Probing the Effect of Vehicles on Topical Delivery: Understanding the Basic Relationship Between Solvent and Solute Penetration Using Silicone Membranes

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Received October 21, 2000; accepted March 21, 2001

Purpose. In the present study we examined the relationship between solvent uptake into a model membrane (silicone) with the physical properties of the solvents (*e.g.,* solubility parameter, melting point, molecular weight) and its potential predictability. We then assessed the subsequent topical penetration and retention kinetics of hydrocortisone from various solvents to define whether modifications to either solute diffusivity or partitioning were dominant in increasing permeability through solvent-modified membranes.

Methods. Membrane sorption of solvents was determined from weight differences following immersion in individual solvents, corrected for differences in density. Permeability and retention kinetics of ^{3}H-hydrocortisone, applied as saturated solutions in the various solvents, were determined over 48 h in horizontal Franz-type glass diffusion cells.

Results. Solvent sorption into the membrane could be related to differences in solubility parameters, MW and hydrogen bonding ($r^2 = 0.76$). The actual and predicted volume of solvent sorbed into the membrane was also found to be linearly related to Log hydrocortisone flux, with changes in both diffusivity and partitioning of hydrocortisone observed for the different solvent vehicles.

Conclusions. A simple structure-based predictive model can be applied to the sorption of solvents into silicone membranes. Changes in solute diffusivity and partitioning appeared to contribute to the increased hydrocortisone flux observed with the various solvent vehicles. The application of this predictive model to the more complex skin membrane remains to be determined.

KEY WORDS: solvent sorption; silicone membrane; hydrocortisone; topical absorption.

INTRODUCTION

The interaction of constituents of topical formulations with the skin is one of the most important considerations for tailoring effective delivery vehicles, increasing efficacy by reformulation, or predicting the likely penetration of solutes. Finding the right balance between drug solubility in each of the formulation ingredients, subsequent diffusion and penetration of drug and vehicle, and subsequent structural interactions of the drug and formulation components with structures within the skin affect the targeting of topical drugs to the stratum corneum, epidermis, or beyond (1). The recognized barrier to topical penetration, the stratum corneum, is a complex molecular structure composed of various lipid and protein domains. The extent to which a drug or its vehicle diffuses within, and interacts with, these structures ultimately determines its penetration kinetics. However, interpretation of data examining the complex interactions between various vehicles and the stratum corneum for the purpose of creating predictive models is difficult, due to the number and diverse nature of the types of interactions possible. For this reason, simple membranes, such as polydimethylsiloxane (silicone) and polyethylene, transport through which is controlled by parameters similar to those in the stratum corneum, have been used. This significantly aids the understanding of basic processes of diffusion and simple drug-vehicle and vehicle-membrane interactions (2–6).

Traditional methods used to relate solute flux to drug-skin, drug-vehicle, and vehicle-skin interactions include the use of reference polymeric membranes, maximum flux studies, repetition studies with various vehicles to define reversibility of interactions (7,8), and interrelating membrane fluxes to solute uptake into stratum corneum (9). Twist and Zatz used silastic membranes to show that the alcohol-enhanced penetration of a series of parabens could be correlated with the amount of alcohol sorbed by the membrane (2,10). Twist and Zatz reported that the major effect on solute flux, J, was via enhanced partitioning into the membrane rather than an increase in membrane diffusivity, and further suggested that maximum flux (J_m) was dictated by an optimum balance between the alcohol-membrane interaction and paraben concentration (11). Most (12) suggested that the J_m of benzocaine in various silicone rubber membranes occurred when the solubility parameter δ_v (vehicle) was intermediate between δ_i (solute) and δ_m (membrane), providing the solvent had a low molecular volume and had a high mobility within the membrane. Most attributed enhanced benzocaine J_m to increased diffusivity for some vehicle and membrane combinations studied, but not others, and concluded that the degree of importance depended on the overall combination of the different solvent and membrane physical characteristics (12).

