In Vitro Human Epidermal and Polyethylene Membrane Penetration and Retention of the Sunscreen Benzophenone-3 from a Range of Solvents

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Purpose. To study epidermal and polyethylene membrane penetration and retention of the sunscreen benzophenone-3 (BP) from a range of single solvent vehicles and evaluate solvent effects on permeability parameters.

Methods. The solubility of BP was measured in a number of solvents. Penetration of BP across human epidermis and high density polyethylene (HDPE) membranes was studied from 50% saturated solutions in each solvent.

Results. Maximal BP fluxes from the solvents across the two membranes varied widely. Highest fluxes were observed from 90% ethanol (EtOH) for epidermis and from isopropyl myristate (IPM) and C_{12-15} benzoate alcohols (C_{12-15} BA) for HDPE membrane. Both the flux and estimated permeability coefficient and skin-vehicle partitioning of BP appeared to be related to the vehicle solubility parameter (δ_v). The major effects of solvents on BP flux appear to be via changes in BP diffusivity through the membranes.

Conclusions. Minimal penetration of sunscreens such as BP is best achieved by choosing vehicles with a δ_v substantially different to the solubility parameter of the membrane.

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ABBREVIATIONS: BP, benzophenone-3; BSA, bovine serum albumin; C_{12-15} BA, C_{12-15} benzoate alcohols; DMSO, dimethylsulfoxide; EtOH, ethanol; HDPE, high density polyethylene membrane; IPM, isopropyl myristate; LP, liquid paraffin; PG, propylene glycol; SC, stratum corneum; UV, ultraviolet. List of symbols: cal/cm^3, calorie per cubic centimetre; ΔC, concentration gradient of solute across membrane; C_m, concentration of solute in membrane; C_s, concentration of solute in skin; C_v, concentration of solute in vehicle; $\delta_{epidermis}$, solubility parameter of epidermis; δ_i, solubility parameter of solute; δ_m, solubility parameter of polyethylene membrane; δ_s, solubility parameter of skin; δ_v, solubility parameter of vehicle; d, apparent diffusion parameter; D, effective diffusion coefficient; L, membrane thickness; h, hour; J_s, flux obtained from skin; J_m, flux obtained from membrane; K_m, membrane/vehicle partition coefficient; K_s, skin/vehicle partition coefficient; K_m, membrane apparent partition parameter; K_s, skin apparent partition parameter; K_p, permeability coefficient; R_m, membrane retention; R_s, skin retention.

KEY WORDS: benzophenone-3; sunscreen; penetration; retention; vehicle; human epidermis.

INTRODUCTION

The awareness of deleterious effects of solar radiation and evidence of the linkage between sun exposure and skin cancer (1–3) have led to an increase in sun care product usage throughout the world. In particular, the formulation of sunscreen products with very high Sun Protection Factors (up to 50) has increased dramatically in recent years. Sunscreen agents are widely incorporated into skin products, make up and hair care ranges designed for daily use in the form of emulsions, oils, gels, lipsticks, mousses, aerosols, powders and ointments. Sunscreens exert their effect on the skin surface, with the requirement against washing or rubbing off, desirable preparations should orientate sunscreens to locate within the outermost layer of the skin [e.g., stratum corneum (SC)] to achieve the highest protection at lowest possible level of transdermal penetration.

Despite the extensive use of sunscreen products, little attention has been paid to their potential skin penetration and possible subsequent toxic effects after topical application. Certain sunscreens have been found to significantly penetrate the skin. For example, Hayden and colleagues (4) found that in humans up to 2% of an applied dose of benzophenone-3 (BP) and its metabolites, glucuronides of 2,4-dihydroxybenzophenone and 2,3,4-trihydroxy-benzophenone, were excreted in the urine following topical application of a commercially available product. Sunscreen permeation was found to be both structure and formulation related. We have previously found from *in vitro* human skin studies that BP was the only sunscreen that penetrated across the skin under 'in use' conditions, however, significant levels of all sunscreen agents studied were found to be retained in the epidermis (5). It is apparent that sunscreen agents which are readily absorbed into the SC do not necessarily permeate into deeper tissues or are absorbed into the systemic circulation. During a market products survey, we found that diffusion of sunscreen agents across the epidermis varied significantly with formulation: alcohol based spray > oil based formulation > emulsions (6). Treffel and Gabard (7) showed that sunscreen agents were better retained in the skin after application of an emulsion-gel than from petroleum jelly with the reservoir of the agents found mainly in the SC. Lazar and colleagues (8) also demonstrated differences in sunscreen penetration amongst emulsion type formulations. The group additionally showed that up to 95% of sunscreens studied remained in the epidermis and that levels up to 5% diffused across into the dermis (8).

