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A method of predicting percutaneous absorption rates from vehicle to vehicle: an experimental assessment

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Summary

The solubility of water in a range of polar solvents was determined. The absorption rate of tritiated water from half-saturated solutions of water in each of the solvents (vehicles) was measured through human abdominal epidermis in vitro and results were expressed as permeability constants. In agreement with theory, the tritiated water permeability constant was inversely proportional to the mole fraction solubility of water in the vehicles. This change in permeability constant with the reciprocal of solubility was found to be attributable to changes in the stratum corneum : vehicle partition coefficient whilst no distinct solubility-related variations in the calculated stratum corneum diffusion constant were apparent. These results are in accord with skin permeability and thermodynamic theory which, for a particular penetrant, indicate that the absorption rate will be proportional to the thermodynamic activity of the penetrant in the vehicle if the properties of the stratum corneum are not changed by the vehicles. The comparison of penetrant solubilities provides one means of relating the thermodynamic activity in one vehicle to that in another. Thus measurement of the percutaneous absorption rate (or a related parameter) for a penetrant in one, or preferably several, vehicles may permit calculations of absorption rates from other vehicles based on solubility data. The relationships employed in the calculations are: absorption rate equals permeability constant multiplied by the applied concentration; permeability constants are inversely proportional to the mole fraction solubilities of the penetrant in the vehicles. This predictive treatment should be equally successful whether based on in vitro or in vitro measurements of absorption rates.

Introduction

It is now possible to measure the rates of absorption of chemicals through mammalian skin using in vivo and in vitro methods. Both the in vivo and in vitro studies are time-consuming, repetitive and technically difficult. For maximum relevance to man, human skin should be used but access to this tissue is limited. It would be desirable to be able to predict the absorption pattern of a penetrant from any vehicle, from permeability properties measured from one vehicle. This type of prediction would reduce the experimental effort required when assessing the toxic effects of a chemical contacting the skin in different vehicles or when selecting an optimum formulation of a drug for topical use.

Rather than a difference in concentration, the driving force for the net transfer of material across the stratum corneum is a difference in chemical potential (or thermodynamic activity) (Higuchi, 1960). If we assume that the membrane diffusion

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constant for a penetrant, the thickness and the solvent properties of the membrane, are unchanged by the vehicle, then the rate of absorption is proportional to the chemical potential in the various vehicles (Dugard, 1983).

The chemical potential of a penetrant is a product of the solute concentration and its activity coefficient in the vehicle (Glasstone, 1953). Activity coefficients are difficult to measure. However, manipulations can be made based on the fact that, for equilibrium states, the chemical potential of a solute is equal in both phases. This is so for such equilibria as the vapour–liquid equilibrium, partition systems and saturated solutions of a penetrant in contact with excess saturating penetrant.

Theoretically, the chemical potential of a penetrant will be maximum in a saturated solution and a maximum rate of absorption will be expected from a saturated solution. The chemical potential of a particular chemical is the same in all saturated solutions regardless of the solvent. Ideally, the absorption rate will be proportional to the degree of saturation (Flynn and Smith, 1972; Hadgraft et al., 1973; Barr et al., 1985; Bennett et al., 1985).

Once the absorption rate of a penetrant has been measured from a system in which the penetrant has a known thermodynamic activity, it should be possible to calculate rates from other systems if the penetrant activity is known.

Materials and Methods

Tissue

Human epidermal membranes were separated from abdominal post-mortem samples by a heat separation method (Kligman and Christophers, 1963). Discs were cut from this tissue with punches for use in absorption experiments (3.1 cm diameter) and in determination of partition coefficients (1.6 cm diameter).

Solvents and tritiated water solutions

The solvents employed as vehicles were commercial samples used without additional purification (Table 1). Tritiated water (spec. act. 5 Ci/ml) was obtained from the Radiochemical Centre, Amersham, U.K., and half-saturated solutions in the vehicles were prepared using water containing 50 μCi/ml tritiated water. For tritiated water absorption from water experiments, a solution of 5 μCi/ml tritiated water was employed.