Methods of quantifying solvent-drug and solvent-membrane interactions using solubility parameters (δ) have been suggested to be useful in predicting drug flux (J) (13–15). Sloan *et al.* (13) found that a relationship existed between the experimental permeability coefficients (k_p) of theophylline through mouse skin from a number of solvent vehicles and their theoretical partition coefficients (K), calculated from the solubility parameters δ_v, δ_I, and δ_m—in their case mouse skin. The relationship was shown to exist for vehicles or mixtures of vehicles with δ_v in the range 12–18 (cal cm^{-3})$^{1/2}$, with larger than predicted increases in J and k_p seen in the δ_v range 8–12 (cal cm^{-3})$^{1/2}$ where vehicle effects on the membrane were suggested to be greatest. Initially, Sloan *et al.* (13) assumed that diffusivity (D) of solute was constant for each of the solvents applied. However, they later reported that modulation of the barrier properties of the skin may be associated with propylene glycol and isopropyl myristate vehicles and

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0724-8741/01/0700-0999$19.50/0

may have significantly altered D (14). The group suggested that k_p was generally inversely dependent on drug solubility in the vehicle, the minimum k_p being defined by $\delta_i = \delta_v$ (13–15).

The relative importance of solubility parameters and other solvent properties, such as molecular size and hydrogen bonding capacity, on membrane diffusion processes appears poorly defined. In addition, in the majority of previous studies, relationships have been examined using only simple series of homologous alcohols or aqueous solutions of alcohols in contact with membranes (2,10,11). In the present study we examined the relationship between solvent uptake into a model membrane (silicone) with the physical properties of a wide range of structurally unrelated solvents and their ability to partition into the membrane structure and subsequent solute penetration and retention kinetics. In addition, we sought to define drug-solvent-membrane interactions for solvents where solvent-enhanced penetration is suggested to be maximal (i.e., where δ_v approaches δ_m), to establish whether modifications to diffusivity or partitioning were dominant in increasing drug permeability. The δ_m for silicone has been reported to be ~7.5 $(\text{cal cm}^{-3})^{1/2}$ (12). We therefore used saturated solutions of a model solute, hydrocortisone, applied in a range of solvents with δ_v ranging from 6 to 11 $(\text{cal cm}^{-3})^{1/2}$ for the determination of J and R_m (the amount of solute retained in the membrane at the end of a diffusion experiment). We further attempted to model hydrocortisone penetration through the membrane to identify relationships with other permeability parameters and solute, solvent, and membrane physical properties.

EXPERIMENTAL SECTION

Materials

^{3}H-Hydrocortisone was purchased from New England Nuclear (Boston, MA). Acetone; butyl acetate; butanol; cineole; decanol; diethylether; dioctylphthalate; ethanol; ethyl acetate; heptane; hexane; hexanol; hydrocortisone; isopropyl myristate (IPM), liquid paraffin (LP); methoxyethanol; octanol; oleic acid; oleyl alcohol; pentanol; phenethyl alcohol; phenoxyethanol; polyethylene glycol 400 (PEG 400); propanol; and squalane were all supplied by Sigma-Aldrich Chemical Co, Sydney, Australia. Olive oil (cold pressed extra virgin) was a product of Lupi Imperia, Italy; acetonitrile and methanol (HPLC grade) were purchased from Crown Scientific, Brisbane, Australia; and silicone membrane (Samco Corning 300 μm) was obtained from Alpha Laboratories Ltd, Eastleigh, UK). Ultima Gold liquid scintillation cocktail was purchased from Packard Services, Brisbane Australia. Labeled ^{3}H-hydrocortisone was prepared by solubilizing about 1.5 g hydrocortisone in ethanol, adding 100 μCi of radiolabeled solute, evaporating the solvent under nitrogen and drying in a warm oven for 10 h. The activity per mg of hydrocortisone was then determined by measuring the DPM of preweighed amounts of solid.

Methods

Membrane Solvent Sorption Uptake

Solvent sorption into the membrane was determined from the weight difference (Mettler ME22 microbalance) of pieces of membrane (about 250–300mg) soaked in individual solvents for 24 h at 35°C. Solvent sorption is expressed as a volume fraction (V_F) using $V_F = V_s/(V_s + V_m)$, where V_s is the membrane weight increase/density of the solvent and V_m is the volume of membrane/1.3 (density of silastic). Stepwise linear regression, using a Macintosh IIsi computer and Statview software, was used to identify predictors of solvent sorption from various known physicochemical parameters, *e.g.,* molecular weight (MW), melting point, differences in δ_m and δ_v and hydrogen bonding capacity (Table I). The Pearson correlation coefficient indicates the linear correlation coefficients required for both one- and two-tailed analyses for specified numbers of data points/degrees of freedom in order to achieve levels of statistical significance.

