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Alcohol enhanced permeation in model membranes. Part I. Thermodynamic and kinetic analyses of membrane permeation

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ABSTRACT

While it is well recognised that formulation components influence drug permeation, few studies have addressed the influence of vehicles on drug transport in artificial or biological membranes Previously we have investigated the effects of temperature on the uptake of model vehicles (i.e. alcohols) into silicone membrane. The present study evaluates the permeation of the model drug methyl paraben in the presence of butanol or heptanol. Drug permeation through silicone membranes was studied at different temperatures for each vehicle. Thermodynamic and kinetic analyses of the permeation data were conducted to elucidate the possible mechanisms of drug transport. Independent examination of the partition and diffusion coefficients estimated for the permeation studies at different temperatures showed a break point occurring near 20 °C for butanol, but not heptanol. This transition temperature separated two different mechanisms of solute diffusion and partitioning, which may be associated with a change in the properties of the solvent. This was not observed from an analysis of flux data, owing to compensatory influences on the diffusion and partition behaviour of the drug. The study underlines the importance of appropriate temperature control when studying drug permeation.

1. Introduction

Drug permeation through biological membranes depends not only on the physicochemical properties of the drug, but also on the formulation. The use of excipients that interact with the membrane, changing their physicochemical properties and consequently modulating solute transport, is a common strategy to improve dermal delivery. In this context, understanding the physicochemical determinants of vehicle-membrane interactions is crucial for selection of optimal penetration enhancers and effective formulation design.

In vitro studies using human skin are ideal for monitoring drug delivery and evaluation of formulations, and provide a good representation of the processes *in vivo* (Franz, 1975). Nevertheless, these studies are associated with several difficulties and limitations for assessing the effects of formulation components, particularly because of the complex nature of biological tissue and inter- and intra-individual variability of skin samples. Artificial model membranes offer a simple and reproducible alternative to study the basic physicochemical mechanisms of drug permeation, and provide a basis for understanding more complex interactions with human skin. The utility of such models, particularly of silicone membranes, for the screening of topical formulations and assessing their contribution to the overall mechanisms of drug transport across human skin is well documented in the literature (Nakano and Patel, 1970; Pellett et al., 1997; Dias et al., 2007; Watkinson et al., 2009a,b). Notwithstanding this, a recent inter- and intra-laboratory silicone membrane transport study (Chilcott et al., 2005) has reported a significant coefficient of variation between laboratories (~35%), with a fourfold difference in the highest and lowest average flux values. If artificial membranes such as silicone are to have utility as models for membrane transport then the reasons underlying this variability must be understood. Membrane-solvent interactions have been investigated using solvent uptake by many workers, including Twist and Zatz (1988). High solvent sorption can alter the physicochemical properties of the membrane and result in changes in the partition and diffusion properties of the drug, and thus modified permeation. Twist and Zatz (1988) correlated the alcohol uptake into polydimethylsiloxane (silicone) membranes with enhanced permeation of methyl and propyl paraben from the corresponding saturated alcohol solutions. Their findings related flux enhancement to increased drug solubility in the membrane and, to a lesser extent, increased diffusivity. An optimum balance between solute and vehicle concentrations was required for maximum permeation, owing to reduced solvent activity (and hence membrane sorption) of the solvent, as the solute concentration increased (Twist and Zatz, 1990). However, the authors did not address the actual

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mechanism of the alcohol–membrane interactions and the possible implications for membrane transport.

We have previously investigated the uptake of a homologous series of aliphatic alcohols with 2–10 carbon numbers into silicone membranes at different temperatures by a gravimetric method (McAuley et al., in press). An increase in alcohol membrane sorption with carbon number from ethanol to butanol (4 carbon atoms), was observed after which sorption decreased exponentially with increasing aliphatic chain length. The results were generally in agreement with the findings of Twist and Zatz (1988) obtained at 37 °C, but the highest membrane uptake was observed for butanol rather than propanol. A van't Hoff analysis of the equilibrium constants estimated at different temperatures was conducted for the alcohols with higher uptake (propanol, butanol, pentanol, hexanol, heptanol and octanol). Similar plots were obtained for all alcohols and two individual linear trends in the profiles were evident, separated by a break point occurring near 17 °C. Non-linearity in the van't Hoff plots reflected, in this case, a change in the mechanism of alcohol sorption possibly associated with the properties of the silicone-solvent system. Below the transition temperature the process was entropy driven whereas above it was dominated by the significant associated enthalpy. Additionally, changes in membrane volume related with solvent uptake suggested a different organization of the alcohol molecules inside the silicone membrane for temperatures above and below the transition temperature, which is likely to impact on the partitioning of solutes into the membrane.

