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Influence of membrane–solvent–solute interactions on solute permeation in model membranes

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Abstract

The interaction of the components of topical formulations with the skin is an important consideration for effective drug delivery and efficacy. The relative importance of solubility parameters and other solvent properties on membrane diffusion processes has not been fully elucidated in the literature. In this paper, the effect of different vehicles on the permeation of caffeine, salicylic acid and benzoic acid through silicone membranes was evaluated. Polydimethylsiloxane membranes were used as model membranes for comparing the release characteristics of saturated solutions of model permeants because of their homogeneity and uniformity. Log P (octanol–water partition coefficient) and solubility parameter values were calculated for the compounds under study. In vitro diffusion studies indicated that the permeation profiles of all solutes showed a similar pattern. The permeation rates of benzoic acid and salicylic acid through silicone membrane from saturated solutions were higher than those for caffeine reflecting the more lipophilic nature of these compounds in comparison with caffeine. Solvent uptake studies confirmed that the vehicles that were highly sorbed by the membrane altered its properties and hence the flux. Vehicles that were not sorbed by the membrane showed similar steady-state fluxes for the model drugs. This suggests that the diffusion process is mainly influenced by the interactions between the vehicles and the membrane. Solubility parameter alone cannot explain the interactions between the membrane and the vehicles in all cases. Rather, it is likely that membrane flux reflects a combination of different solvent and solute characteristics, such as size, shape and charge distribution.
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Keywords: Solubility parameter; Vehicle; Dermal; Transdermal; Permeation; Flux

1. Introduction

Methods of quantifying solvent–drug and solvent–membrane interactions using solubility parameters (δ) have been suggested as useful in predicting drug flux (J). The theory of the solubility parameter was first developed by Hildebrand and co-workers based on regular solution theory (Hildebrand and Scott, 1950). A number of authors have considered the role of solubility parameter in skin permeation for example Liron and Cohen (1984) and Sloan et al. (1986). The solubility parameter is defined as the square root of the cohesive energy densities, which corresponds to the energy of vaporisation per unit volume (Eq. (1)).

$$\delta = \left(\frac{\Delta E_v}{V_m}\right)^{1/2} \quad (1)$$

where V_m represents the molar volume and E_v is the energy of vaporisation.

The solubility of a solid in a vehicle can be expressed by the following equation (Martin, 1993):

$$-\ln X_2 = \frac{\Delta H_f}{RT}\left(\frac{T_0 - T}{T_0}\right) + \frac{V_2 \Phi_1^2}{RT}(\delta_1 - \delta_2)^2 \quad (2)$$

where X_2: molar fraction solubility; Φ_1: volume fraction of solvent; V_2: molar volume of solute; R: gas law constant; T: temperature in degrees Kelvin; T_0: melting point of the solid; (H_f: molar heat of fusion; δ_1: the solubility parameter of the solvent; δ_2: the solubility parameter of drug

For a particular temperature, the first term of the equation is constant. Therefore, the solubility would be expected to increase with the decrease in the difference $(\delta_1 - \delta_2)^2$.

Permeation of a solute through a membrane is influenced by the solute activity gradient in the membrane and also by its mobility within the membrane. Solute and/or solvent

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interactions with the membrane can alter the membrane physicochemical properties. This will lead to a modified permeation through the membrane that will result from the diffusivity and partitioning of the drug in the altered membrane.

Garrett and Chemburkar (1968) reported that with increasing ethanol content, an increase in the diffusion rate of 4-aminopropiophenone through silicone membrane from saturated water/ethanol solutions was observed. Twist and Zatz (1988a,b) studied the permeation of methyl paraben through silicone membrane from saturated solutions of a series of alcohols and found that the permeation rate was not constant; uptake of neat alcohol was well correlated with the flux data. In addition, these vehicles mainly affected the partition of the drug in the membrane with less influence on the diffusion coefficient. In a further investigation (Twist and Zatz, 1990) it was observed that an increase in the paraben concentration reduced the alcohol activity, its uptake by the membrane and consequently the partition coefficient of the paraben. Therefore, it is important to have an understanding of the physical and chemical properties of the vehicles and their potential to interact with both permeant and membrane for rational design of dermal and transdermal formulations.