In the present study, penetration of BP through human skin and HDPE membranes from a range of vehicles (polar to nonpolar) at constant thermodynamic activity was investigated. *In vitro* human epidermal penetration studies are conventionally used to investigate vehicle effects on solute permeation and skin distribution through the use of constant thermodynamic solute activity in the tested formulations (9). BP solubility, permeability parameter and vehicle solubility parameter relationships were compared between the two membranes in order to estimate the degree of solvent-membrane interaction (10–12). The effect of vehicle on skin retention of BP following the penetration studies was also determined.

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MATERIALS AND METHODS

Materials

BP and bovine serum albumin (BSA, fraction V) were supplied by Sigma-Aldrich Chemical Co (Sydney, NSW, Australia), light liquid paraffin (LP) was the gift of Aloe Vera Industries Pty Ltd (Loganholme, QLD, Australia) propylene glycol (PG) was purchased from David Craig & Co. (Rocklea, QLD, Australia) analytical grade absolute ethanol was supplied by Banksia Scientific (Brisbane, QLD, Australia) silicone oil 200/350 and IPM were donated by Unit Pack Pty Ltd (Sumner Park, QLD, Australia) C_{12-15} BA was a gift from Russell McLean & Associates (St Ives, NSW, Australia) coconut oil was purchased from The Oil Garden (Brisbane, Australia) and HDPE 20 μm membrane was donated by Beaver Plastics (QLD) Pty Ltd (Coopers Plains, QLD, Australia). HPLC-grade methanol was used for HPLC analysis and all other chemicals used in the study were of analytical grade.

High Performance Liquid Chromatography (HPLC) Instrumentation

A model LC-6A Liquid Chromatograph (Shimadzu, Japan) equipped with a SIL-9A Autoinjector (Shimadzu), a Nova Pak C_{18} steel column (4 μm, 3.9 × 150 mm I.D., Waters-Millipore) protected by a Nova Pak C_{18} guard column (Guard-Pak™, Waters, Milford MA, USA) with an in-line prefilter (2 μ, 4 mm I.D., Alltech Australia), a model 486 Tunable UV Absorbance Detector (Waters-Millipore, USA) and a C-R4A Chromatopac Integrator (Shimadzu) were used for the analysis of BP.

HPLC Conditions

The mobile phase consisted of aqueous methanol (90% v/v) filtered through a 0.45 μm membrane (Nylon 66, Alltech Australia) and degassed before use. The flow rate was 1.0 ml/min and the injection volume was 5 μl. The UV detection wavelength was 315 nm and the column temperature was ambient (~25°C).

Methods

Determination of BP Solubility

A moderate excess of BP was placed in 10 ml of each solvent (H_2O, 90% EtOH, PG, IPM, coconut oil, C_{12-15} BA, LP, silicone oil) and stirred in the dark at 32°C ± 0.1°C for 72h. The mixtures were then centrifuged at 10,000 g for 10 min. This step was repeated with the resultant supernatants injected onto the HPLC.

Membrane Diffusion Studies

Experiments were conducted with University of Queensland and Wesley Hospital Medical Ethics Committee approval. Human epidermal tissue (abdominal region of two females) was obtained by blunt dissection of full-thickness skin and heat separation (13). Epidermis was air dried and stored at −20°C.

