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Influence of membrane–solvent–solute interactions on solute permeation in skin

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Abstract

The relative importance of solubility parameters and other solvent properties on membrane diffusion processes has not been fully elucidated in the literature. Previously, we have studied the effect of different vehicles on the permeation of caffeine, benzoic acid (BA) and salicylic acid (SA) through silicone membranes. The present paper investigates diffusion of the selected permeants from different saturated solutions through human epidermis.

The permeation of caffeine was strongly affected by the vehicle chosen and the maximum enhancement observed for the permeation of caffeine was 288-fold. A maximum of 12-fold enhancement in the flux was observed for the permeation of SA and a maximum of 10-fold enhancement was observed for the permeation of BA. The diffusion profiles obtained for SA in the different solvents were very similar when compared with those obtained for BA but the permeation rates were higher for BA than for SA. This similarity results from the similar chemical structure and lipophilicity.

Keywords: Solubility parameter; Skin; Vehicle; Flux

1. Introduction

Although many researchers have studied the effect of vehicles on skin permeation, their mode of action has not yet been totally established. Vehicles affect the skin barrier function, with a consequent modulation of its properties. Their effects are usually attributed to a number of different processes. Stratum corneum lipids can be extracted, for example, ethanol (Bommannan et al., 1991). A second possibility is fluidization of the lipid structure, for example, oleic acid (Naik et al., 1995). Some compounds may also stabilise the skin lipids with a consequent increase of the barrier function (Hadgraft et al., 1996). This is advantageous in some cases, for instance, when formulating sunscreens where it is desirable for them to be retained at the skin surface. Finally, excipients can permeate into the skin lipids and change their solubility properties; if solubility is improved there will be a concomitant increase in drug permeation.

The physicochemical properties of both the permeant and the excipients will determine skin permeability. Determination of the relative solubility parameters of the skin, the vehicle and the permeant can also be of use when optimising skin permeation. When two entities possess a similar solubility parameter they will be mutually soluble. It may be hypothesised that if the solubility parameter of the vehicle alters that of the skin so that it is closer to the solubility parameter of the drug, permeation may be enhanced.

Similarly, permeants with a solubility parameter close to that of the skin will have a higher permeation rate through the skin. Roy and Flynn (1989) studied the relationship between the solubility parameter of a series of narcotic analgesics and their permeation through cadaver skin. They found that the narcotics with a solubility parameter close to 10 $(cal/cm^3)^{1/2}$ had a higher permeability coefficient. Interestingly, the permeability coefficient of a series of alkanoic acids through porcine skin were reported to be parabolically related to solubility parameters, with a maximum permeability near a solubility parameter of 10 $(cal/cm^3)^{1/2}$ (Liron and Cohen, 1984). Hence, the solubility parameter of the skin is thought to be $\sim$10 $(cal/cm^3)^{1/2}$.

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Previously, we have investigated the effect of different vehicles on the permeation of caffeine, benzoic acid (BA) and salicylic acid (SA) through silicone membranes (Dias et al., 2007). In the present study, the permeants caffeine, benzoic acid and salicylic acid were applied to the skin in different vehicles, at the same thermodynamic activity, to assess the effect of vehicles on skin permeation. A range of vehicles was selected and their solubility parameters calculated.

2. Materials and methods

Caffeine was purchased from May & Baker Ltd. (UK). BA was purchased from Fisons, Scientific Equipment (UK) and SA from Fisher Scientific (UK). Isopropyl myristate (IPM) was obtained from Croda Universal Ltd. (UK), decanol (DEC), mineral oil (MO) and butyl acetate from Aldrich (UK), propylene glycol (PG), octanol (OCT), chloroform, methanol and butanol (BUT) from Fisher Scientific (UK) and isopropyl lactate (IL), butyl lactate (BL), ethyl lactate (EL) and ethyl hexyl lactate (EHL) were gifts from Purac Biochem, Gorinchem (Netherlands).

Human skin tissue was obtained following cosmetic surgery with appropriate informed consent and approval. Tissue was stored in a freezer until required. Storage of skin tissue below −20 °C for periods of up to 466 days has been shown to have no significant effect on the permeability of water (Harrison et al., 1984).

Full thickness skin was thawed overnight. After removal of the adipose tissue by blunt dissection the epidermis was separated by a heating method, immersing the skin in water maintained at 60 °C for 1 min (Kligman and Christophers, 1963). It was then pinned on a corkboard and the epidermis was carefully peeled away from the dermis. The epidermis was mounted on filter paper and stored in aluminium foil in a freezer, below −20 °C. Prior to the experiments, the skin was left to defrost overnight and then cut into appropriate sizes to fit the diffusion cells. The same donor's skin was used for each set of experiments.