The present investigation builds on the findings of the earlier study and explores the implications for butanol or heptanol uptake on membrane transport of methyl paraben. Butanol exhibited the highest uptake of all the alcohols in the previous study and heptanol was selected as representative of alcohols with a chain length >4. Thermodynamic and kinetic analyses of the membrane transport data obtained at different temperatures are evaluated to gain a mechanistic understanding of the processes involved in the solute transport across the membrane.

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. Solubility studies

Saturated solutions of methyl paraben were produced by adding excess amounts of the solute to each alcohol in a glass vial containing a Teflon coated magnetic flea. The vials were allowed to equilibrate with stirring for at least 24 h at 32 °C (±0.5 °C) to produce saturated solutions with visible excess chemical. The saturated suspensions were then sampled and filtered using a syringe and filtration unit (13 mm PTFE filter media device, 0.2 μm pore size, Whatman®) previously conditioned at the same temperature to avoid further precipitation/solubilisation of the drug. The obtained saturated solutions were suitably diluted with ethanol and quantified by HPLC.

2.3. Permeation studies using silicone membranes

Permeation studies were conducted in Franz-type diffusion cells using pre-treated silicone membranes and "symmetric" conditions (same solvent in both donor and receptor compartments) to prevent changes in the membrane thickness during the experiment and to avoid the existence of solvent gradients across the membrane. Donor solutions of methyl paraben in 1-butanol and 1-heptanol were prepared at a concentration of 1.52 mg/ml (0.01 M). The silicone membranes were cut to appropriate size and pre-treated with the solvent for 24 h at the experimental temperature before starting the experiment. The donor and the receptor phase were also equilibrated at the experimental temperature. The receptor phase was degassed for ~3 min in a Hilsonic ultrasonicator (Hilbre Ultrasonics Ltd, England) prior to the permeation studies. Permeation experiments were conducted at 40, 30, 20, 15, 10 and 5 (±1)°C. The pre-treated membranes were carefully blotted with absorbent paper tissue before mounting in the Franz cells which were equilibrated for 30 min before starting the experiment. The actual temperature of the membranes once mounted in the Franz cells was also measured (Digitron TM-22 Differential Digital Thermometer, RS Components, Corby, UK) for the range of experimental temperatures tested. The volume of donor solution used was 1 ml and the donor compartment was covered with Parafilm® during the experiment to prevent evaporation. Collections of 200 μl were taken every 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 min, with volume replacement using fresh receptor phase. At the end of the experiment, the membranes were carefully blotted to remove excess solvent and the thickness was measured (Electronic Outside Micrometer, 0–25 mm, 0.001 mm, RS Components, UK).

2.4. HPLC analysis

The HPLC System comprised of a Hewlett Packard HP1050 Series injector, HP1050 Series quaternary pump, HP1100 Series degasser and a HP1050 Series UV Detector. The data acquired with PRIME Software version 4.2.0 (HPLC Technology Co. Ltd). Quantification of methyl paraben was achieved by injecting 20 μl of the sample in the HPLC system equipped with a reverse-phase C_{18} column (Phenomenex® Synergi 4 μm Fusion-RP 80A) and eluting the sample at room temperature with a methanol:water (60:40 v/v) mobile phase (flow rate 1.0 ml min^{-1}). Detection of the analyte was at 254 nm. The method was validated and proved to be suitable for accurate quantification of methyl paraben (coefficient of variance ≤10–15%; $r^2 \geq 0.999$) within the concentration range from 0.063 to 70 μg ml^{-1}. The estimated lower detection limit was 0.02 μg ml^{-1}, and the tailing factor was below the maximum acceptable value (Twist and Zatz, 1988). The method also showed good injection reproducibility (coefficient of variance < 5%, $n = 3$).

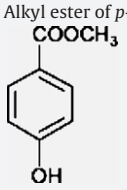
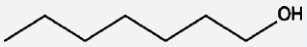
2.5. Data analysis

Permeation data was fitted to a finite dose model expressed as a Laplace transform (Eq. (1)) using Scientist©(Micromath, St. Louis, USA).

$$\overline{\text{Amount}} = \frac{C_v \cdot V \cdot K\sqrt{\frac{D}{s}}}{s^2 \cdot \left[A \cdot K \cdot \sqrt{\frac{D}{s}} \cdot \cosh\left(\sqrt{\frac{s \cdot h^2}{D}}\right) + V \cdot \sinh\left(\sqrt{\frac{sh^2}{D}}\right)\right]} \quad (1)$$

where s is the Laplace variable, K and D are the partition and diffusion coefficients, h is the thickness and A is the area of the membrane, V is the volume of donor phase, and C_v is the drug concentration in the vehicle. This allows the determination of D, the membrane diffusion coefficient and K, the partition coefficient of methyl paraben when applied in the specific vehicle. Permeability coefficients (k_p), steady-state fluxes (J_{ss}) and lag times (t_{lag}) can also be calculated, following Eqs. (2), (3) and (4), respectively.