Prior to use human epidermis was thawed at room temperature and HDPE membranes cleaned with distilled water before mounting between the chambers of horizontal Franz-type diffusion cells. Surface diffusion area was 1.18 cm^2 and the receptor chamber volume approx 3.4 ml. Saturated solutions of BP in vehicles (90% ethanol (EtOH), PG, IPM, C_{12-15} BA, coconut oil, LP, and silicone oil) were centrifuged and diluted 1:1 to produce the 50% saturated solutions employed throughout to allow a comparison of permeation of BP under conditions of equal thermodynamic activity. Saturated BP in H_2O was used to avoid donor depletion of BP as a consequence of its extremely low water solubility (0.00043%). Constant thermodynamic activity was maintained by using an infinite dose under occluded conditions. The receptor chambers were filled with 4% BSA in phosphate buffered saline, pH 7.4. Diffusion cells were equilibrated at 37°C ± 0.1°C in a light-proof black water-bath (to protect the sunscreen from photodegradation) for at least 1h prior to vehicle application. Aliquots (0.5 ml) of vehicles were introduced into the donor chambers (1 ml for BP in H_2O) and sealed with a glass cover-slip to prevent evaporation. The receptor fluids were stirred throughout with magnetic fleas and samples (0.1 ml) were taken from the receptor chamber periodically (up to 6 h). Six replicates were used for the epidermis and triplicates for the HDPE membrane. At the end of the diffusion studies, remaining solution in each donor chamber was wiped out using soft tissue and the membranes rinsed with distilled water three times. BP remaining within the membranes were extracted twice with absolute methanol (recovery >99%) and quantified by HPLC (14). Membrane retention and apparent diffusion parameters obtained from the semisaturated solutions for the HDPE membrane were further compared with the values obtained from 2% BP in IPM, C_{12-15} BA and LP solutions.

Data Analysis

The solubility parameter of a solute, δ_i, is a sum of intermolecular attractive forces (15) and has been used to predict the skin penetration of topically applied solutes (10,16–17). It has been suggested that solute thermodynamic activity in solution can be directly related to $(\delta_i-\delta_v)^2$ where δ_v is the solubility parameter of the vehicle (18). The thermodynamic activity of a particular concentration of solute in a vehicle will decrease as δ_i approaches δ_v, that is where solute solubility in the vehicle is maximal. Membrane flux may also be a function of the relative values of δ_v and δ_m as maximum increases in flux have been found as δ_v approaches δ_m for hairless mouse skin (18). Values for δ_v were taken from Vaughan (15) or calculated using one dimensional method (19), with δ_v for 90% EtOH calculated based on mole fraction.

Membrane flux (J, μg $cm^{-2}h^{-1}$) was assumed to be related to the permeability coefficient (Kp, cm h^{-1}) and the concentration gradient of the solute across the membrane (ΔC, μg cm^{-3}):

$$J_x = Kp\ \Delta C = K\ D\ \Delta C\ /\ L_x \qquad (1)$$

where x is either skin (s) or HDPE membrane (m).

where Kp is the product of the membrane/vehicle partition coefficient (K), the effective diffusion coefficient (D, diffusivity) and the membrane thickness (L). Kp values are often used to compare penetration profiles for solutes examined under different conditions and relate to the rate of diffusion of a solute within a membrane adjusted for differences in concentration. As negligible (<5%) donor depletion was occurred during in the infinite dose study and receptor sink conditions were maintained, ΔC is defined by the initial BP vehicle concentration (C_v). By definition, K_m equals C_m/C_v (or $K_s = C_s/C_v$) where

C_m (or C_s) is the concentration of BP in the membrane (or skin). If C_m (or C_s) can be approximated as R_m/V_m (or R_s/V_s) where R_m (or R_s) is the retention of BP in the membrane (or skin) and V_m (or V_s) is the volume of the membrane (or skin) effectively exposed for a given application area of BP, then the ratio of flux to membrane retention (J_m/R_m or J_s/R_s) defines an apparent diffusion parameter d_m (or d_s) of BP in the membrane (or skin):

$$d_m = J / R_m = D / V_m L_m \; ; \; d_s = J / R_s = D / V_s L_s \quad (2)$$

An apparent partition parameter κ_m (or κ_s) may be defined from R_m (or R_s) and C_v as:

$$\kappa_m = R_m / C_v \; ; \; \kappa_s = R_s / C_v \quad (3)$$

If the membrane concentration-distance profile during a steady-state penetration study is approximately linear then $\kappa_m \cong 0.5K_m \cdot V_m$ and $\kappa_s \cong 0.5K_s \cdot V_s$.