The aim of the present work was to investigate the effect of different vehicles on the permeation of caffeine, salicylic acid and benzoic acid through silicone membranes. Solubility parameters were calculated for the model compounds and for all vehicles studied. Polydimethylsiloxane membranes were used as model membranes for comparing the release characteristics of different formulations because of their homogeneity and uniformity. The interaction of the different solvents with the membrane was also investigated by gravimetric and calorimetric measurement.

2. Materials and methods

2.1. Materials

Caffeine was obtained from May and Baker Ltd. (UK), benzoic acid from Fisons (UK). Isopropyl myristate was obtained from Croda Universal Ltd., decanol, mineral oil and butyl acetate from Aldrich (UK), glycerol from ICN biochemicals. Propylene glycol, octanol, butanol and salicylic acid were obtained from Fisher Scientific (UK). Isopropyl lactate, butyl lactate, ethyl lactate and ethyl hexyl lactate were obtained from Purac Biochem, Gorinchem (Netherlands). Polydimethylsiloxane membranes with a thickness of 400 μm were purchased from Samco (St. Albans, UK).

2.2. Solubility parameter and Log P (octanol–water partition coefficient)

The three dimensional solubility parameters were calculated using the cohesive energies determined by the group contributions method according to Van Krevelen and Hoftyer (1976). The Log *P* (octanol–water partition coefficient) values were determined using Advanced Chemistry Development Labs. (Toronto, Canada) software.

2.3. Solubility studies

Excess drug was added to each solvent or co-solvent mixture and stirred with a magnetic bar for 48 h in a water bath maintained at 32 °C. Solutions were centrifuged for 10 min at 5000 rpm. The supernatant solution was then diluted and assayed either by HPLC (caffeine) or UV spectroscopy (benzoic acid salicylic acid). Experiments were performed in triplicate and mean values with S.D. and CV were calculated.

2.4. Diffusion cell studies

Diffusion studies of a variety of solutions of caffeine, benzoic acid and salicylic acid across silicone membrane were performed using Franz type diffusion cells with a receptor phase of 2.5 ml and a diffusional area of 1 cm^2. Sheets of silicone membrane were cut to size and soaked overnight in the receptor solution. The membrane was then placed between the two compartments of the diffusion cells and silicone grease used to produce a leakproof seal between the membrane and compartments.

The receptor compartment was filled with pH 7.4 phosphate buffered saline (PBS) and saturated solutions of the drugs were placed in the donor compartment. Excess solute was present to maintain saturation throughout the experiment. Uniform mixing of the receptor phase was obtained with a magnetic stirrer that was placed in the receptor compartment. The diffusion cells were placed on a stirring bed immersed in a water bath at 37 °C to maintain a temperature of ∼32 °C at the membrane surface.

At predetermined times 0.4 ml of the receptor phase was removed through the arm of the cell and replaced with pre-warmed buffer. Samples were analyzed by HPLC for quantification of caffeine. The whole content of the receptor phase was withdrawn at each sampling interval for UV analysis for benzoic and salicylic acid. The receptor phase was then refilled with pre-warmed buffer. Diffusion experiments were performed under occluded conditions by covering the donor compartment with microscope cover slips (this also ensured that volatile solvents did not evaporate significantly. Experiments were performed in quadruplicate for 12 h. Flux values were calculated by monitoring the cumulative amount of drug diffused and measuring the slope of the graph once steady state diffusion was reached. At least three points were plotted on the linear part of the graph. Lag times were close to zero for salicylic acid, less than 30 min for benzoic acid and less than 3 h for caffeine.

2.5. Solvent uptake

Uptake of vehicles into silicone membrane was determined gravimetrically. Silicone membrane was cut to size and weighed using a balance (Sartorius Research, 10 μg accuracy). The membranes were then placed in a sample bottle containing the vehicle and soaked overnight. The membranes were blotted dry with tissue paper and reweighed. To facilitate monitoring of solvent uptake, the experiments were performed at room temperature in triplicate. The amount of vehicle taken up into the membrane was expressed as weight percent.