Vehicle Solubility

The saturation concentration of hydrocortisone in each solvent was determined by suspending excess ^{3}H-hydrocortisone in 2.5 ml of solvent and mixing the solutions for 24 h on a chuck wheel at room temperature. The suspensions were centrifuged, and supernatants were filtered through a 0.22 μm membrane and analyzed for ^{3}H-hydrocortisone. All radiation assays were performed using the preset channels of a Packard Tri-Carb 2700TR series liquid scintillation analyser.

Permeation Studies

Horizontal Franz-type glass diffusion cells, exposed membrane surface area about 1.2–1.3cm^{-2}, with a degassed 20% ethanol:80% distilled water receptor phase (~3.5 ml), chosen due to the low solubility of hydrocortisone in aqueous buffer solutions, constantly stirred by magnetic fleas and maintained at 35°C, were used to perform diffusion studies.

Hydrocortisone Permeability from Various Solvents

The flux of ^{3}H-hydrocortisone from saturated solutions of each of the solvents was determined using the diffusion cell apparatus previously described. Saturated solutions were left to equilibrate on a chuck wheel overnight at room temperature. The steady-state flux was determined over a 48-h period with the entire receptor phase removed and replaced with fresh solution at each sampling point. Membrane retention, R_m, of hydrocortisone was determined by removal of the exposed surface area and cleaning thoroughly with tissue followed by liquid scintillation counting.

Data Analysis

Ficks first law of diffusion is commonly employed in the interpretation of solute diffusion through a membrane, with flux of the solute (J) defined as follows:

$$J = \frac{K \cdot Cv \cdot D}{l} \quad (1)$$

where K is the membrane/solvent partition coefficient, Cv is the concentration of solute in the solvent, D is the diffusion coefficient of the solute in the membrane, and *l* is the diffusional pathlength.

In the present study the thermodynamic activity of hydrocortisone in each solvent was maintained constant because saturated solutions were used. In this case values for J would have been expected to remain constant, unless interactions

Table I. Solvents Used in the Membrane Sorption Studies, the Significantly Predictive Parameters of Uptake Identified by Regression Analysis, and Comparison of the Measured vs. Predicted V_Fs

Solvent	δ_v	MW	H- Bonding		V_F	
			α	β	Measured	Predicted
Squalane	6.03	422	0.00	0.00	0.090	0.045
Liquid paraffin (LP)	7.09	340	0.00	0.00	0.129	0.184
Hexane	7.28	86	0.00	0.00	0.688	0.584
Diethylether	7.37	74	0.00	0.45	0.662	0.650
Heptane	7.41	100	0.00	0.00	0.704	0.576
50:50 LP:IPM	7.56	305	0.00	0.45	0.318	0.311
Olive oil	7.87	350	0.00	1.35	0.025	0.290
Oleic acid	7.91	282	0.60	0.45	0.002	0.003
Isopropylmyristate (IPM)	8.02	270	0.00	0.45	0.414	0.317
Cineole	8.72	154	0.00	0.90	0.679	0.460
Dioctylphthalate	8.90	390	0.00	0.88	0.048	0.087
Butyl acetate	8.93	116	0.00	0.45	0.598	0.447
Oleyl alcohol	8.95	242	0.37	0.48	0.002	0.069
Ethyl acetate	9.19	88	0.00	0.45	0.475	0.473
Decanol	9.78	158	0.37	0.48	0.036	0.122
Acetone	9.87	58	0.04	0.49	0.144	0.433
Octanol	10.09	130	0.37	0.48	0.058	0.133
Hexanol	10.50	102	0.37	0.48	0.144	0.134
Pentanol	10.80	88	0.37	0.48	0.133	0.422
Butanol	11.18	74	0.37	0.48	0.175	0.108
Polyethylene glycol 400	11.61	400	0.37	4.53	0.002	–0.071
Acetonitrile	11.70	41	0.07	0.32	0.000	0.246
Propanol	11.73	60	0.37	0.48	0.109	0.074
Phenethyl alcohol	11.79	122	0.33	0.56	0.004	0.028
Phenoxyethanol	11.87	138	0.37	0.93	0.002	–0.018
Methoxyethanol	11.98	76	0.37	0.93	0.004	0.064
Ethanol	12.55	46	0.37	0.48	0.004	0.013
Methanol	14.33	32	0.43	0.47	0.000	–0.175