RESULTS

Solubility

BP was more soluble in semipolar solvents such as C_{12-15} BA, coconut oil and IPM (Table I). The observed solubility decreased dramatically in extremely polar (e.g., H_2O, 0.00043%) or nonpolar solvents (e.g., silicone oil, 0.4%).

Penetration

Membrane and skin penetration and retention parameters for BP are shown in Table I, with penetration-time profiles are shown in Figure 1. The highest flux of BP across skin was observed with the EtOH vehicle ($p < 0.05$), followed by the semipolar emollients: IPM, coconut oil, PG and C_{12-15} BA ($P < 0.05$), with no significant difference found between the LP, silicone oil and H_2O vehicles. For HDPE, the fluxes from C_{12-15} BA and IPM were significantly higher than for other solvents

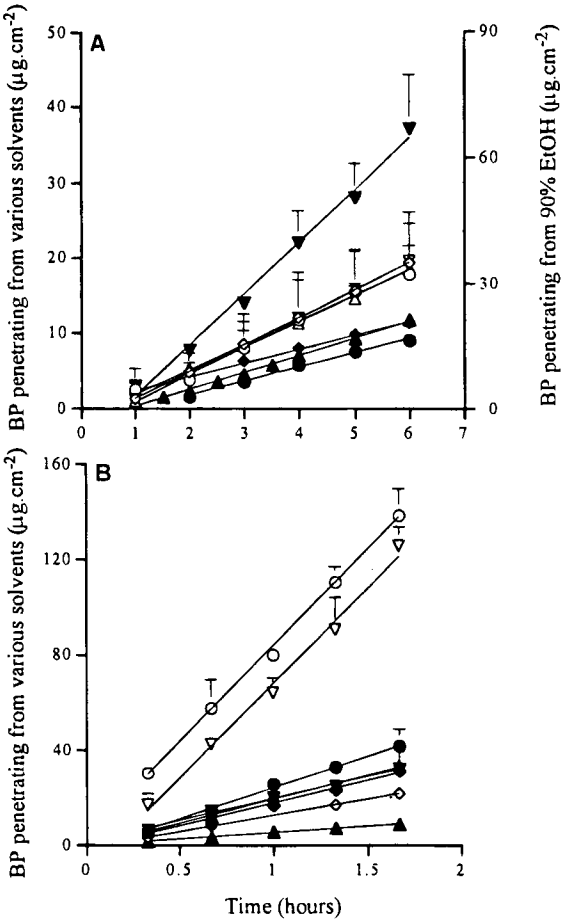

Fig. 1. Penetration profiles of BP across (A) human epidermis and (B) HDPE membranes. Data represents mean ± sd of 6 and 3 replicates for the epidermis and HDPE membranes respectively. Vehicles: LP (●), PG (◇), IPM (○), silicone oil (◆), EtOH (▼), coconut oil (△), C_{12-15} BA (▽) and H_2O (▲).

