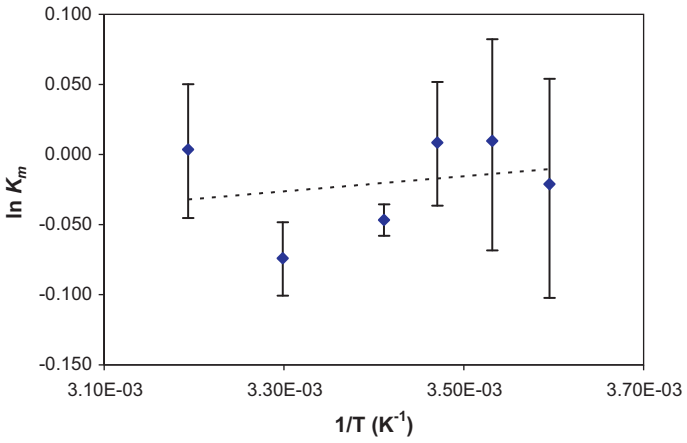

Fig. 4. Van't Hoff plot of the butanol–membrane partition coefficients (K_m) estimated in the equilibrium experiments (Mean ± SD; $n = 5$).

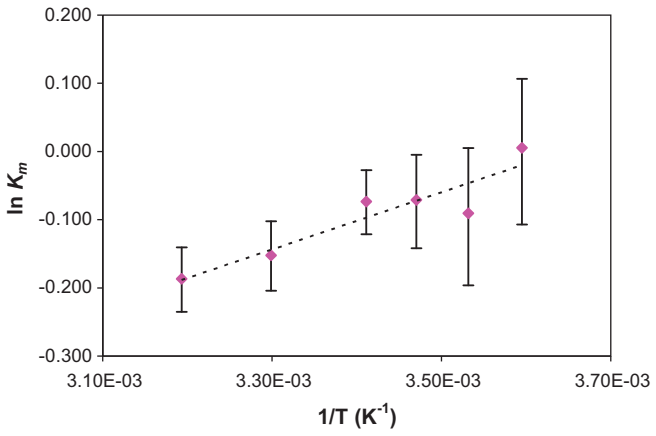

Fig. 5. Van't Hoff plot of the heptanol–membrane partition coefficients (K_m) estimated in the equilibrium experiments (Mean ± SD; $n = 5$).

Finally, the findings from the equilibrium experiments differ considerably from the partitioning trends of methyl paraben in butanol and heptanol obtained in the membrane transport studies (Oliveira et al., 2010). This is the result of the fundamental differences between K_m and K, already discussed in the previous Section 3.2.

3.4. Model of alcohol enhanced permeation in silicone membranes

The observations from the membrane transport (Oliveira et al., 2010) and equilibrium experiments led to the formulation of a conceptual model of alcohol enhanced permeation in silicone membranes. It is hypothesized that alcohol enhanced transport is entirely dependent on solvent uptake into the membrane. The proposed mechanism is that the alcohol molecules associate in "pools" within the membrane. Although not acting entirely like bulk liquid at temperatures above ~16 °C, these will enable the solute molecules to exist within the alcohol fraction inside the membrane at a concentration similar to that in the outside vehicle. This will result in relatively large total amounts of solute per gross volume of the membrane, thus increasing the vehicle–membrane partition coefficient as defined by Fick's law of diffusion (i.e. K; Eq. (1)).