The diffusion experiments through human epidermis were performed using Franz-type diffusion cells, as described previously (Dias et al., 2007). Samples were taken every 2 h until 12 h and then a sample was taken at the end of 24 h. In all cases the whole receptor medium was removed for quantification of the permeants and replaced with pre-warmed buffer (PBS pH 7.4). 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 5 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 a Uvikon 860. After appropriate dilution samples were analysed at 225 and 295 nm, respectively. One control for each vehicle (without drug) was used to ensure only benzoic or salicylic acid absorbance was recorded at these wavelengths.

The pH of saturated solutions of SA and BA in water was evaluated using a pH meter (Hanna instruments, HI 8521). The pH meter was calibrated using pH 4 and pH 7 standard buffer solutions (Sigma).

2.1. Data analysis

Steady-state fluxes were first calculated using Fick's first law of diffusion, by monitoring the cumulative amount of permeant diffused and measuring the slope of the graph once steady-state diffusion was reached. The values were confirmed by a curve fitting method (Diez-Sales et al., 1996). Statistical analysis using ANOVA was performed on the steady-state flux values obtained for all permeants, with a significance level of $P = 0.05$.

3. Results and discussion

3.1. Caffeine

The calculated solubility parameter and log P values of caffeine have previously been reported by us as 14.0 $(cal/cm^3)^{1/2}$ and −0.07, respectively, as has the solubility data in each vehicle (Dias et al., 2007). Table 1 shows flux values, solubilities and permeability coefficients together with the solubility parameter of the selected solvents.

The permeant was applied at the same thermodynamic activity (a saturated solution). There is a marked increase in the

Table 1
Flux values solubilities and permeability coefficients for caffeine and solubility parameters of the selected solvents (mean ± S.D., $n \geq 3$)

Solvent	Solubility parameter	Caffeine solubility (mg/ml)	$k_p \times 10^{-3}$ (cm/h)	Flux (μg/cm^2/h)
Mineral oil	7.0	0.65 ± 0.04	99.5 ± 18.1	9.1 ± 1.6
IPM	8.4	0.93 ± 0.08	10.4 ± 2.6	9.7 ± 2.4
Butyl acetate	8.5	5.27 ± 0.06	20.8 ± 5.3	109.5 ± 28.2
Decanol	9.5	3.02 ± 0.35	6.96 ± 0.8	21.0 ± 2.5
Octanol	9.8	4.90 ± 0.10	33.6 ± 9.3	144.0 ± 34.5
Butyl lactate	10.6	20.3 ± 0.80	0.24 ± 0.17	4.9 ± 3.4
Butanol	11.3	9.80 ± 1.50	0.46 ± 0.07	3.6 ± 1.5
Ethyl lactate	11.2	25.7 ± 2.9	0.02 ± 0.006	0.5 ± 0.1
Ethanol	12.1	6.03 ± 0.45	0.80 ± 0.62	4.8 ± 3.8
PG	14.0	12.1 ± 0.89	0.15 ± 0.04	1.8 ± 0.5
Water	23.4	20.0 ± 0.75	0.14 ± 0.03	2.9 ± 0.7

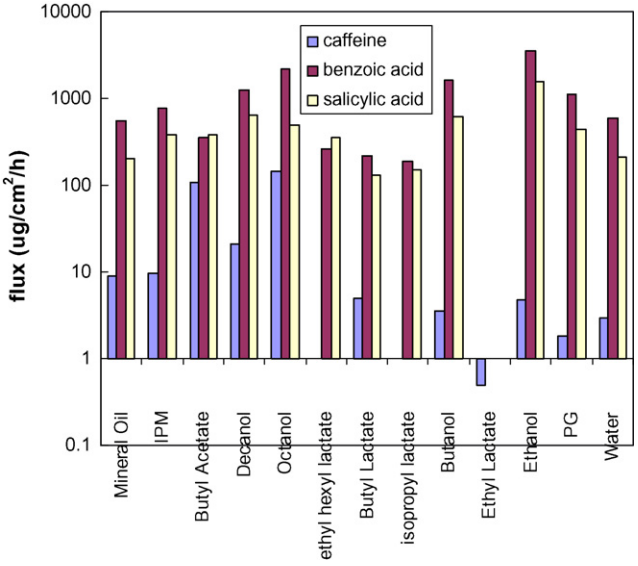

Fig. 1. The steady-state fluxes from the various solvents for caffeine, benzoic acid and salicylic acid ($n \geq 3$).