Table I. Penetration (Experimental) and Solubility Parameters of BP from Each of the Solvents Studied[a]

	Solvents							
	LP	IPM	Silicone oil	C_{12-15} BA	EtOH	PG	Coconut oil	H_2O
sol	29±3.8	112±4.4	4±0.1	170±0.7	19.4±1.0	78±8.4	133±7.2	0.004±0.0004
%	2.9	11.2	0.4	17	1.9	7.8	13.3	0.00043
J_s	1.91	3.55	1.85	3.68	12.3	3.59	3.38	2.3[b]
J_m	27.0	80.4	19.2	79.8	18.6	13.2	20.4	6.0[b]
R_s[c]	18 ± 6.4	37 ± 9.9	11 ± 0.8	60 ± 23	45 ± 12	29 ± 8.5	76 ± 29	28 ± 1.7[b]
R_m[c]	5.0 ± 0.6	13 ± 0.8	3.9 ± 0.5	11 ± 1.5	19 ± 2.5	5.5 ± 0.6	11 ± 1.9	3.2 ± 1.5[b]
Kps	1.3×10^{-5}	6.3×10^{-5}	9.3×10^{-5}	4.3×10^{-5}	12.7×10^{-5}	9.2×10^{-5}	5.1×10^{-5}	1.15
Kpm	3.1×10^{-5}	2.4×10^{-5}	16×10^{-5}	1.6×10^{-5}	3.2×10^{-5}	0.6×10^{-5}	0.5×10^{-5}	0.095
d_s	0.11	0.10	0.17	0.06	0.27	0.12	0.04	0.08
d_m	5.4	6.0	4.8	7.2	1.2	2.4	1.8	1.8
κ_s	1.2×10^{-3}	6.6×10^{-4}	5.5×10^{-3}	7.0×10^{-4}	4.6×10^{-3}	7.4×10^{-4}	1.1×10^{-3}	14
κ_m	3.5×10^{-4}	2.3×10^{-4}	2.0×10^{-3}	1.3×10^{-4}	1.9×10^{-3}	1.4×10^{-4}	1.7×10^{-4}	1.6
δ_v[d]	7.1	8.0	6.0	7.6	14.9	14.0	8.9	23.0

[a] Units: J = $\mu g cm^{-2} h^{-1}$; R = μg; d = $c^2 h^{-1}$, κ = cm^{-3}, δ_v = $(cal/cm^3)^{1/2}$.
[b] Data from saturated solution divided by 2 so as to be equivalent to a semisaturated solutions used for all other solvents.
[c] Mean ± sd of 6 replicates.
[d] Data cited from Ref 15.

($p < 0.05$). Figure 2 shows that the membrane fluxes are maximal when EtOH (δ_v = 14.9) and IPM or C_{12-15} BA (δ_v = 8 or 7.6 cal cm^{-3}) are used as vehicles for the skin and HDPE respectively.

The relationship between log Kp and log κ for BP with respect to δ_v are shown in Figure 3. Log Kp for BP was found to decrease when δ_v approached δ_i [BP: δ_i = 13 $(cal/cm^3)^{1/2}$] for all vehicles with the exception of EtOH. The relationship for apparent partition parameter log κ versus δ_v parallels that for the log Kp versus δ_v.

Retention and Solute Diffusivity Within the Membrane

The highest epidermal retention (R_s) of BP was found following application of BP in semipolar emollients and EtOH. Lower BP retention was found with extremely polar and nonpolar solvents. R_s for BP was: coconut oil > C_{12-15} BA > EtOH > IPM > PG > H_2O > LP > silicone oil. A similar result was found for BP R_m: EtOH > IPM > coconut oil > C_{12-15} BA > PG > LP > H_2O > silicone oil (Table I and Figures 4B and 4C). Figures 5A and 5B show the relationship between BP d_m or d_s and δ_v for the different vehicles. BP d_m was greatest when the vehicle δ_v was closest to δ_m, whereas d_s did not increase as expected when δ_v approximated the theoretical δ_s of 10–15 $(cal\ cm^{-3})^{1/2}$. No relationship was apparent between BP d_m or d_s and BP retention in the two membranes (Figure 5C and 5D).