Table 1
Structure and physicochemical properties of methyl paraben, butanol and heptanol.

Description	Methyl paraben	Butanol	Heptanol
	Alkyl ester of *p*-hydroxybenzoic acid	Aliphatic alcohol	Aliphatic alcohol
Structural formula			
Molecular weight ($g\,mol^{-1}$)	152.15	74.12	116.2
log K_{ow}	1.96[a] 1.44[b]	0.82[b]	2.41[b]
Solubility parameter $(cal\,cm^{-3})^{1/2}$	13.51[c]	10.78[c]	9.84[c]
Density ($g\,cm^{-3}$)	–	0.821 (5 °C)[d] 0.817 (10 °C)[d] 0.814 (15 °C)[d] 0.810 (20 °C)[d] 0.802 (30 °C)[d] 0.795 (40 °C)[d]	0.833 (5 °C)[d] 0.829 (10 °C)[d] 0.826 (15 °C)[d] 0.822 (20 °C)[d] 0.815 (30 °C)[d] 0.808 (40 °C)[d]

[a] Data from Abraham et al. (1994).
[b] Fragment based log octanol–water partition coefficient estimated using Molecular Modelling Pro Demo software (version 6.2.3) according to the Hansch and Leo's group contribution method.
[c] van Krevelen and Hoftyzer type 3-D solubility parameters estimated using Molecular Modelling Pro Demo software (version 6.2.3) according the van Krevelen's group contribution method.
[d] Data from Wilhoit and Zwolinski (1973).

$$k_p = \frac{KD}{h} \quad (2)$$

$$J_{ss} = k_p C_v \quad (3)$$

$$t_{lag} = \frac{h^2}{6D} \quad (4)$$

3. Results and discussion

3.1. Solubility

The chemical structures and physicochemical properties of methyl paraben, butanol and heptanol are shown in Table 1. The solubility of methyl paraben in both butanol and heptanol was determined at each experimental temperature (Table 2) and the values are in agreement with previously reported solubilities of methyl paraben in butanol (Alexander et al., 1977). The solubility of methyl paraben in butanol is higher than in heptanol for all the experimental temperatures studied ($p < 0.05$). There is also a linear increase ($p < 0.05$, $r^2 > 0.9$) in the solubility of methyl paraben in both butanol and heptanol over the experimental temperature range (data not shown). Furthermore, the enthalpies of solution (ΔH_{sol}) of methyl paraben in each alcohol were very similar. The values calculated from the slopes of the respective van't Hoff plots (Fig. 1) were 14.2 (±0.68) kJ mol^{-1} for butanol and 14.2 (±0.50) kJ mol^{-1} for heptanol. The former is in excellent agreement with the enthalpy of solution of methyl paraben in butanol reported by Alexander et al. (1977), of 14.2 kJ mol^{-1}.

Table 2
Solubility of methyl paraben in butanol and heptanol at different temperatures. Numbers in parentheses represent ±SD ($n = 3$).

T (K)	Butanol ($mol\,L^{-1}$)	Heptanol ($mol\,L^{-1}$)
278.15	0.887 (±0.023)	0.596 (±0.010)
283.15	0.999 (±0.015)	0.702 (±0.010)
288.15	1.099 (±0.001)	0.758 (±0.019)
293.15	1.215 (±0.013)	0.845 (±0.005)
303.15	1.407 (±0.055)	1.017 (±0.023)
313.15	1.814 (±0.018)	1.209 (±0.031)

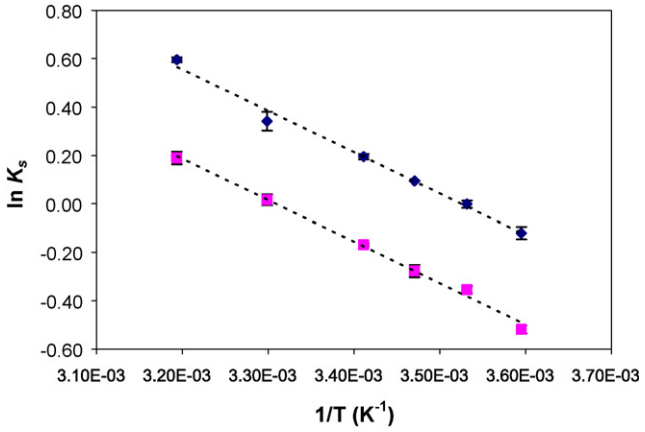


Fig. 1. Van't Hoff plot of the solubilities (K_s in mol/L) of methyl paraben in both (■) butanol and (■) heptanol. Mean ± SD ($n = 3$).