between the solvent and the membrane altered D and/or K values for hydrocortisone. Membrane:vehicle partition coefficients were calculated from the ratio of $R_m \times 2$ (assumed to be the concentration of hydrocortisone at the membrane vehicle interface based on the existence of a linear concentration gradient across the membrane) to the solubility of hydrocortisone in each of the solvent vehicles. Estimations of the diffusivity (D) of solutes within the membrane were calculated from J/C_m, where C_m was approximated as the retention of solute in the membrane, R_m, at the end of the study period. The diffusional pathlength through the membrane was assumed to remain constant.

Solubility parameters (δ) for each of the solvents were taken from Vaughan (16). The solubility parameter for silicone membrane was taken from the literature (12) and that of hydrocortisone calculated using the method of Fedors (17). Stepwise linear regression, using a Macintosh IIsi computer and Statview software, was used to find the best predictors of hydrocortisone J and k_p using the known physicochemical parameters of the solvents MW, mp, differences in δ_m, δ_v, and δ_i and the measured quantity R_m. The Pearson correlation coefficient was then used to identify significant linear relationships.

RESULTS

Membrane Solvent Uptake

The V_Fs of each vehicle (Table I) are shown as a function of δ_v in Fig. 1A. It can be seen that the highest sorption occurred between δ_v values of 7–9.5, but that higher MW solvents in this range had extremely low sorption. Regression analysis of solvent physical properties showed that MW, the size of the difference between δ_v and δ_m, and the presence of hydrogen donor (α) and acceptor (β) groups calculated according to Abraham (18) (Table I) were significant predictors of sorption ($p<0.05$). However, β was the least significant predictor, $p = 0.034$, compared with others shown in Equation 2, for which $p<0.005$.

$$V_F = 0.735 - 0.0015\,MW - 0.10\,|\delta_v - \delta_m| - 0.512\,\alpha + 0.087\,\beta \quad (r^2 = 0.764,\ p < 0.05) \qquad (2)$$

The pattern of distribution of predicted vs. actual solvent V_F values is shown in Fig. 1B.

Hydrocortisone Vehicle Solubility

The solubility of hydrocortisone ($\delta = 13.9$) in the range of solvents studied (Table II), with δ_v ranging from 6.03–11.18 $(\text{cal cm}^{-3})^{1/2}$, increased as expected as the solvent δ_v approached that of the solute (Fig. 2). Solubility could also be approximated by the difference between the solubility parameters of the solute and solvents using a simple linear regression:

$$\text{Hydrocortisone solubility (mg/ml)} = 18.418 - 2.779|\delta_v - \delta_i| \quad (r^2 = 0.8) \qquad (3)$$

However, although significant, Fig. 2 shows that with the particular solvents chosen for this study, the best relationship between solubility and δ_v may not be simply linear.