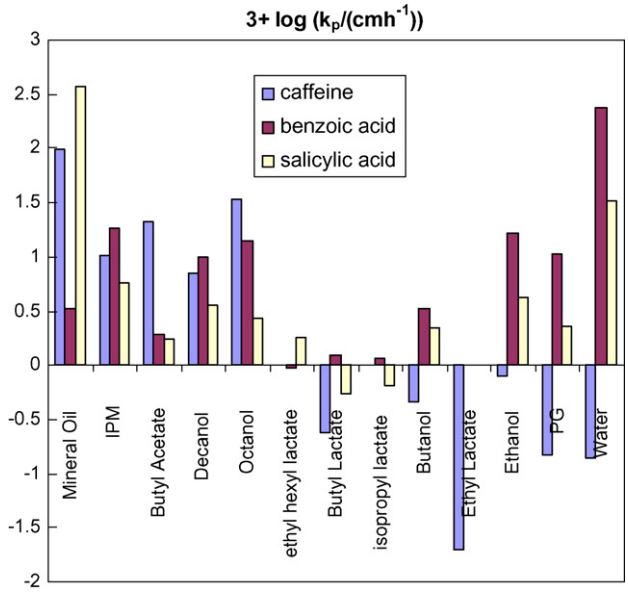

Fig. 2. The changes in permeability coefficient for the three permeants with solvent.

steady-state flux of caffeine when octanol and butyl acetate were used as solvents. Compared with the flux of caffeine from water, the flux is increased 50 and 38 times, respectively. The flux from propylene glycol was very similar to water. This was reported by Rahman et al. (1992) when the permeation of caffeine from different vehicles was studied through mouse skin. IPM and mineral oil increased the permeation of caffeine to a similar extent, whereas ethyl lactate appears to retard the flux. The results are shown in Fig. 1.

The flux of caffeine through the skin is significantly higher than for the other two permeants as can be seen in Table 2 and Fig. 2. If the solvents do not affect the barrier properties of the skin the steady-state fluxes should be equal. This is the case for the flux values for butyl lactate, butanol, ethanol, water and propylene glycol which do not differ significantly from each other ($P > 0.05$). This suggests that these solvents are not altering the barrier properties of the skin towards caffeine. The fluxes from mineral oil, isopropyl myristate, butyl acetate, decanol and octanol are all significantly higher than the previous set and it is apparent that these solvents are modulating the barrier properties of the skin. The flux from ethyl lactate is significantly lower than the rest. Those solvents with a solubility parameter lower than 10 appear to enhance the flux. Since the steady-state fluxes and the solubilities are known it is possible to calculate the permeability coefficients. These are provided in Table 1 and shown also in Fig. 2.

The four solvents that lead to increased flux also can be seen to have high permeability coefficients. It is unlikely that these solvents will extract the skin lipids. Equally they would not be anticipated to alter the diffusion coefficient of caffeine in the skin significantly. They must therefore be permeating into the skin lipids and altering the solubility properties in a favourable way. The degree to which they can achieve this will depend on their uptake into the skin and the solubility of caffeine in the modified environment. The reason for the low flux and permeability coefficient from ethyl lactate is unclear.

Previously, we have observed that the flux of caffeine from mineral oil ($\delta \sim 7.05\,(\text{cal/cm}^3)^{1/2}$) showed a low flux value

Table 2
Solubility parameters, vehicle solubility, permeability coefficients and flux values for BA and SA (mean ± S.D., $n \geq 3$)