The solubility of water in each vehicle at 30°C was determined by shaking excess tritiated water with the vehicle, allowing separation and equilibration for 3 days before a final centrifugation and sampling of both layers. Corrections were applied for tritium exchange and the presence of vehicle in the water phase. The measured solubilities for the single solvents and combinations are shown in Table 1.

Skin absorption measurements

Discs of epidermal membrane were clamped between the two chambers of a glass diffusion cell similar to that previously described (Scheuplein, 1965). The area of epidermis available for absorption was 1.8 cm^2 and experiments were conducted at 30°C. On day 1 of the experiment the absorption of tritiated water from water as a vehicle was determined to test the integrity of each membrane and provide base data for assessing irreversible membrane damage caused by solvent contact. Tritiated water was placed in the 'donor' chamber and the 'receptor' chamber was filled with a known volume of water which was stirred continuously. 25 μl samples of the receptors were taken hourly for 6 h and added to scintillation vials containing 10 ml of scintillation fluid (Permafluor I, Beckman, diluted 4 up to 10 with toluene containing 375 ml methanol per 2.5 litre total). Radioactivity was assayed in an Intertechnique SL30 liquid scintillation counter. 25 μl samples were also taken from the donor solution at the beginning and end of the experiment.

A graph of 'penetrated [^{3}H]water versus time' was drawn and the rate of absorption calculated from the slope of the linear region of the graph. A permeability constant was then calculated by dividing the absorption rate by the applied concentration (as in Eqn. 1). Membranes displaying an initial water permeability constant of 1.5×10^{-3} cm/h or above were presumed to have been damaged in preparation and rejected. Following absorption measurements, the donor and receptor solutions were replaced with distilled water and left overnight.

TABLE 1

DETAILS OF SOLVENTS USED AS VEHICLES: SUPPLIER AND EXPERIMENTALLY DETERMINED SOLUBILITY OF WATER IN THE SOLVENT

	Solvent combination	Solubility of water in solvent		Reciprocal of water solubility
		% w/w	mole fraction	(1/mole fraction)
1	*sec*-Butanol (a)	64.7	0.77	1.3
2	*iso*-Butanol (a)	20.5	0.50	2.00
3	*n*-Butyl lactate (b)	19.3	0.60	1.67
4	Cyclohexanol (a)	15.4	0.48	2.08
5	Propylene carbonate (a)	11.9	0.429	2.33
6	Methyl *iso*-butyl carbinol (a)	6.76	0.320	3.13
7	Cyclohexanone (b)	5.12	0.218	4.59
8	Glycerol triacetate (b)	3.31	0.293	3.41
9	*n*-Decanol (c)	3.00	0.250	4.00
10	Isophorone (b)	2.59	0.167	5.99
11	Methyl *iso*-butyl ketone (b)	1.51	0.078	12.8
12	Methyl *n*-butyl ketone (c)	1.35	0.070	14.3
13	*n*-Butyl acetate (b)	0.90	0.055	18.2
14	Amyl acetate (a)	0.80	0.054	18.5
15	Propylene carbonate/*n*-Butyl lactate/*sec*-Butanol	41.1	0.62	1.62
16	Propylene carbonate/*n*-Butyl lactate/Glycerol triacetate	38.8	0.62	1.62
17	*n*-Butyl lactate/*sec*-Butanol	32.5	0.59	1.7
18	Propylene carbonate/*n*-Butyl lactate/Glycerol triacetate/*sec*-Butanol	29.4	0.55	1.82
19	Propylene carbonate/*n*-Butyl lactate	20.1	0.45	2.2
20	*n*-Butyl lactate/Glycerol triacetate	15.9	0.43	2.3
21	Propylene carbonate (70%)/Glycerol triacetate (30%)	10.97	0.29	3.4
22	Propylene carbonate/Glycerol triacetate	10.51	0.30	3.3
23	Propylene carbonate/Glycerol triacetate	10.30	0.30	3.3
24	Propylene carbonate/*n*-Butyl lactate/*n*-Butyl acetate/Glycerol triacetate	9.2	0.11	3.6
25	*n*-Butyl acetate (10%)/Propylene carbonate (90%)	8.82	0.23	4.3
26	Propylene carbonate/Glycerol triacetate	6.86	0.27	3.9
27	*n*-Butyl acetate (30%)/Propylene carbonate (70%)	6.04	0.17	5.8
28	Propylene carbonate/*n*-Butyl lactate	3.40	0.10	9.8