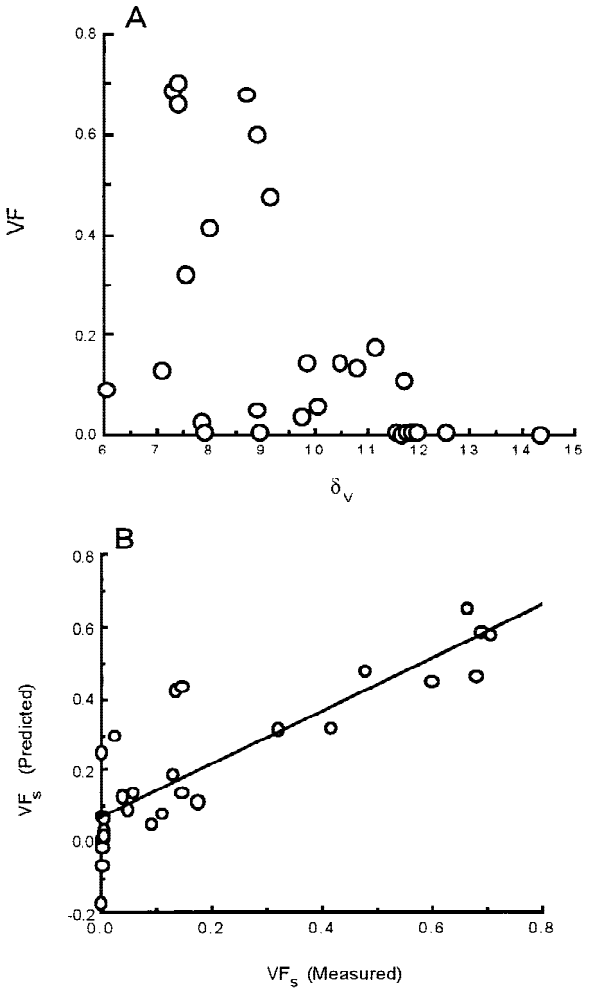

Fig. 1. (A) Relationship between the volume fraction of solvent sorbed into silastic membrane (V_Fs) and solubility parameter of the solvent (δ_v). (B) Relationship between solvent sorption predicted (V_Fs [predicted]) using Equation 2 and experimental values (V_Fs [measured]).

Hydrocortisone Membrane Flux and Retention

The J_m and R_m (Table II) of hydrocortisone from each vehicle in the δ_v range 6.03–11.18 (cal $cm^{-3})^{1/2}$ are shown in Fig. 3A. A linear relationship found between J_m and R_m, $r^2 = 0.85$, could only be seen when all data points were considered (Fig. 3B). However, this relationship is dominated by the high flux for butyl acetate because significance was lost when this point was excluded from the regression. A more significant linear relationship was found between hydrocortisone permeability coefficient (k_p) and R_m, $r^2 = 0.96$ (Fig. 3C). No significant linear relationships were observed between J_m and either membrane:vehicle partition coefficient or diffusivity within the membrane (estimated from J_m/R_m). An exponential relationship was observed between hydrocortisone J_m from the various solvents and the V_F values based on physicochemical characteristics theoretically predicted from Equation 2 (Fig. 4) when data for the very low penetrating solvents olive oil and oleic acid were excluded from the relationship, and also to the experimental V_F values ($r^2 = 0.77$).

Figure 5 shows that changes in both diffusivity (estimated from J_m/R_m) and apparent partition coefficient (K) were observed with changes in J_m. More important, no linear correlations could be identified between these changes and the flux of hydrocortisone through the membrane.

DISCUSSION

The effect of solvents on the membrane penetration and retention of solutes has been one of the most difficult aspects of topical drug delivery design to estimate theoretically. The processes of partitioning into the membrane and subsequent diffusion within it are both likely to be influenced by the presence of solvent molecules within the system. For many years it has been recognized that the ability to predict, at least qualitatively, the effect of vehicles or the rate at which drugs or solutes diffuse through the skin would have clinical and toxicological applications (13). Experiments attempting to determine the effect of solvents on percutaneous absorption are often difficult to interpret due to the highly complex nature of the stratum corneum and its interactions with vehicles. For this reason, it is advantageous to test new permeation techniques or mathematical models intended for applications to skin transport by performing preliminary studies utilizing less complex membranes (2). Silicone and other similar polymer membranes are ideal for modeling percutaneous absorption, as the permeation process consists of initial partition of the

Table II. Hydrocortisone Solubility in Each of the Applied Solvents, Experimental Flux, and Retention Values (±SD) Following Application of Saturated Solutions to Silastic Membranes

Solvent	δ_v	Solubility mg/ml	J mg/cm^2/h	R_m mg/g
Squalane	6.03	0.07	0.0020 ± 0.0001	0.43 ± 0.13
Liquid paraffin (LP)	7.09	0.10	0.0022 ± 0.0005	0.45 ± 0.10
50:50 LP:IPM	7.56	0.88	0.0045 ± 0.0006	0.15 ± 0.10
Olive oil	7.87	0.77	0.00003 ± 0.0000	0.04 ± 0.03
Oleic acid	7.91	0.46	not detectable	0.05 ± 0.03
Isopropylmyristate (IPM)	8.02	1.13	0.0068 ± 0.0007	0.09 ± 0.01
Dioctylphthalate	8.90	1.04	0.0017 ± 0.0003	0.53 ± 0.01
Butyl acetate	8.93	3.63	0.2345 ± 0.0628	1.41 ± 0.19
Oleyl alcohol	8.95	2.10	0.0014 ± 0.0004	0.04 ± 0.01
Ethyl acetate	9.19	5.03	0.0438 ± 0.0038	0.21 ± 0.06
Decanol	9.78	11.25	0.0019 ± 0.0005	0.13 ± 0.03
Butanol	11.18	12.26	0.0019 ± 0.0002	0.14 ± 0.03
Propanol	11.73	12.94	0.0098 ± 0.0001	0.03 ± 0.00