Solvent	δ (cal/cm^3)$^{1/2}$	Benzoic acid			Salicylic acid		
		Solubility (mg/ml)	$k_p \times 10^{-3}$ (cm/h)	Flux (mg/cm^2/h)	Solubility (mg/ml)	$k_p \times 10^{-3}$ (cm/h)	Flux (mg/cm^2/h)
Mineral oil	7.0	163.9 ± 15.0	3.33 ± 0.68	0.55 ± 0.11	0.53 ± 0.04	377.36 ± 28	0.20 ± 0.02
IPM	8.4	41.3 ± 0.8	18.5 ± 4.34	0.76 ± 0.18	66.0 ± 13.1	5.73 ± 0.47	0.38 ± 0.03
Butyl acetate	8.5	197.8 ± 32.6	1.91 ± 0.22	0.36 ± 0.05	218.0 ± 7.4	1.74 ± 0.48	0.38 ± 0.10
Decanol	9.5	123.8 ± 22.2	9.99 ± 3.7	1.24 ± 0.46	136.9 ± 0.6	3.57 ± 2.80	0.65 ± 0.24
Octanol	9.8	152.6 ± 9.4	14.2 ± 5.1	2.17 ± 0.78	186.1 ± 9.4	2.68 ± 0.75	0.50 ± 0.14
Ethyl hexyl lactate	10.1	135.8 ± 4.61	0.95 ± 0.30	0.26 ± 0.04	194.4 ± 6.3	1.82 ± 0.53	0.35 ± 0.10
Butyl lactate	10.6	183.0 ± 9.9	1.23 ± 0.54	0.22 ± 0.10	234.1 ± 15.4	0.55 ± 0.05	0.13 ± 0.01
Isopropyl lactate	11.1	164.7 ± 23.9	1.16 ± 0.34	0.19 ± 0.03	222.3 ± 40.4	0.65 ± 0.05	0.15 ± 0.01
Butanol	11.3	239.7 ± 11.6	3.29 ± 2.15	1.65 ± 0.66	283.7 ± 0.9	2.19 ± 0.55	0.62 ± 0.15
Ethanol	12.1	340.1 ± 16.1	16.7 ± 2.23	3.58 ± 0.24	368.2 ± 4.6	4.25 ± 0.52	1.57 ± 0.19
PG	14.0	240.8 ± 9.4	10.7 ± 2.64	1.12 ± 0.14	192.8 ± 19.4	2.27 ± 0.73	0.44 ± 0.14
Water	23.4	2.6 ± 0.1	235 ± 32.2	0.60 ± 0.04	2.4 ± 0.2	88.34 ± 7.99	0.21 ± 0.02

through silicone membrane, indicating that this vehicle did not significantly influence the silicone membrane. The highest flux for caffeine in silicone membranes was obtained for IPM, for which the three-dimensional solubility parameter calculated was 8.4 $(cal/cm^3)^{1/2}$. This contrasts with the results observed for skin permeation where mineral oil and IPM gave comparable fluxes for caffeine. The enhanced effect of IPM was attributed to a more pronounced effect on diffusion as the IPM altered the phase transition of the membrane (Dias et al., 2007). IPM was also sorbed by silicone membranes to a greater extent than mineral oil (Dias et al., 2007). Cross et al. (2001) noted a similar non-specificity in the effect of vehicle on silicone membranes where the effect on diffusion coefficient depended simply on the volume increase in membrane caused by the absorbed vehicle.

3.2. Benzoic acid

The calculated solubility parameter and log P values for BA were 11.2 $(cal/cm^3)^{1/2}$ and 1.89, respectively (Dias et al., 2007). Examination of Table 2 shows that steady-state fluxes vary depending on the vehicle used. A six-fold enhancement was observed for the saturated solution of benzoic acid in ethanol as compared with the permeation from water. BA shows a significantly higher permeation rate than caffeine ($\log P$ −0.07) probably because of its more favourable $\log P$ allowing it to partition into the skin lipids more easily.

The variation in flux is less marked than for caffeine and the solvents that enhanced permeation significantly were decanol, octanol, butanol, ethanol and propylene glycol. Again it is likely that this is a reflection of their uptake into the skin lipids and the concomitant alteration of the solubility properties. There is a marked difference in the behaviour compared with caffeine. Hatanaka et al. (1993) found that ethanol enhanced the permeation rate of lipophilic drugs, whereas no effect on the skin permeation of hydrophilic drugs was observed. If the solvent permeates the skin very rapidly compared with the drug, it may be possible to create localised areas in which the permeant is supersaturated. This will lead to increased flux. Ethanol might be enhancing the permeation of benzoic acid as a result of a supersaturated state of the permeant in the solvent. A similar effect was not observed for the permeation of caffeine. As for the results for caffeine, high flux values were obtained for BA in IPM. This was similar to the results found in silicone membranes but in permeation through skin it was not significantly different when compared to water ($P > 0.05$). It is interesting to note the interplay between the permeability coefficients and the solubilities where the solvents are not influencing the barrier properties of the skin. For example, if mineral oil and water are compared, the differences between the solubilities and permeability coefficients are large whereas the fluxes are statistically equal.