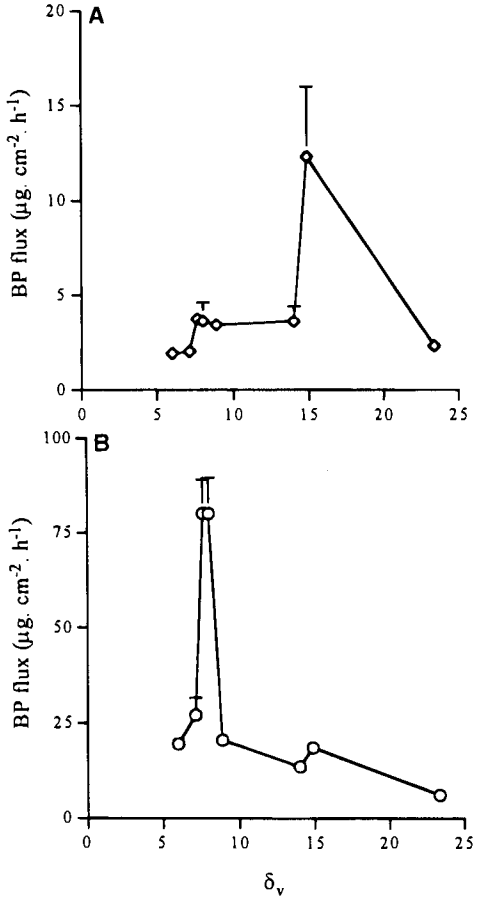

Fig. 2. Relationship between BP membrane flux and vehicle solubility parameter δv for epidermis (A) and HDPE (B). Data represents mean ± sd of 6 and 3 replicates for the epidermis and HDPE membranes, respectively.

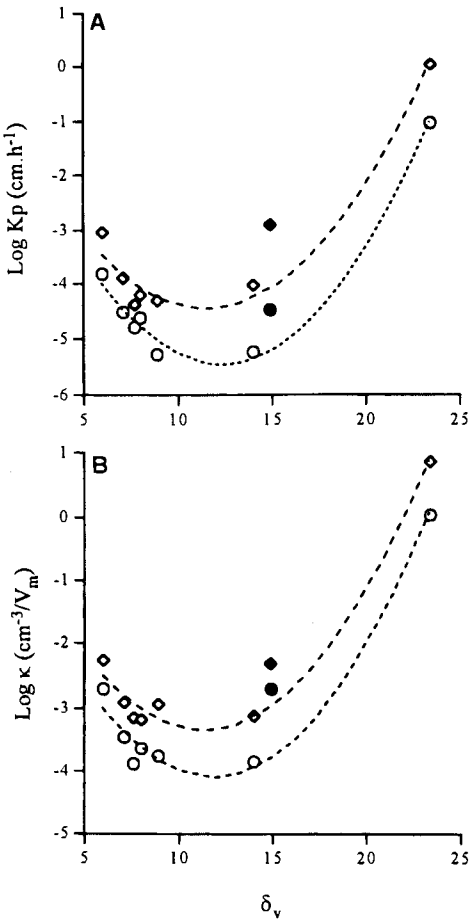

Fig. 3. Relationship between log experimental Kp (A) and apparent partition parameter κ (B) of BP and vehicle solubility parameter, δv, for human epidermis (◇) and HDPE (○). (closed symbol represents the outlying values for EtOH vehicle). Data represents mean ± sd of 6 and 3 replicates for the epidermis and HDPE membranes respectively.

DISCUSSION

Solvent-Membrane Interactions

Percutaneous absorption involves partitioning of a solute from its vehicle to the skin and subsequent diffusion of the solute through the skin. If the vehicle does not affect the skin's properties identical solute flux would be expected from solutions in which the solute had equal thermodynamic activity. A higher flux from a given vehicle most likely reflects an increased permeability of the barrier due to a vehicle-skin interaction (11). In the present study, we found that EtOH had the greatest effect on epidermal flux followed by the semipolar emollients. HDPE membrane was more affected by the more nonpolar solvents, with the highest fluxes being seen for the IPM and C_{12-15} BA vehicles.