Table 1
Physicochemical properties of caffeine, benzoic acid and salicylic acid

Drug	MW (g/mol)	Log *P*	Solubility parameter $(cal/cm^3)^{1/2}$
Caffeine	194.2	−0.07	14.0
Benzoic acid	122.12	1.89	11.2
Salicylic acid	138.12	2.06	14.7

2.6. Differential scanning calorimetry (DSC)

In order to investigate the effect of selected solvents on the membrane, sheets of silicone membrane were pre-treated overnight with isopropyl myristate (IPM), decanol, propylene glycol (PG) and water before DSC measurements. The membranes were then dried with tissue to remove the excess solvent, and cut to appropriate size to fit in the steel pans. Approximately 10 mg were placed in each pan. DSC scans were performed on the silicone membrane either untreated or pretreated with the solvents, at a heating rate of 5 °C/min over a range of −50 °C to 100 °C using a DSC-7 (Perkin-Elmer, Connecticut, USA). The instrument was calibrated using indium as a standard. All DSC curves were evaluated with regard to the reported phase transition of the silicone membrane, which was reported to be −40 °C (Martin, 1993).

2.7. Analysis

Caffeine was analysed by HPLC using a Milton Roy Constametric IIIG pump, flow rate 1 ml/min, with a detection wavelength of 273 nm, an Apex reverse phase ODS 5 μm column and a mobile phase of 85% water and 15% acetonitrile. Retention time was 6 min and calibration curves were constructed using peak area measurements and five standards. Reproducibility was evaluated prior to injection of the samples and during the analysis, and CV were <10% in all experiments. Benzoic acid and salicylic acid were analysed by UV spectroscopy using an Uvikon 860. Samples were analysed at 225 and 295 nm, respectively.

3. Results and discussion

3.1. Solubility studies

The molecular weights, calculated log *P* and calculated solubility parameters of caffeine, benzoic acid and salicylic acid are presented in Table 1. Caffeine is a more hydrophilic molecule than either benzoic acid or salicylic acid. The solubility of caffeine, benzoic acid and salicylic acid in the vehicles studied is shown in Table 2. The first peak solubility for caffeine is seen for the vehicles with a solubility parameter of ∼11 $(cal/cm^3)^{1/2}$ and the second one of ∼14 $(cal/cm^3)^{1/2}$, which corresponds to the theoretical solubility parameter of caffeine. Finally, there is also a high solubility value for caffeine in the mixture PG/water (50:50) (δ of 21.5), followed by another high value for water (δ of 23.4). Caffeine exists as monomers in nonpolar solvents and as dimers or higher aggregates in water (Guttmann and Higuchi, 1957; Cesaro et al., 1976). Herrador and González (1997) have proposed a hydrophobic hydration of caffeine in water-rich solvent mixtures, which is described as an enhanced hydrogen bonding in the neighbourhood of nonpolar groups in water. Bustamante et al. (2002) have also proposed that variation in solute–solvent interactions and differences in the self-association degree may contribute to variations in the solubility profiles observed for caffine in different solvents mixtures.

The solubility of benzoic acid was also high in vehicles with a solubility parameter in the region of 11–13 $(cal/cm^3)^{1/2}$, which corresponds to the calculated solubility parameter of benzoic acid. Benzoic acid is known to self-associate to form dimers and trimers when dissolved in non-polar solvents, through intermolecular hydrogen bonds and other attraction forces (Beerbower et al., 1984). This may explain some of the high solubility values in some of the vehicles (mineral oil, butyl acetate and oleic acid).

The solubility parameter of salicylic acid was estimated to be 14.7 $(cal/cm^3)^{1/2}$. Therefore, a maximum solubility for a vehicle with a solubility parameter of about 15 $(cal/cm^3)^{1/2}$ was anticipated. However, as can be see from Table 2, a maximum solubility for ethanol was observed (δ of 12.1 $(cal/cm^3)^{1/2}$). To investigate the effects of vehicles on salicylic acid diffusion through hairless mouse skin Sloan et al. (1986) reported the use of two values of δ for salicylic acid. A value of 11$(cal/cm^3)^{1/2}$ based on the peak solubility method (Khalil and Martin, 1967) and a value of 14.4 $(cal/cm^3)^{1/2}$ which incorporates neighbouring group interactions between CO_2H and OH were used to calculate theoretical partition coefficient of salicylic acid in different vehicles. Of the vehicles studied, salicylic acid exhibited the highest solubility in 1-propanol (δ of 12) in line with our data. Barra et al. (2000) studied the solubility of salicylic acid in a range of solvents and found two distinct regions of maximum solubility, one at ∼11 $(cal/cm^3)^{1/2}$ and another at ∼15 $(cal/cm^3)^{1/2}$, which corresponds to the theoretical solubility parameter of salicylic acid. Salicylic acid is capable of intramolecular hydrogen bonding. Consequently, the polarity of the molecule will be different, as only one hydroxyl group will be free to confer polarity to the overall molecule. This change in the polarity of the molecule will result in a change in the solubility parameter and, hence more than one maximum solubility may be observed.