3.3. Salicylic acid

For SA calculated solubility parameter and log P values were 14.7 $(cal/cm^3)^{1/2}$ and 2.06, respectively (Dias et al., 2007). The diffusion profiles obtained for SA in the different solvents were very similar, but slightly lower, when compared with those obtained for benzoic acid. This similarity results from the similar chemical structure and lipophilicity of the two molecules, which is evident in their log P values of 2.1 and 1.9 for SA and BA, respectively. Table 2 and Fig. 1 show that the flux from ethanol is increased by a factor of 7.5 compared with water. This may be a result of transient and localised supersaturation in the microenvironment or at the solvent membrane interface.

3.4. Comparison with silicone membranes

For the solvents in general there does not appear to be any systematic relationship between the flux and the solubility parameter. This is also the case for salicylic acid in which the results are very similar in behaviour.

There is no simple relationship between the permeability coefficients for caffeine and either benzoic acid or salicylic acid. However, excepting the mineral oil value, there is a linear relationship between the permeability coefficients of benzoic acid and salicylic acid. This is shown in Fig. 3.

This is very similar to the relationship found in the silicone membrane experiments ($y = 0.44x - 0.0003$; Dias et al., 2007). In both the experiments with silicone and skin the values for mineral oil did not fit the equations. This was attributed to the intermolecular hydrogen bonding that can occur for benzoic acid compared with the intramolecular hydrogen bonding in salicylic acid (Dias et al., 2007).

3.5. Comparison of theoretical versus actual permeability coefficients

For all permeants the theoretical permeability coefficients, k_p, were determined according to the Potts and Guy equation for aqueous solutions Potts and Guy (1992). For caffeine, the estimated and experimental k_p was of the same order of magnitude, 1.16×10^{-4} and 1.45×10^{-4} cm/h, respectively. For benzoic acid and salicylic acid the estimated permeability coefficients were 8.02×10^{-3} and 7.54×10^{-3} cm/h, whereas the experimental k_p values were 2.35×10^{-1} and 8.83×10^{-2} cm/h,

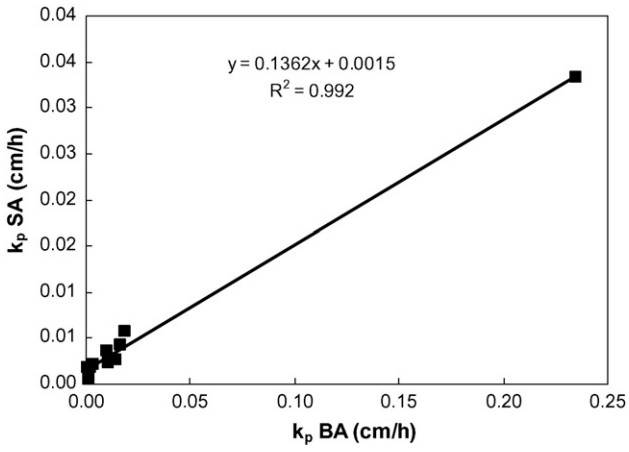

Fig. 3. The relationship between the permeability coefficients for benzoic acid and salicylic acid. The value for mineral oil has been omitted.

Table 3
ANOVA statistical analyses of the steady-state flux values obtained for the permeation of caffeine, BA and SA for $P = 0.05$

Caffeine		Benzoic acid		Salicylic acid	
Solvent	Different from	Solvent	Different from	Solvent	Different from
PG	IPM, MO	Ethanol	IPM, PG, IL, Water, MO, EHL, BA, BL	Ethanol	All others
IPM	EL, Water, BUT	Octanol	IPM, PG, IL, Water, MO, EHL, BA, BL, BUT, DEC	Decanol	IL, BL, Water
Mineral Oil	Water, EL	Decanol	IL, Water, MO, EHL, BL	Octanol	IL, BL
Ethyl lactate	ETH			Butanol	IL, Water, BL
Decanol	All others				
Butyl acetate	All others				
Octanol	All others				

respectively. These unexpected high permeability coefficients might be a consequence of the very high concentrations used (saturated solutions) which produced a low pH, which was found to be 2.47 for salicylic acid and 2.83 for benzoic acid. The low pH might be altering the skin barrier, with a consequent increase in the permeation (Allenby et al., 1969). Also salicylic acid is known to be a keratolytic which will alter the barrier properties of the skin.