All chemicals, as supplied had a nominal purity of at least 95%. The suppliers were (a) Cambrian Chemicals Ltd., Croydon, U.K. (b) BH Chemicals Poole, U.K. and (c) Merck, Damstadt, F.R.G. The data on solubility of water in the vehicles refers to the saturated state. In the experiments half-saturated solutions were used throughout.

The absorption of tritiated water from half-saturated solutions in the various vehicles was measured on day 2. The receptor solution was water alone in all cases. Following the solvent experiment, donor and receptor solutions were replaced with water alone overnight. On day 3, a further measurement of the permeability constant for tritiated water from water was made to assess membrane damage. Experiments with water alone, in contact with the tissue on day 2, served as controls for the assessment of solvent induced damage.

Stratum corneum: vehicle partition coefficient determination

Two discs of epidermis were placed in 1 ml of a half-saturated solution of tritiated water in the vehicle and left to equilibrate for 3 days at 30°C and a 25 μl sample was then taken from the solution. The discs of tissue were taken from the vehicle, quickly blotted dry (a process which removes most of the 'viable' epidermal cells from the stratum corneum) and placed in glass scintillation vials containing 2 ml of a tissue solubilizer (Soluene 350, Packard). The vial and solubilizer

TABLE 2

WATER PERMEABILITY PARAMETERS

Solvent	Damage ratio [a]	Permeability constant [b] ($cm/h \times 10^2$)	Partition coefficient [b]	Diffusion coefficient [c] ($cm^2/s \times 10^8$)	Outside to inside water diffusion rate [d] ($\mu l/cm^2/h$)
(1) *sec*-Butanol	1.5	1.72 ± 0.16 (4)	1.52 ± 0.084 (11) *	1.26	3.38
(2) *iso*-Butanol	1.94	2.30 ± 0.15 (9)	1.90 ± 0.15 (11)	1.34	1.96
(3) *n*-Butyl lactate	1.14	1.20 ± 0.09 (9)	1.84 ± 0.16 (10)	0.72	0.97
(4) Cyclohexanol	1.25	1.29 ± 0.05 (7)	3.34 ± 0.21 (9)	0.43	0.86
(5) Propylene Carbonate	0.87	0.63 ± 0.11 (10)	1.79 ± 0.14 (9)	0.39	0.34
(6) Methyl *iso*-butyl carbinol	3.86	6.79 ± 0.06 (7)	4.69 ± 0.32 (6)	1.61	2.15
(7) Cyclohexanone	1.68	4.11 ± 0.05 (8)	3.73 ± 0.26 (11)	1.22	1.00
(8) Glycerol triacetate	1.35	2.21 ± 0.12 (10)	11.1 ± 0.43 (32)	0.22	0.36
(9) *n*-Decanol	3.07	4.52 ± 0.23 (5)	13.8 ± 1.27 (6)	0.36	0.66
(10) Isophorone	1.69	4.00 ± 0.03 (10)	7.80 ± 0.41 (9)	0.57	0.50
(11) Methyl *iso*-butyl ketone	1.29	10.3 ± 0.05 (7)	31.6 ± 1.45 (6)	0.36	0.77
(12) Methyl *n*-butyl ketone	1.77	9.3 ± 0.25 (6)	32.5 ± 0.62 (7)	0.32	0.62
(13) *n*-Butyl acetate	1.73	15.9 ± 0.25 (6)	40.6 ± 3.5 (6)	0.43	0.71
(14) Amyl acetate	3.60	15.3 ± 0.14 (4)	51.5 ± 4.9 (6)	0.33	0.60
(15) Propylene carbonate/*n*-Butyl lactate/*sec*-Butanol	3.85	1.02 ± 0.15 (10)	1.34 ± 0.06 (5)	0.85	2.09
(16) Propylene carbonate/*n*-Butyl lactate/Glycerol triacetate	1.27	1.46 ± 0.12 (10)	1.64 ± 0.07 (4)	0.99	2.83
(17) *n*-Butyl lactate/*sec*-Butanol	0.94	0.79 ± 0.24 (10)	1.0 ± 0.3 (5)	0.88	1.28
(18) Propylene carbonate/ *n*-Butyl lactate/ Glycerol triacetate/ *sec*-Butanol	1.44	0.54 ± 0.03 (10)	1.73 ± 0.06 (5)	0.35	0.79
(19) Propylene carbonate/ *n*-Butyl lactate	1.47	0.60 ± 0.16 (10)	3.7 ± 0.16 (4)	0.18	0.61
(20) *n*-Butyl lactate/ Glycerol triacetate	0.94	0.79 ± 0.24 (10)	1.0 ± 0.3 (5)	0.87	1.28
(21) Propylene carbonate/ Glycerol triacetate	1.31	1.85 ± 0.40 (10)	10.8 ± 0.42 (5)	0.19	1.02
(22) Propylene carbonate/ *n*-Butyl lactate	1.20	1.19 ± 0.10 (10)	7.4 ± 0.69 (5)	0.18	0.63
(23) Propylene carbonate/ Glycerol triacetate	1.17	1.56 ± 0.22 (8)	7.7 ± 1.0 (5)	0.23	0.82
(24) Propylene carbonate/ *n*-Butyl lactate/ *n*-Butyl acetate/ Glycerol triacetate	1.09	2.16 ± 0.09 (10)	6.47 ± 0.29 (5)	0.3	0.99
(25) *n*-Butyl acetate/ Propylene carbonate	1.53	1.75 ± 0.16 (10)	9.45 ± 0.65 (5)	0.21	0.72
(26) Propylene carbonate/ Glycerol triacetate	1.14	1.38 ± 0.05 (9)	9.6 ± 0.39 (4)	0.1	
(27) *n*-Butyl acetate/ Propylene carbonate	1.43	2.48 ± 0.25 (10)	16.11 ± 0.99 (5)	0.17	0.75
(28) Propylene carbonate/ *n*-Butyl lactate	1.30	3.20 ± 1.0 (10)	12.7 ± 1.4 (4)	0.28	0.61