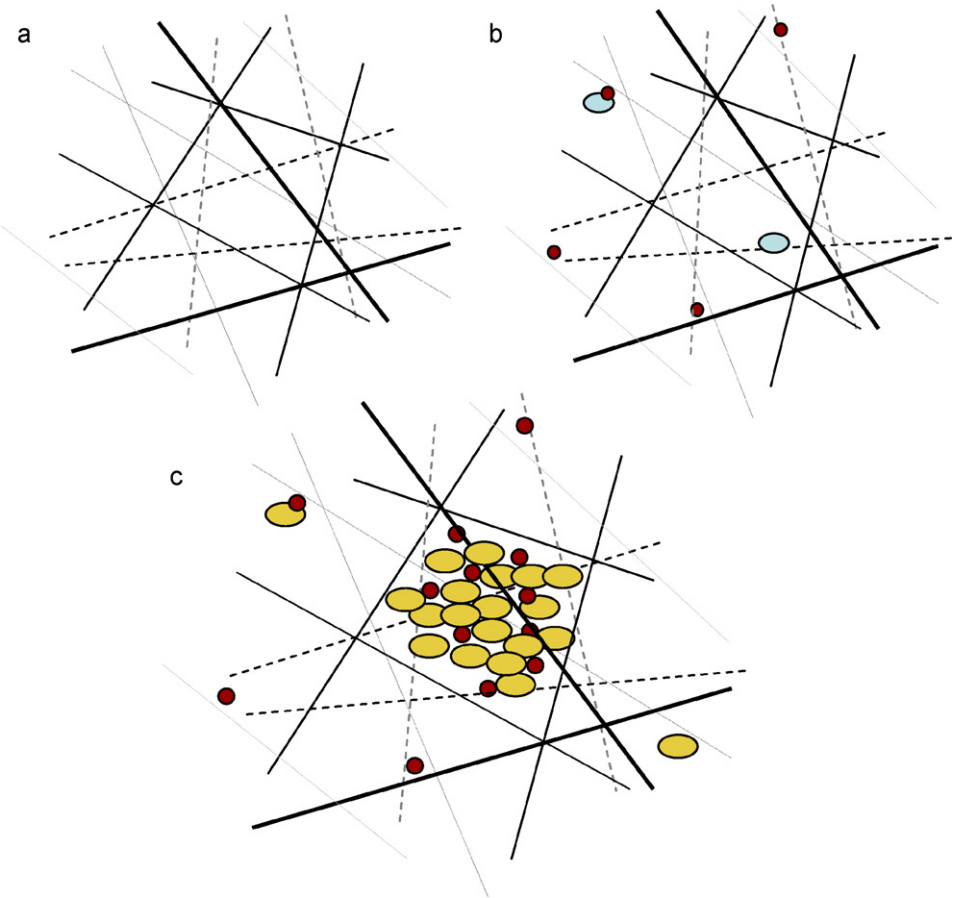

Fig. 6. Conceptual model for solvent interactions with silicone membranes. Drug molecules are represented by the smaller circles, whereas the alcohol molecules are represented by the larger oval shapes (● and ● represent heptanol and butanol molecules, respectively).

The uptake of alcohol molecules into the membrane will also have a major impact on the diffusion coefficient (i.e. D) of the solute across the silicone membrane. In this context, depending on the degree of uptake, the diffusional behaviour of the membrane will be ultimately dependent on the properties of the imbibed alcohol.

The conceptual model proposed for alcohol enhanced permeation in silicone membranes is depicted in Fig. 6. Silicone is a hydrophobic elastomer at room temperature (Fig. 6a). The silicone matrix is composed of long polydimethylsiloxane chains, occasionally cross-linked and randomly dispersed in a random coil (Krevelen, 1990). The use of alcohols such as heptanol, with a larger molecular volume, will result in this alcohol occupying a relatively smaller available volume inside the silicone membrane (i.e. smaller membrane uptake; Fig. 6b). Consequently, the solute will partition into a relatively smal alcohol fraction within the membrane. Conversely, alcohols such as butanol will be taken up to a greater extent (Fig. 6c). The vehicle will thus "drag" the solute molecules inside the membrane, promoting a higher membrane concentration (i.e. increased K). Since the drug is assumed to exist in the alcohol fraction inside the membrane, the alcohol enhancement effect will be entirely dependent on the degree of solvent uptake, and also on the concentration of the solute in the vehicle.

A model of alcohol enhanced permeation in silicone membranes was also proposed by Twist and Zatz (1990), based on their findings on membrane equilibrium and transport studies using a series of parabens (i.e. methyl, propyl and butyl paraben) and 1-propanol as representative alcohol. The authors postulated that the extent of paraben partitioning with the membrane was dependent on the degree of alcohol (i.e. 1-propanol) sorption and on the concentration of the solute in the vehicle. This was attributed to the formation of alcohol clusters inside the silicone membrane which would "pull" in the solute. According to Twist and Zatz, the solute concentration within these alcohol clusters would be much lower (i.e. less than half) than that of the applied vehicle. The authors also considered the diffusivity of the solute to be unaffected by alcohol uptake, but primarily dictated by the polymer matrix.

Based on our findings, the model presented in this paper differs from that proposed by Twist and Zatz (1990) in two main points: in considering that (1) the concentration of the drug in the solvent fraction inside the membrane is similar to that in the outside vehicle; and (2) the diffusional behaviour of the membrane, and thus the diffusion coefficient of the solute diffusing through the membrane, will be ultimately affected by both the degree of sorption and the properties of the alcohol taken up by the membrane.

4. Conclusions

The results from the equilibrium experiments reported in this paper showed a linear relationship between the amount of methyl paraben extracted from the silicone membrane and the corresponding solvent uptake ($r^2 \sim 0.97$), indicating a direct dependence of the total amount of solute extracted from the silicone membrane on the degree of solvent sorption. However, the vehicle–membrane partition coefficients (i.e. K_m), calculated for both alcohols taking into account the specific information of alcohol uptake into the membrane, were approximately one. This suggests that the effective concentrations of methyl paraben inside and outside the membrane were the same for butanol and heptanol. The distinctive trends observed in the extracted amounts of methyl paraben from the silicone membrane were thus attributed to the different volume fractions occupied by the alcohols inside the membrane at different temperatures. In other words, vehicles highly taken up by the silicone membrane occupy larger volume fractions inside the membrane, albeit maintaining the same solute concentration as the outside vehicle. Hence, high solvent sorption promotes high overall solute concentrations with respect to the membrane volume. This was apparent in the results from the membrane transport studies (Oliveira et al., 2010), showing significantly higher vehicle–membrane partition coefficients (i.e. K) obtained using butanol, the alcohol with the highest uptake into the membrane, compared with heptanol as vehicle.

The reported findings for both transport (Oliveira et al., 2010) and equilibrium experiments support a model of alcohol enhanced permeation in silicone membranes where high solvent sorption promotes high concentrations of the solute in the gross volume of the membrane (i.e. modify K) by "carrying" the solute molecules into the solvent fraction inside the membrane. High solvent uptake will also affect the diffusional properties of the silicone membrane (i.e. D), which will ultimately be dominated by the properties of the imbibed alcohol.

The proposed model of solvent enhanced permeation in silicone membranes will be validated using a range of excipients commonly used in topical formulations in future studies. The implications of the proposed model of solvent enhanced permeation for skin transport will also be explored.

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