3.2. Solvent uptake

The uptake of the selected vehicles into silicone membrane was evaluated. In Fig. 1 the solvent uptake is plotted as a function of the solubility parameter of the vehicle. The highest solvent uptake was observed for IPM [δ of 8.4 $(cal/cm^3)^{1/2}$]. It appears that increasing the solubility parameter of the vehicle decreases the solvent uptake. For vehicles with lower solubility parameters there is also a decrease in the solvent uptake. The data suggest that the solubility parameter of the membrane should be around 8 $(cal/cm^3)^{1/2}$. However, decanol, octanol and oleic acid do not follow this trend, suggesting that there are other factors such as molecular size and shape, which may influence the interactions between the solvent and the membrane. Cross et al.

Table 2
Vehicle solubility parameter and solubility of caffeine, benzoic acid and salicylic acid in vehicle

Vehicle	δ Vehicle $(cal/cm^3)^{1/2}$	Caffeine solubility (mg/ml)	Benzoic acid solubility (mg/ml)	Salicylic acid solubility (mg/ml)
Mineral oil	7.0	0.65 ± 0.04	163.90 ± 15.0	0.53 ± 0.04
IPM	8.4	0.93 ± 0.08	41.30 ± 0.80	66.0 ± 13.10
Butyl acetate	8.5	5.27 ± 0.06	197.80 ± 32.6	218.0 ± 7.40
Oleic acid	8.67	6.09 ± 0.66	245.50 ± 20.0	121.20 ± 3.30
IPM/decanol (80/20)	8.7	3.89 ± 0.19	67.60 ± 3.60	84.92 ± 7.88
IPM/decanol (50/50)	9.1	4.75 ± 0.41	104.80 ± 12.70	108.38 ± 7.47
Decanol	9.5	3.02 ± 0.35	123.80 ± 22.20	136.9 ± 0.60
Octanol	9.8	4.90 ± 0.10	152.60 ± 9.40	186.1 ± 9.40
Butyl lactate	10.2	20.3 ± 0.80	135.80 ± 4.61	234.1 ± 15.40
Butanol	10.6	9.80 ± 1.50	183.0 ± 9.90	283.70 ± 0.90
Isopropyl lactate	10.8	30.7 ± 2.90	239.70 ± 11.60	222.34 ± 40.
Ethyl lactate	11.1	25.7 ± 2.90	164.70 ± 23.90	194.4 ± 6.30
Decanol/PG (80/20)	11.3	4.73 ± 0.48	206.70 ± 4.70	225.1 ± 40.6
Ethanol	12.1	6.03 ± 0.45	340.10 ± 16.10	368.2 ± 4.60
Decanol/PG (50/50)	12.7	7.58 ± 0.80	225.10 ± 2.20	267.2 ± 15.40
PG	14.0	12.10 ± 0.89	240.8 ± 9.40	192.8 ± 19.40
Glycerin	17.4	6.19 ± 0.40	22.6 0 ± 0.50	24.99 ± 3.01
PG/water (50/50)	21.5	52.3 ± 2.40	33.70 ± 5.80	26.38 ± 0.25
Water	23.4	20.0 ± 0.08	2.60 ± 0.10	2.40 ± 0.20

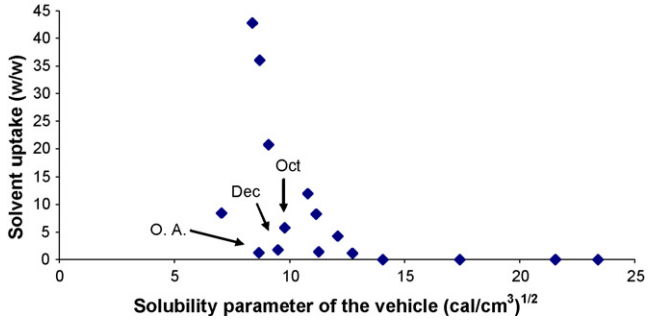

Fig. 1. Relationship between amount of vehicle sorbed into the membrane and its solubility parameter (Oct—octanol, Dec—decanol, O.A.—oleic acid).