3.2. Permeation studies

The permeation parameters diffusion (D) and vehicle-membrane partition coefficients (K) were estimated for each vehicle by non-linear modelling of the permeation data as described in the Section 2. The data were subsequently used to calculate steady-state flux, permeability coefficient and lag time for each experimental temperature and vehicle. The results are summarized in Table 3 for butanol and heptanol, respectively.

Fig. 2 shows the steady-state fluxes (J_{ss}) of methyl paraben estimated from the permeation parameters in Table 3 for each alcohol and experimental temperature. There is a significant increase in the permeation of methyl paraben across the silicone membrane with temperature for both vehicles ($p < 0.05$), which can be explained in terms of higher kinetic energy of the permeant and faster diffusion through the membrane (Blank et al., 1967; Smith and Haigh, 1992). Highest fluxes were obtained for butanol at all temperatures ($p < 0.05$), which was also the solvent with comparatively higher uptake into the membrane (McAuley et al., in press). This is in agreement with the findings of Twist and Zatz (1988, 1990) and Gelotte and Lostritto (1990) for the alcohol enhanced permeation of methyl

Table 3
Estimated diffusion coefficient (D), vehicle-membrane partition coefficient (K), steady-state flux (J_{ss}), permeability coefficient (k_p) and lag time (t_{lag}), obtained by non-linear modelling of the permeation data of methyl paraben across silicone membranes using butanol and heptanol at the different experimental temperatures ($3 \leq n \leq 5$).

T (K)	D ($cm^2\ min^{-1}$)		K		J_{ss} ($\mu mol\ cm^{-2}\ min^{-1}$)		k_p ($cm\ min^{-1}$)		t_{lag} (min)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Butanol										
278.15	9.83E−06	5.82E−07	0.331	0.030	1.21E−03	9.48E−05	1.21E−04	9.49E−06	12.3	1.0
283.15	1.09E−05	1.61E−06	0.410	0.069	1.61E−03	1.01E−04	1.61E−04	1.01E−05	11.4	0.8
288.15	1.89E−05	9.12E−07	0.305	0.030	2.12E−03	1.12E−04	2.12E−04	1.12E−05	6.5	0.3
293.15	2.09E−05	3.43E−06	0.367	0.071	2.72E−03	1.67E−04	2.72E−04	1.67E−05	6.1	1.0
303.15	2.68E−05	2.57E−06	0.511	0.050	5.02E−03	6.27E−05	5.03E−04	6.27E−06	4.6	0.5
313.15	3.29E−05	3.93E−06	0.623	0.105	7.45E−03	3.05E−04	7.45E−04	3.05E−05	3.8	0.6
Heptanol										
278.15	4.60E−06	4.08E−07	0.166	0.043	2.92E−04	5.05E−05	2.93E−05	5.06E−06	24.0	2.2
283.15	5.38E−06	5.63E−07	0.174	0.019	3.64E−04	2.43E−05	3.64E−05	2.43E−06	20.2	2.1
288.15	8.71E−06	8.68E−07	0.159	0.015	5.30E−04	1.22E−05	5.30E−05	1.22E−06	13.0	1.4
293.15	1.13E−05	1.54E−06	0.155	0.030	6.69E−04	4.84E−05	6.69E−05	4.84E−06	9.9	1.3
303.15	1.83E−05	2.19E−06	0.162	0.026	1.13E−03	7.53E−05	1.13E−04	7.54E−06	6.1	0.7
313.15	2.94E−05	4.52E−06	0.169	0.024	1.90E−03	6.24E−05	1.90E−04	6.25E−06	3.8	0.5

paraben and benzocaine through silicone membranes; suggesting that flux enhancement is highly dependent on the degree of alcohol sorption into the membrane. Differences between fluxes of methyl paraben obtained for the two alcohol donors were the result of both increased D and K of methyl paraben in butanol compared with heptanol, as illustrated by Figs. 3 and 4.