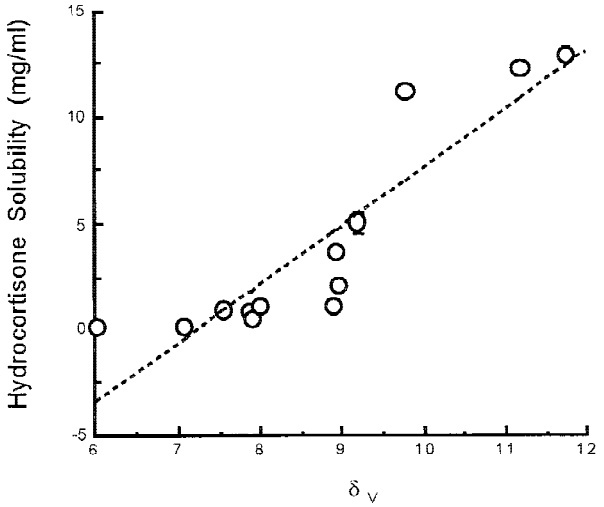

Fig. 2. Relationship between experimentally determined hydrocortisone solubility in each solvent and solvent solubility parameter (δ_v).

solute into, and then diffusion through, the polymer matrix in a manner similar to that in skin (3).

Synthetic membranes are often considered as being reasonably inert to topical formulation ingredients and have been used extensively to dissociate vehicle–solute effects on permeation from those involving vehicle–skin interactions (19,20). However, consideration of the theoretical basis of the solubility parameter approach to prediction of drug and vehicle flux through skin published by Sloan *et al.* (13) suggests that the phenomenon of increased permeability (J_m and k_p) should occur for any membrane structure where δ_v approaches δ_m. The present study showed (Equation 2) that it is not only the proximity of δ_v and δ_m that determines the degree of interaction of a solvent and the membrane to which it is applied, but also the molecular size of the solvent and the degree of hydrogen bonding that occurs between the solvent and the membrane during its permeation into the membrane. This result is consistent with observations that drug flux through skin can be approximated from vehicle–membrane partitioning behavior, described by Sloan using the proximity of solubility parameters (13), molecular weight (21,22) and more recently hydrogen bonding with the stratum corneum (23).

The present study has also shown that this simple predictive solvent sorption model can be used to relate the effects of solvents on the flux of hydrocortisone through the silicone membrane (Fig. 4). The exponential relationship observed is consistent with the earlier observations of Twist and Zatz (2), who saw the same relationship for paraben penetration through silicone following its application in a vehicle of increasing ethanol concentration. Interpretation of their data for methylparaben flux through silicone (2), using Equation 2, showed the expected linear relationship between Log flux and predicted volume fraction of ethanol sorbed into the membrane with an r^2 of 0.89.

Figure 4 shows that the vehicle has a significant effect on the J_m of hydrocortisone applied to silicone membranes as saturated solutions. Few studies have defined the vehicle-enhanced J for a solute through membranes in contact with different vehicles in terms of relative increases in diffusivity or membrane solubility. Gelotte and Lostritto (24) reported