(2001) observed that the highest sorption of solvents into silicone membrane occurred between δ values in the range 7–9.5, which corresponds to the findings in the present study. These authors also observed that molecular weight is a significant predictor of sorption in line with the anomalous results for decanol, octanol and oleic acid in the present work.

3.3. Differential scanning calorimetry

DSC thermograms of untreated and vehicle pretreated silicone membrane samples are shown in Fig. 2. The solvents investigated by DSC were selected to encompass the range of solubility parameters studied [7–23.4 $(cal/cm^3)^{1/2}$]. There is a clear shift in the silicone membrane phase transition, when the membrane is treated with the solvents. This implies that the solvents are interacting with the membrane. When the membrane is pre-treated with IPM there is a shift in the phase transition to a lower temperature and hence it is anticipated that there is a higher degree of interaction with the membrane. The shift in the phase transition of the membrane indicates that this vehicle does significantly affect the structure of the membrane. Interestingly, water also appears to interact with the membrane as a shift in the phase transition of the silicone membrane to higher temperature was observed. However, the data in Fig. 1 showed no significant uptake from this vehicle into the membrane. The uptake of vehicle was evaluated by a gravimetric method. Hence, it is possible that this technique was not sensitive enough to detect uptake of small amounts of vehicle, which can still affect the membrane as seen in DSC studies. Pellett et al. (1994) have previously demonstrated water sorption into silicone membranes and measured its diffusion in the membrane using Attenuated Total Reflectance Fourier Transform Infra Red spectroscopy. Neither PG nor decanol shifted the silicone membrane melting point temperature and therefore do not appear to interact significantly with the membrane.

3.4. Diffusion studies through silicone membrane

The flux values of caffeine, benzoic acid and salicylic acid from saturated solutions through silicone membranes are given in Table 3. In an ideal situation, all saturated solutions of the same

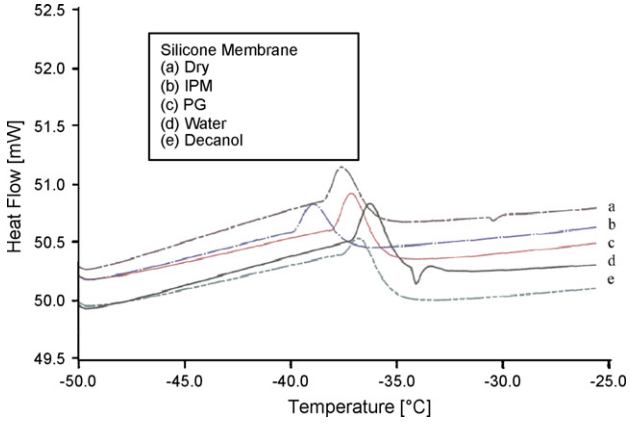

Fig. 2. DSC thermograms for the silicone membrane untreated and pretreated with the solvents.

Table 3
Steady state fluxes for caffeine, benzoic acid and salicylic acid through silicone membrane

Vehicle	Caffeine flux ± S.D. (μg/cm^2/h)	Benzoic acid flux ± S.D. (μg/cm^2/h)	Salicylic acid flux ± S.D. (μg/cm^2/h)
Mineral oil	8.0 ± 0.5	789.7 ± 42.2	130.8 ± 8.4
IPM	85.8 ± 12.7	2367.2 ± 0.5	2023.1 ± 257.3
Oleic acid	6.7 ± 0.4	772.6 ± 60.7	250.8 ± 11.0
IPM/decanol (80/20)	70.3 ± 2.1	2113.4 ± 173.8	1062.9 ± 28.5
IPM/decanol (50/50)	60.3 ± 7.2	1333.4 ± 78.6	838.6 ± 31.0
Decanol	27.1 ± 2.1	919.2 ± 64.6	522.7 ± 27.7
Octanol	22.8 ± 1.0	1300.8 ± 128.6	833.6 ± 65.9
Butanol	37.3 ± 6.7	1366.3 ± 115.2	1227.9 ± 108.8
Decanol/PG (80/20)	14.0 ± 0.9	663.5 ± 17.2	294.8 ± 11.0
Ethanol	13.3 ± 2.8	1546.3 ± 45.8	1333.4 ± 128.8
Decanol/PG (50/50)	11.4 ± 1.3	526.5 ± 20.0	272.5 ± 14.4
PG	9.5 ± 0.7	448.8 ± 42.3	108.4 ± 14.1
Glycerin	5.9 ± 0.4	424.6 ± 61.0	78.9 ± 1.2
PG/water (50/50)	7.5 ± 0.7	439.8 ± 25.8	117.7 ± 8.3
Water	8.9 ± 0.4	269.8 ± 45.4	118.5 ± 1.6