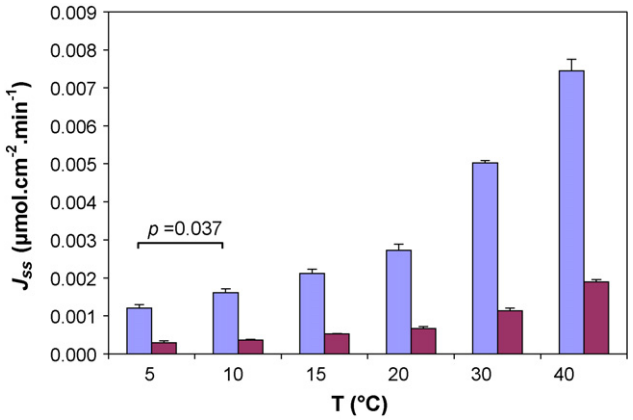


Fig. 2. Steady-state fluxes (J_{ss} in $\mu mol\ cm^{-2}\ min^{-1}$) estimated for the permeation of methyl paraben in ( ) butanol and ( ) heptanol at each experimental temperature (mean ± SD; $3 \leq n \leq 5$).

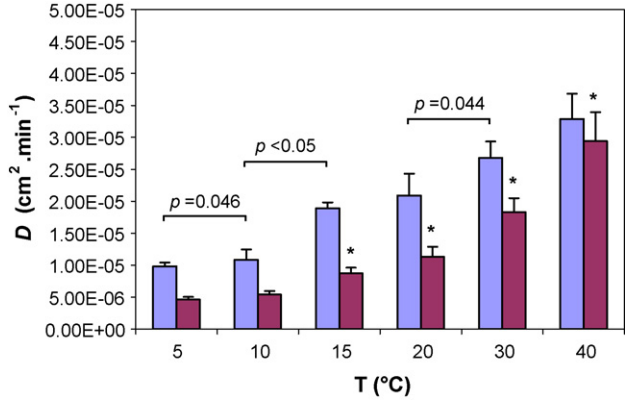


Fig. 3. Diffusion coefficients (D in $cm^2\ min^{-1}$) estimated for the permeation of methyl paraben in ( ) butanol and ( ) heptanol at each experimental temperature (mean ± SD; $3 \leq n \leq 5$). The asterisks represent significant differences between neighbouring values of the same vehicle (Student's t-test, $p < 0.05$).

There is a marked increase in K for the permeation of methyl paraben in butanol at temperatures higher than 20 °C compared with lower temperatures. For the higher temperature range, increased K appears to be the main contributor to the overall flux enhancement of this solvent compared to heptanol. This is in good agreement with the solvent uptake data and the temperature dependent sorption behaviour of butanol into the silicone membrane observed previously (McAuley et al., in press) suggesting that the partitioning of solutes is greatly influenced by the extent of solvent interaction with the membrane.

3.3. Kinetic analysis of J_{ss} and D

If permeation of a compound is studied under conditions of constant concentration (i.e. thermodynamic activity) in the applied formulation over a range of different temperatures, the steady-state flux activation energy (Ea_J) will be a combination of the diffusion activation energy (E_{diff}) and the enthalpy change associated with partitioning of the drug into the membrane (ΔH_m), assuming constant diffusional path length (Burgess et al., 2005), and as expressed in Eq. (5).

$$Ea_J = \Delta H_m + E_{diff} \quad (5)$$

The temperature dependence of any rate parameter such as flux can be described by an Arrhenius relationship, i.e. by plotting its logarithm versus the reciprocal of the absolute temperature

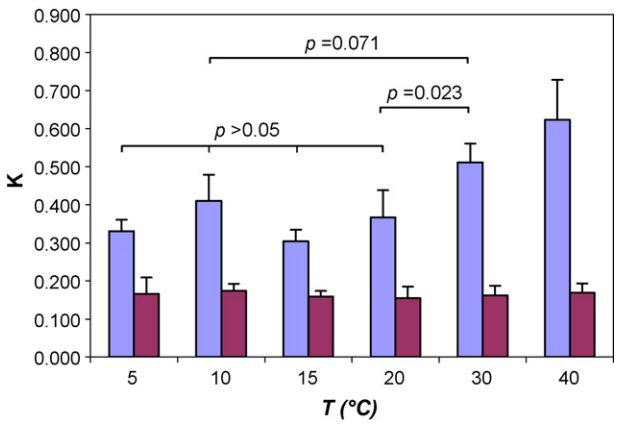


Fig. 4. Partition coefficients (K) estimated for the permeation of methyl paraben in ( ) butanol and ( ) heptanol at each experimental temperature (mean ± SD; $3 \leq n \leq 5$).