Previous studies have demonstrated that vehicle effects on hairless mouse skin were greatest when δ_v approached δ_m (16–17). Sloan *et al.* (16) found that the flux of theophylline

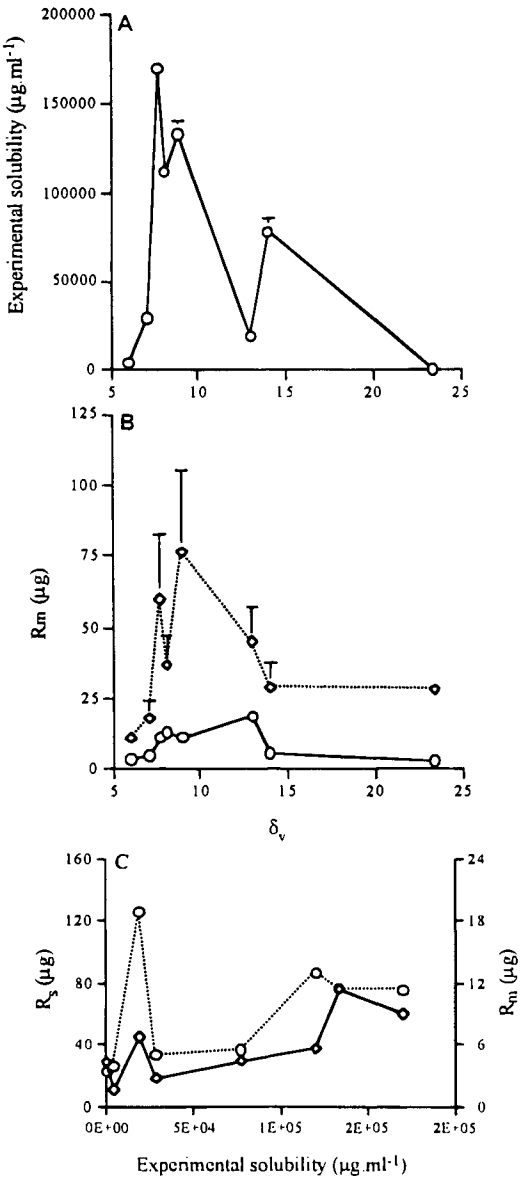

Fig. 4. Relationship between experimental solubility and (A) and Rs (◇) or Rm (○), (B) of BP and vehicle solubility parameter, δv, and Rs (◇) or Rm (○) of BP and experimental solubility (C) for human epidermis (◇) and HDPE membrane (○). Data represents mean ± sd of 6 and 3 replicates for the epidermis and HDPE membranes, respectively.

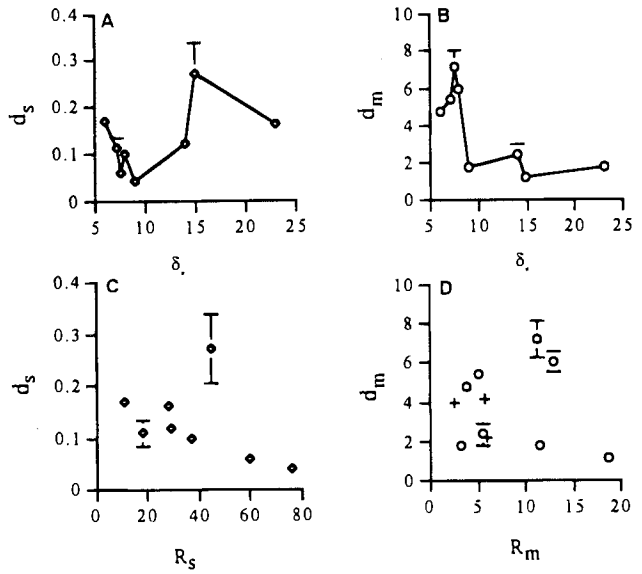

Fig. 5. Relationship between diffusivity (d) and vehicle solubility parameter, δv (A-B) and diffusivity, δ_s and δ_m, with membrane retention R_s and R_m (C-D). Data represents mean ± sd of 6 and 3 replicates for the epidermis and HDPE membranes, respectively.

generally increased in vehicles in the δ_v range 8 to 12 $(cal/cm^3)^{1/2}$, with similar results later seen for 5-fluorouracil (17). In the present study, the δ_v of vehicles having the greatest effect on membrane flux corresponded to δ_s values between 8–14 $(cal/cm^3)^{1/2}$ and δ_{HDPE} values around 8 $(cal/cm^3)^{1/2}$. These values compare favourably to the literature data with δ_s values generally reported to be around 10 for human, porcine (20), and hairless mouse skin (21), and δ_m values of 8.5 (15). The present data suggests that semipolar solvents may modify the skin barrier as they possess δ_v values close to that of the δ_s. These results also suggest that the solvents accelerant effects on solute fluxes may be minimised by choosing those vehicles which have solubility parameters substantially different to the epidermis.