Figure 1 shows that both benzoic acid and salicylic acid (lipophilic permeants) had higher permeation rates compared to caffeine. This is a result of the physicochemical characteristics of the three permeants. BA and SA have log P values of ~2, whereas caffeine has a log P of −0.07. Yano and Noda (1986) have shown that there is a parabolic relationship between the flux and log P, with a peak around 2. Because of their lipophilicity, both BA and SA are capable of permeating through the skin readily and their permeation will not be as affected by the interactions of the vehicle with the skin. Interestingly, the permeation rate of BA was higher than that of SA. This was also observed in the permeation studies through silicone membrane (Dias et al., 2007) where dimerization of BA was hypothesised as creating a more favourable environment for interaction with the silicone membrane. Hence, it may be possible that BA dimers also partition better into the skin lipids than SA. Because the SA molecule will be more polar than the BA dimer, it might be interacting with the polar head groups of the ceramides, leading to a reduction in the permeation rate. The additional lipophilicity of the BA dimer may be expected to increase the permeation.

3.6. ANOVA analysis of flux data

Although the vehicles used affected BA and SA permeation rates, their influence was more pronounced on the permeation of caffeine. The latter permeant is hydrophilic and hence its permeation rate will be low. Consequently, interactions between the formulation components and the skin will alter the skin barrier properties and the permeation of caffeine will be significantly enhanced. Statistical analysis using ANOVA was performed on the steady-state flux values obtained for the permeation of caffeine, BA and SA and the results obtained are presented in Table 3.

The permeation rate obtained for the saturated solution of SA in ethanol was significantly different from all other solvents studied, whereas decanol, octanol and butanol were only statistically different from the lactates and water. For BA only ethanol, decanol and octanol were significantly different from other vehicles studied (Table 3).

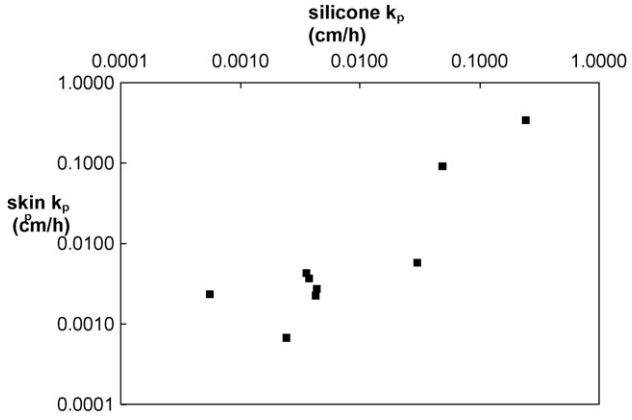

Fig. 4. The relationship, for salicylic acid, between the permeability coefficients (cm/h) in silicone (Dias et al., 2007) and skin.

No simple correlation could be found between the permeability coefficients or the steady-state fluxes as measured in silicone and skin. For BA and SA there was a general trend that the lower the permeability coefficient in silicone the lower it is in skin. This is shown in Fig. 4 for salicylic acid which is plotted on a logarithmic scale because of the wide range in values. It is interesting to note that the values of the two sets of permeabilities are of the same order of magnitude. However, the permeability coefficient does include the term for the thickness of the membrane and the silicone membrane (400 μm) is substantially thicker than the thickness of the skin. But the major route of permeation for the permeants selected is through the intercellular channels of the skin which has been estimated as being between 350 μm (Albery and Hadgraft, 1979) and 500 μm (Potts and Guy, 1992).

4. Conclusions

The permeation of caffeine was enhanced by the vehicles chosen because of their interaction with the skin. Evidence in the literature has generally considered that vehicles act by promoting partition into the skin. The present study indicates that although vehicles promote changes in partitioning and diffusion it is likely to be the partition that is the dominant factor. Drugs with a log P of about ~2 have a higher permeation rate due to

their lipophilicity. Using the solvents chosen, it was not as easy to enhance the permeation of BA and SA as caffeine.

Decanol with a solubility parameter of 9.5 and octanol with a solubility parameter of 9.8 promoted the flux of the three permeants. Since it has been suggested that the stratum corneum may have a solubility parameter of ∼10 (Liron and Cohen, 1984) it might be hypothesised that such vehicles should mix freely with the stratum corneum lipids and have maximal enhancement properties. Conversely the lactates, with solubility parameters in the range 10.15–11.15 appeared to have little effect on permeation and in some instances appeared to retard permeation. Clearly, there is no simple relationship between flux across human epidermis and values previously reported for silicone for the permeants studies, suggesting that the modes of action of the vehicles were quite different for the two membranes.

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