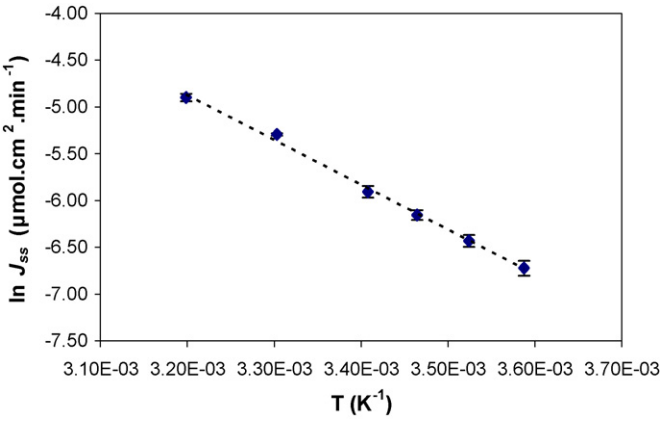


Fig. 5. Arrhenius plot of the estimated flux (in µmol cm^{-2} min^{-1}) for the permeation of methyl paraben in butanol across silicone membranes. Mean ± SD ($3 \le n \le 5$).

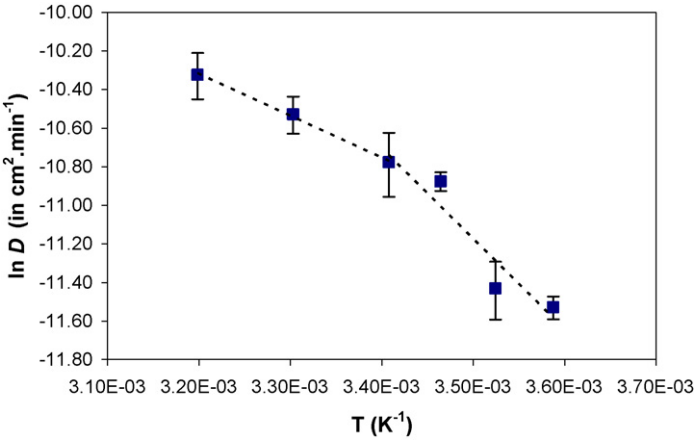


Fig. 7. Arrhenius plot of the estimated diffusion coefficient (in cm^2 min^{-1}) for the permeation of methyl paraben in butanol across silicone membranes. Mean ± SD ($3 \le n \le 5$).

(Kelvin); allowing calculation of the activation energy involved in the process. The Arrhenius plots constructed for butanol and heptanol vehicles (Figs. 5 and 6) show a linear dependence of ln J_{ss} with 1/T. This suggests that there is no change in the mechanisms of transfer of methyl paraben through the silicone membrane within the experimental temperature range. The estimated flux activation energies, calculated using the slopes, are very similar for both alcohols (40 ± 1 kJ mol^{-1} for butanol and 41 ± 1 kJ mol^{-1} for heptanol). This is indicative of similar energy requirements for solute transfer across the silicone membrane from butanol and heptanol.

Similarly the activation energy for solute diffusion (E_{diff}) can be calculated from Arrhenius plots of the estimated diffusion coefficients of methyl paraben at different temperatures (Figs. 7 and 8). Fig. 7 shows a break point occurring around 15–20 °C, which is not present in the Arrhenius plot constructed with the data estimated for heptanol (Fig. 8). This is contrary to what has been observed for the same range of temperatures in the kinetic analysis of the flux, and is an indication of a change in the mechanism of drug diffusion of methyl paraben through the silicone membrane using butanol as vehicle. The calculated diffusion activation energies (Ea_{diff}) are 18.0 ± 0.1 kJ mol^{-1} above the transition temperature for butanol and 39 ± 9 kJ.mol^{-1} below the transition temperature; for heptanol the Ea_{diff} value is 41 ± 2 kJ mol^{-1}. Butanol is the alcohol with highest uptake into the silicone membrane (McAuley et al., in press). The decrease in the activation energy at higher temperatures is possibly related with increased alcohol uptake, causing the membrane to swell and thus facilitating drug diffusion. Furthermore, the work of McAuley et al. (in press) suggests that the fraction of solvent molecules inside the membrane may have different properties at high and low temperatures, with possible impact on the diffusion behaviour of the membrane-solvent system. The same trend is not apparent in the data obtained for the diffusion of methyl paraben using heptanol, possibly because of the lower sorption of this alcohol into the silicone membrane.

The diffusion coefficient of a compound in a given medium can be described by the Stokes–Einstein equation (Eq. (6)), where k_B is the Boltzmann constant, η the viscosity of the medium, r the radius of the compound (spherical particles) and T is the absolute temperature (Atkins and Paula, 2006).

$$D = \frac{k_B T}{6\pi\eta r} \tag{6}$$

An approximate prediction of the dependence of D on temperature can thus be made using Eq. (7):

$$\frac{D_{T_2}}{D_{T_1}} = \frac{T_2 \eta_{T_1}}{T_1 \eta_{T_2}}. \tag{7}$$

As temperature increases a fluid tends to become less viscous, consequently facilitating the diffusion of molecules (Bessire and Quitevis, 1994; Atkins and Paula, 2006). Since the mobility of solvents typically exhibits Arrhenius-type behaviour, the empirical variation of the viscosity with temperature can be expressed by