permeant should produce the same steady state flux through a membrane, independent of the nature of the solvent, provided that there are no interactions between the formulation components and the membrane (Higuchi, 1960). Hence, the flux of a drug from saturated solutions from any of the vehicles would be expected to be constant. However, examination of the values presented in Table 3 shows that the fluxes vary with the different solvents used. This implies that the conditions were not ideal and, in many cases, there were interactions between the vehicle and the membrane that altered the flux of the solute through the membrane.

The lower caffeine flux values obtained with the high solubility parameter vehicles correspond to the minimum effect of the vehicle on the membrane, whereas the higher fluxes achieved with the lower solubility parameter vehicles show a clear interaction between these vehicles and the silicone membrane. However, for solubility parameters below that of the membrane the flux appears to be low. In fact, permeation of caffeine from mineral oil (δ ~7.05 (cal/cm^3)$^{1/2}$) showed a low flux value, indicating that this vehicle does not significantly influence the membrane. The highest flux for caffeine, corresponding to the largest interaction, was obtained with the saturated solution in IPM, for which the three-dimensional solubility parameter calculated was 8.4 (cal/cm^3)$^{1/2}$. However, a low flux value was obtained for a vehicle with a low solubility parameter and comparable molecular weight (oleic acid with a δ of 8.7 (cal/cm^3)$^{1/2}$). Even though oleic acid has a solubility parameter close to that of IPM, the former does not interact significantly with the membrane. This may be related to the molecular shape and/or molecular volume as oleic acid has a *cis* double bond, whereas IPM does not. Fig. 3a shows the flux and permeability coefficients for caffeine.

Steady-state diffusion of the drug is described by Fick's first law:

$$J = \frac{\mathrm{DAKC_v}}{h} \tag{3}$$

where J is the flux, D the diffusion coefficient, A is the diffusional area, K is the partition coefficient, C_v is the concentration of the drug in the vehicle and h is the diffusional pathlength. Because it is difficult to determine both D and K, k_p is often quoted:

$$k_p = \frac{DK}{h} \tag{4}$$

Hence, an increase in k_p results from either an increase in D or K provided that h remains constant. In Fig. 3a the per-