The parabolic relationship observed between the membrane retention of BP and theoretical δ_v values (Figure 4B) suggested that the vehicles with δ_v values close to that of the membrane both increased flux and membrane retention of BP. The trend towards higher membrane retention of BP was seen for solvents in which BP was most soluble, with the exception of EtOH. EtOH may be an exception to ideal vehicle behaviour as it has been reported to cause skin damage by the extraction of lipids from the SC thereby increasing SC permeability and facilitating solute penetration (9,22,23). For example, the solubility of lipophilic drugs such as nitroglycerin and oestradiol in the SC have been found to increase with an increased concentration of EtOH entering the SC (24–25).

Solute Thermodynamic Activity

The relationship between Log Kp and δ_v (Figure 3) is consistent with relationships observed in previous reports for salicylic acid and 6-mercaptopurine (16,18). These results indicate that when δ_v approaches δ_i the increased solubility of a given amount of solute in a vehicle leads to a reduced thermodynamic activity of the solute in the vehicle. This effect subsequently decreases the availability of the solute from the vehicle which leads to a reduction in the observed Kp. EtOH (δ_v 90% = 14.9) has a theoretical solubility parameter around that of the solute used in the present study, BP, δ_i = 13. However, the actual solubility of BP in the aqueous EtOH (90%) was lower than expected (Table I, Figure 4A). As a consequence, EtOH is a deviant in the relationship of log Kp and log κ to δ_v for the various vehicles used in this study.

The parallel plots of log Kp and log κ versus δ_v (Figure 3) suggests that the permeability coefficient of BP from the series of vehicles studied is dominated by vehicle solubility. The amount of solute sorbed into the membrane as a consequence of vehicle uptake will be related to the solute concentration in the

vehicle. Roberts and Anderson (11) observed a similar effect when examining the effect of vehicles on the movement of phenol through epidermal and polyethylene membranes. Although dimethylsulfoxide (DMSO) markedly increased skin diffusivity, the overall permeability coefficient appeared to be dominated by the high solubility of phenol in the vehicle as shown by the low flux of phenol from DMSO through the inert polyethylene membrane relative to other vehicles (11).

Apparent Diffusion Parameter

The increases in diffusivity of BP within the HDPE membrane appeared to be related to the interaction between the membrane and the vehicles as defined by theoretical δ_v values. The d for skin was relatively constant for different δ_v values with the exception of that for EtOH. As stated earlier, EtOH is known to irreversibly alter skin permeability (22). The optimal d for the HDPE membrane was at a δ_v of approx. 7.6–8, consistent with the δ_m and optimal solvent-membrane interaction (Figure 5B). There was no evidence of an increase in d with either BP retention in the skin or the HDPE membrane. When different BP concentrations were examined in different solvents, the relationship between d and R_m was consistent with the original scattergram obtained with different solvents (Figure 5D). This result suggests that the change in d reflects mainly a solvent-skin interaction and not a drug-skin interaction.

CONCLUSIONS

The present study has shown that epidermal and HDPE membrane fluxes of the sunscreen BP from semisaturated solutions was not constant but was related to the δ_v of the vehicle used. Minimal penetration of sunscreens such as BP is most likely to be achieved by choosing vehicles with a δ_v substantially different to the δ_m for the epidermis. In addition, for a given concentration of sunscreen in a vehicle, least sorption of solute into the SC will be likely to occur when ideally the δ_v of the vehicle or formulation is similar to that of the sunscreen as well as different to δ_m.

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