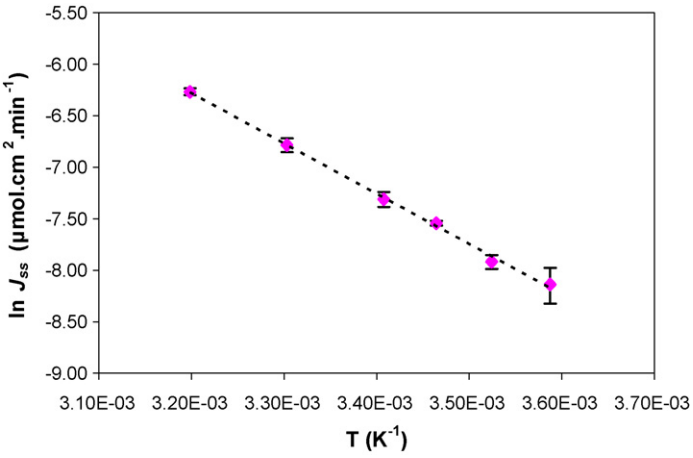


Fig. 6. Arrhenius plot of the estimated flux (in µmol cm^{-2} min^{-1}) for the permeation of methyl paraben in heptanol across silicone membranes. Mean ± SD ($3 \le n \le 5$).

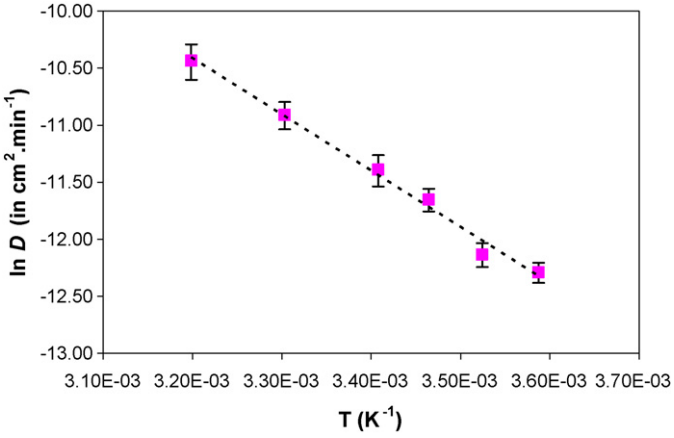


Fig. 8. Arrhenius plot of the estimated diffusion coefficient (in cm^2 min^{-1}) for the permeation of methyl paraben in heptanol across silicone membranes. Mean ± SD ($3 \le n \le 5$).

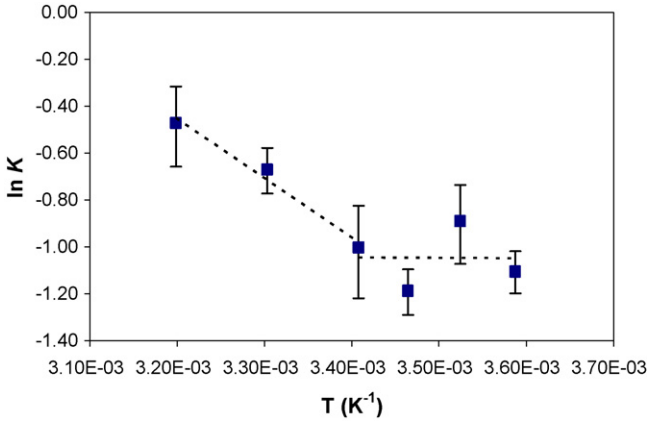


Fig. 9. Van't Hoff plot of the butanol-membrane partition coefficients of methyl paraben estimated from the permeation data. Mean ± SD ($3 \leq n \leq 5$).

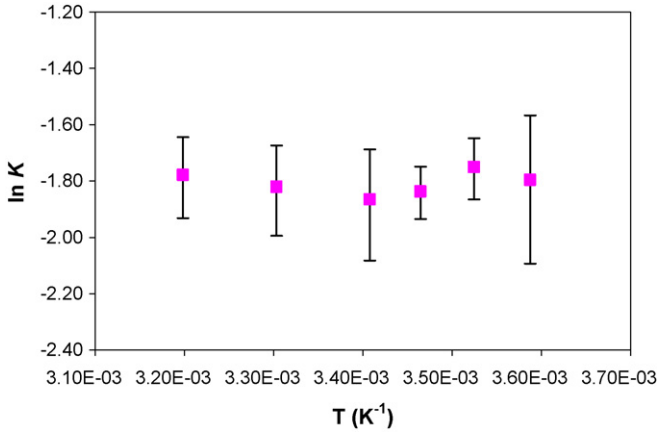


Fig. 10. Van't Hoff plot of the heptanol-membrane partition coefficients of methyl paraben estimated from the permeation data. Mean ± SD ($3 \leq n \leq 5$).