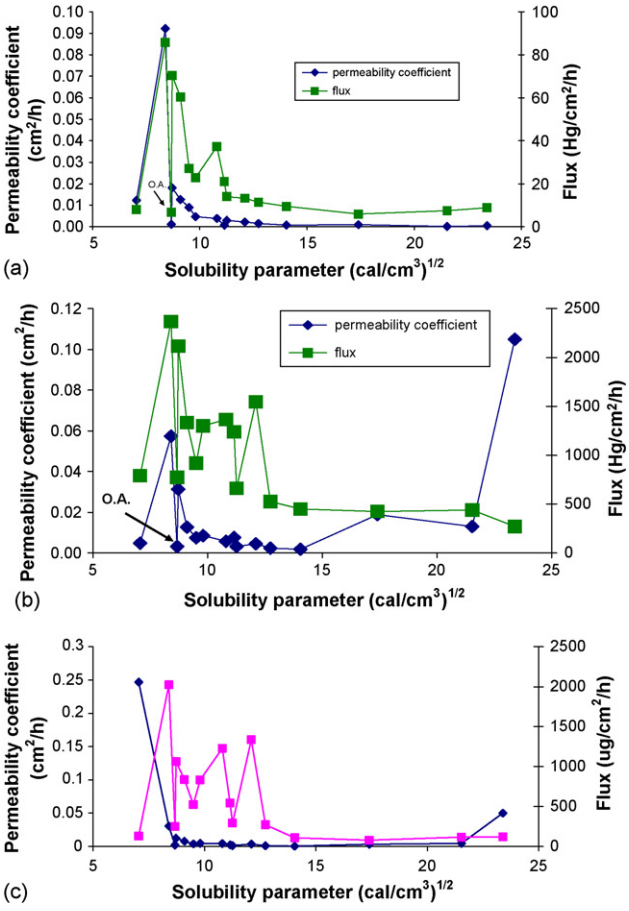

Fig. 3. Relationship between the permeability coefficients of benzoic acid and salicylic acid in silicone membrane.

meability coefficient appears to increase for vehicles with a solubility parameter lower than ~10 $(cal/cm^3)^{1/2}$, with oleic acid being the exception. As mentioned above, these vehicles interact with the membrane changing its properties. Calorimetrtc studies on human skin conducted by Golden et al. (1987) correlated enhanced lipid fluidity with enhanced flux, In the case of IPM; therefore, the DSC data suggest the increase in the permeability coefficient might be a result of predominantly the increased diffusion coefficient (D) rather than an increase in the partition coefficient (K).

The rate of permeation of benzoic acid from the selected vehicles was higher than that of caffeine. This is a result of the different chemical characteristics of the two drugs. Benzoic acid has a log P of 1.89 and therefore is more lipophilic compared with caffeine (log P of −0.07). However, the overall behaviour is similar to that observed for caffeine. The maximum flux was observed for the vehicle with a solubility parameter of 8.4$(cal/cm^3)^{1/2}$). The flux value obtained for mineral oil decreases and the solubility parameter of mineral oil is 7.05 $(cal/cm^3)^{1/2}$, less than that of the membrane, thus confirming that the vehicle influences the membrane characteristics and, hence the flux. Once again the flux obtained from the solutions in oleic acid was very low when compared with that of IPM.

Unlike caffeine, the permeation of benzoic acid from the vehicles with a solubility parameter between 10 and 12 $(cal/cm^3)^{1/2}$ was high. The flux and permeability data for benzoic acid are shown in Fig. 3b. The solubility data in Table 2 show that the saturated solubility of benzoic acid in these vehicles is also high. In this range of solubility parameter (10–12 $(cal/cm^3)^{1/2}$) the vehicles interact with the membrane and an increase in the solubility leads to an increase in the concentration gradient, and consequently an increase in the flux. Conversely, vehicles with higher solubility parameter values do not alter the membrane and therefore, an increase in the solubility does not affect the flux. This can be seen in Fig. 3b where the permeability coefficient (k_p) is plotted together with the steady-state fluxes. The permeability coefficient is very high for IPM and IPM/decanol mixtures and then remains similar up to a solubility parameter of 14 $(cal/cm^3)^{1/2}$. Thereafter, there is again an increase in the k_p, which increases almost 100 times for water. The extent of water permeation into the silicone membrane is low and does not appear to alter its properties significantly. Therefore, the flux of a permeant through silicone membrane from an aqueous vehicle will be directly dependent on the activity of the permeant in the aqueous vehicle.

For salicylic acid the flux profiles were very similar to that of benzoic acid. Flux and permeability coefficient values are shown for salicylic acid in Fig. 3c. The similar molecular structure of the two permeants should account for the comparable diffusion profiles. However, the permeation rates of salicylic acid were in general lower when compared to those of benzoic acid. The largest difference (six times) was obtained for mineral oil. This difference in the permeation can be explained based on the dimerization of benzoic acid in these vehicles unlike salicylic acid where intra-molecular rather than inter-molecular hydrogen bonding occurs. This can be seen from the plot of the permeability coefficient of salicylic acid (k_p SA) versus the permeability coefficient of benzoic acid (k_p BA); in this plot mineral oil has been excluded since dimerisation occurs for BA (Fig. 4).