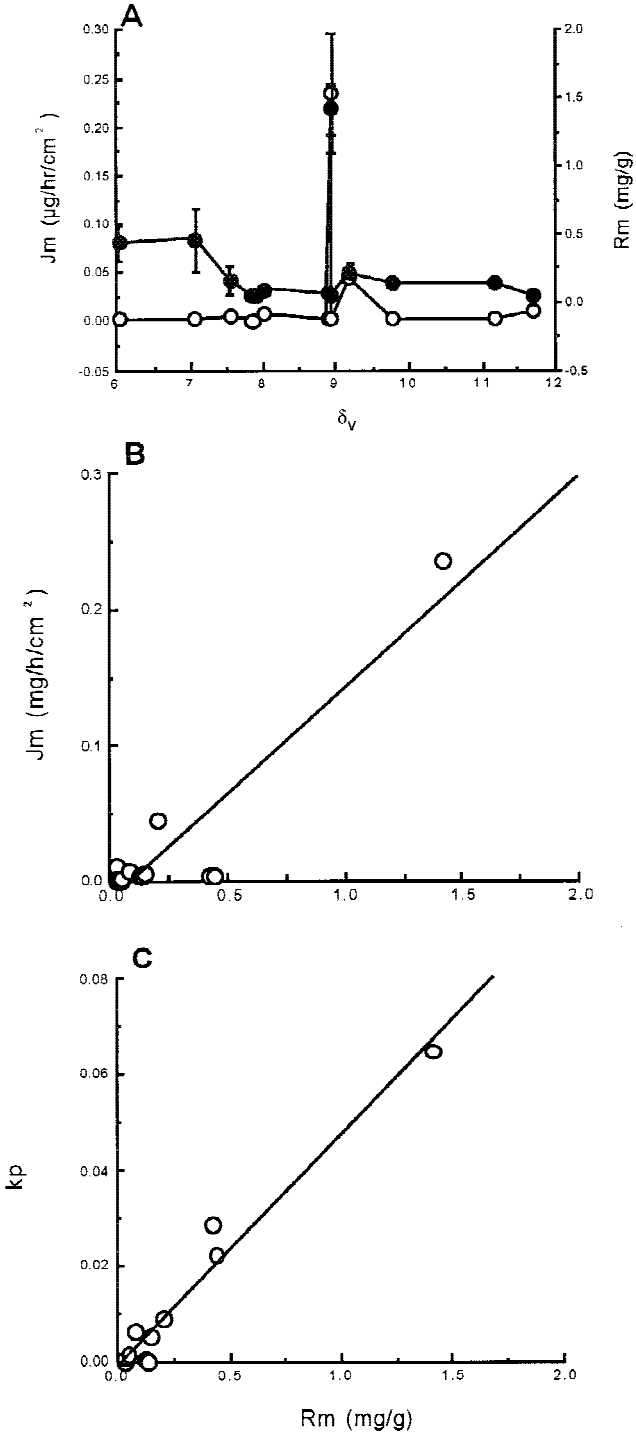

Fig. 3. Relationship between (A) maximum flux (J_m) (○) and membrane retention (R_m) (●) of hydrocortisone following application of saturated solutions to silastic membranes as a function of solvent δ_v, mean±SD, n = 3, and the relationships observed between (B) J_m and R_m, and (C) hydrocortisone permeability coefficient (k_p) and R_m.

increases in both J_m and a calculated diffusivity of benzocaine with increasing sorption of low MW alcohols into silicone membranes, though increased partitioning into the membrane was not seen until alcohol concentrations reached >80%. However, the findings of Sloan's group support an increased membrane partitioning effect (13). This study

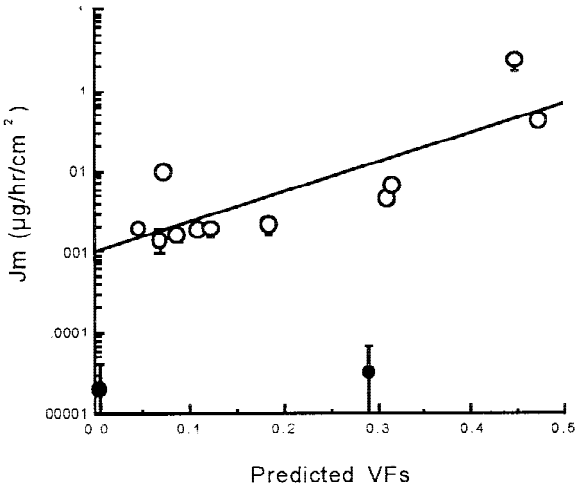

Fig. 4. Relationship between the maximum flux of hydrocortisone following application of saturated solutions to silastic membranes and the volume fraction of solvent sorbed into the membrane predicted using Equation 2. Mean±SD, n = 3. Filled symbols represent the outliers olive oil and oleic acid, which were excluded from the regression.