Eq. (8), where R is the gas constant and E_η represents the viscosity activation energy, i.e. the activation energy for the viscous flow of the solvent (Waldeck and Fleming, 1981; Bessire and Quitevis, 1994)

$$\eta = \eta_0 \exp\left(\frac{E_\eta}{RT}\right) \quad (8)$$

Interestingly, the activation energy for methyl paraben diffusion from butanol vehicles through silicone membranes estimated at temperatures above the break point is close to that reported in the literature for the viscous flow of butanol, which is ~19.2 kJ mol^{-1} (Waldeck and Fleming, 1981; Bessire and Quitevis, 1994). These findings suggest that above ~20 °C the temperature dependence of D is closely related to the change in the properties of the solvent imbibed in the membrane rather than to those of the silicone membrane itself. Conversely, the estimated activation energy for solute diffusion from heptanol donors is independent of temperature, and a linear trend is observed for the entire range of temperatures investigated. Furthermore, the Ea_{diff} calculated for methyl paraben in heptanol is much higher than the corresponding viscosity activation energy which is ~23.7 kJ mol^{-1} (Bessire and Quitevis, 1994) and is of similar magnitude to that for butanol below the transition temperature. This is possibly because of the relatively smaller uptake of heptanol and of butanol at lower temperatures into the silicone membrane. This suggests that, under conditions of low solvent sorption, the properties of the silicone membrane dictate the diffusion behaviour of methyl paraben.

3.4. Thermodynamic analysis of K

A van't Hoff analysis was performed using the estimated vehicle-membrane partition coefficients (Figs. 9 and 10). Similarly for the diffusion coefficients for butanol, Fig. 8 shows two different gradients in the temperature dependence of solute in butanol partitioning into the silicone membrane, separated by a break point occurring near 20 °C. In contrast, the van't Hoff analysis of the data obtained with heptanol did not show any definite trend. The different linear trends in Fig. 8 indicate a change in the mechanism of the partition of methyl paraben into the silicone membrane. Below the transition there is a negligible ΔH_m, indicating that the net interactions of methyl paraben outside (i.e. butanol solution) and inside the butanol-saturated silicone membrane are the same, and the process is entropy driven. Conversely, above the transition temperature there is a relatively large endothermic enthalpy change associated with the partitioning of the drug with the membrane. The results are in line with the previously described temperature dependent sorption behaviour of this alcohol into silicone membranes within the same temperature range (McAuley et al., in press). The values of ΔH_m calculated from the slopes of the linear portions of the graph, constructed with estimated butanol-membrane partition coefficients of methyl paraben, were 21 ± 3 kJ mol^{-1} above the transition and 0.2 ± 0.1 kJ mol^{-1} below the transition. Interestingly, these values are consistent with the ΔH reported by McAuley et al. (in press) above and below the transition temperature for the uptake of butanol into the silicone membrane (15.3 ± 0.4 kJ mol^{-1} and 2.2 ± 3.1 kJ mol^{-1}, respectively).

Despite the non-linearity observed in the Arrhenius and van't Hoff plots constructed with the butanol data (Figs. 7 and 9) indicating a change in the respective mechanisms of diffusion and partition, no break in flux was observed (Fig. 5). This is because of the compensatory trends in the diffusion and partition behaviour of methyl paraben in silicone membranes observed at high and low temperatures. The robustness of the approach is further demonstrated when the calculated and experimental flux activation energy values (Ea_J), for butanol are considered. Using Eq. (5), a value of 39.10 kJ mol^{-1} is obtained above the transition temperature and a value of 39.19 kJ mol^{-1} is obtained below the transition temperature. This compares well with the experimental value determined from the data in Fig. 5 which is 39.85 ± 1.17 kJ mol^{-1}.

4. Conclusions

Over the range of temperatures investigated, independent examination of the partition and diffusion coefficients of methyl paraben permeation across silicone membranes from butanol indicates that relevant changes in the mechanisms of drug partition and/or diffusion may occur which are not evident solely from a kinetic analysis of the flux data. These findings underline the importance of thermodynamic and kinetic analyses when investigating drug transport. The data also suggests that appropriate control over experimental variables such as the membrane temperature may greatly improve the quality of permeation data generated in diffusion experiments. Future studies will focus on empirical measurement of solvent uptake and partitioning of methyl paraben into silicone membranes as a function of temperature to further investigate the trends observed in this study.

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