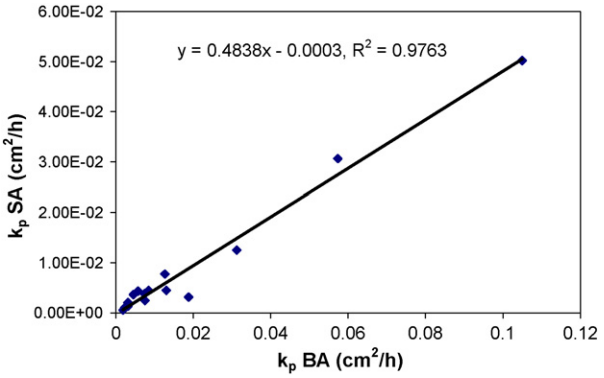

Fig. 4. Permeability coefficient (♦) and steady-state fluxes (■) of (a) caffeine (b) benzoic acid and permeability coefficient of (c) salicylic acid in the selected vehicles as a function of the solubility parameter.

Fig. 3a–c shows the permeability coefficients and steady state fluxes for caffeine and benzoic acid and the steady state fluxes for salicylic acid as a function of the solubility parameter of the vehicles selected. The permeation rate of both salicylic acid and benzoic acid is much greater than that of caffeine. This is a result of the physicochemical properties of the drugs. Benzoic acid (log P of 1.89) and salicylic acid (log P of 2.01) are more lipophilic than caffeine (log P of −0.07). The lipophilic characteristics of these permeants create a more favourable environment for interaction with the silicone membrane, which is also lipophilic. Hence, the solubility of salicylic acid and benzoic acid in the membrane is higher than that of caffeine and the permeation rate is increased. In addition, the similar diffusion profiles of all drugs in the different vehicles implies that the permeation is mainly affected by the interactions between the vehicles and the membrane.

The steady state fluxes were also plotted versus the solvent uptake and relationships examined (Fig. 5). It appears that there is a linear relationship between flux and solvent uptake for the permeation of caffeine. The permeation of BA and SA does not seem to follow a linear trend. It appears to be biphasic, with more influence at lower solvent uptake. This is reflected in the less good correlation coefficient. For all permeants there is a scatter in the region where there is low solvent uptake. This may indicate a different trend for the solvents with low uptake. In

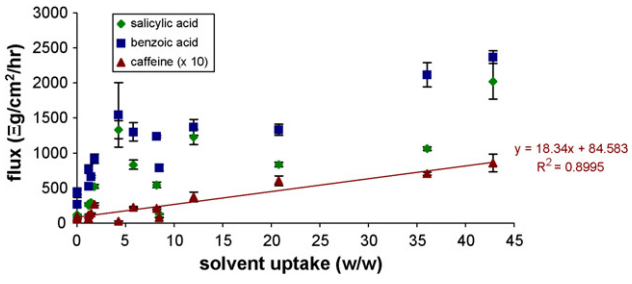

Fig. 5. Relationship between the steady-state fluxes of caffeine, benzoic acid and salicylic acid and the amount of vehicle sorbed into the silicone membrane.

fact, the graph shows a better correlation for the vehicles highly taken up by the silicone membrane.

Twist and Zatz, 1990 found that the alcohol uptake from saturated solutions was considerably less than that of the neat alcohol, with a greater reduction in sorption for the more soluble solute. The solubilities of BA and SA are higher than that of caffeine. The solvent uptake into the membrane, in the present studies, was measured solely for the neat solvent. Hence, the solvent uptake into the membrane when saturated solutions of BA and SA were used might not correspond to the data determined for the neat solvent and the less good correlation obtained for BA and SA might be a consequence of this differential uptake.

The permeation rates of BA and SA through silicone membrane from saturated solutions were higher than those for caffeine. The lipophilic characteristics of BA and SA provide a more favourable environment for interaction with the membrane and the rate of permeation is therefore higher. The permeation profiles of all solutes showed a similar pattern. This implies that the diffusion process is mainly influenced by the interactions between the vehicles and the membrane. The vehicles that were highly sorbed by the membrane altered its properties and hence the flux. Conversely, non-interactive vehicles were not sorbed by the membrane and the steady-state fluxes were similar. Although, the solubility parameter of the vehicles influenced the interactions between them and the membrane and consequently the flux, there were some exceptions that can be explained as deviations from the regular solution theory. Solubility parameter alone cannot explain the interactions between the membrane and the vehicles in all cases. Rather, it is likely that membrane flux reflects a combination of different solvent and solute characteristics, such as size, shape and charge distribution.

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