showed that the J_m of hydrocortisone through silicone from the different vehicles did not show any significant linear correlations with either diffusivity or membrane vehicle partitioning (Fig. 5). This suggested that a combination of both effects must be occurring to varying degrees with different solvents, which resulted in increases in flux. The linear correlation found between hydrocortisone k_p and R_m (Fig. 3C), however, suggested that increased partitioning of hydrocortisone into the membrane may be the main factor in the observed effects on penetration of hydrocortisone. The lack of any correlation between hydrocortisone k_p and estimated diffusivity further supports this assumption.

Thus, it is most likely that changes in both diffusivity and R_m have a role to play in vehicle-enhanced solute permeability through membranes. Indeed, in the present study, hydrocortisone J_m was highest from the lower MW butyl acetate vehicle, which also gave the highest diffusivity and R_m. This study suggests that the relative contribution of changes in diffusivity and R_m to solute flux through a membrane may be determined by the chosen combination of solute and vehicle.

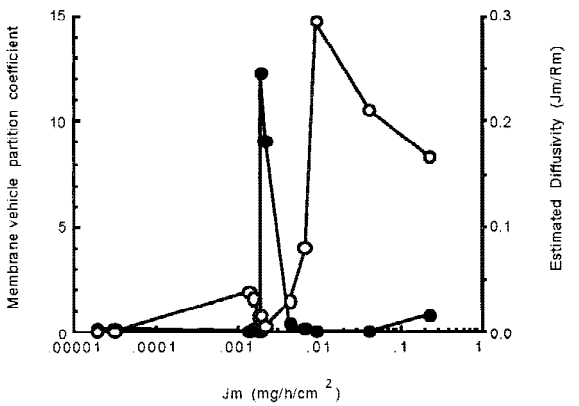

Fig. 5. The relationship observed between estimated diffusivity (○) and apparent membrane:solvent partitioning (●) of hydrocortisone to maximum flux (J_m) following application of saturated solutions in the various solvents to silastic membranes.

These results are consistent with the increases in benzocaine diffusivity with increasing solvent volume in the membrane estimated from increases in membrane swelling seen by Most (12). Most (12) also recognized that, as well as the appropriate relationship between δ_v and δ_m, mobility of the solvent within the membrane was important in this effect and that higher molecular weight solvents with restricted movement in bulky polymers gave lower permeation rates even though δ_v and δ_m values were identical.

The molecular size dependency of sorption into the membrane suggested to exist between dioctyl phthalate, butyl acetate, and oleyl alcohol, all with similar δ_v values, is also consistent with the findings of Mulder *et al.* (25), who showed that the large differences in molar volumes of water and ethanol determined the preferential sorption of water into polymers. Mulder *et al.* (25) concluded from their work that the component of a solution that is sorbed preferentially into the polymer will permeate preferentially and that assumptions of ideal sorption behavior cannot be used in general. These findings were also consistent with the present study where the flux of hydrocortisone was seen to be increased in those solvents with highest sorption and expected permeation. In further support of this effect, solvents with higher sorption did not lead to higher retention of hydrocortisone in the membrane, with the exception of butyl acetate. Thus higher sorption must have been related to a higher permeation through the membrane and not just increased partitioning.

In conclusion, the present study has identified a simple structure-based predictive model for the sorption of a range of structurally different solvents into the skin-imitating membrane silastic based on solubility parameters, molecular size, and hydrogen bonding effects. We have further shown that this prediction of solvent sorption can be related to the flux of topically applied hydrocortisone through the membrane for most solvents. In addition, we observed that changes in both diffusivity and membrane solubility of solutes can be affected by vehicle sorption into silastic membrane, with the degree of importance of the contribution of each effect likely to be determined by the combination of solute and vehicle used. It now remains for the solvent sorption model to be applied to other membranes, including skin, and to determine whether the exponential relationship to flux also exists in these systems.

ACKNOWLEDGMENTS

The authors wish to acknowledge the financial support of the National Health and Medical Research Council of Australia; the Lions Queensland and Northern New South Wales Medical Research Foundation; and Schwarz Pharma, Monheim, Germany.

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