* Values in parentheses are number of determinations.

[a] Damage ratio is the ratio of tritiated water absorption rate from water after solvent contact to that obtained before solvent contact. Results are the mean of values obtained in every permeability experiment.

[b] Results for tritiated water applied to epidermal samples as half-saturated solutions in the solvents. Values are the mean ± S.E. with number of determinations in parenthesis.

[c] Diffusion constants are calculated from the mean permeability constant and partition coefficient using Eqn. 2 and assuming a stratum corneum thickness of 40 μm.

[d] This is the experimentally determined rate of diffusion of [^{3}H]water, for the donor solution through the epidermal membrane and into the receptor solution.

had been previously weighed and the weight of added tissue was found by difference. The vial was sealed and left for 3 h at room temperature for complete tissue digestion before addition of 15 ml scintillation fluid (Dimilume, Packard) and radioactivity content determined by scintillation counting (with a correction for quenching). The partition coefficient (Table 2) was determined from the tissue concentration of tritiated water (in dpm per mg 'wet' weight) divided by the vehicle concentration (in dpm per μl).

Results

The values for the solubility of water in the single solvents, are in reasonable agreement with published figures with the exception of that for *sec*-butanol for which the measured value is higher (Table 1). Published figures for water solubility in *sec*-butanol vary with the purity. The purity for the sample employed was above 95% and the measured solubility was used in the considerations below.

A 'damage ratio' (Table 2) was calculated (Matoltsy et al., 1968) and is the ratio of the permeability to tritiated water from water measured after solvent contact to the initial tritiated water permeability. The mean damage ratios for the solvents were generally higher than the control range (0.99 S.E.M. $\pm$ 0.08, n = 12) with the most damaging solvents being methyl *iso*-butyl carbinol, *n*-decanol and amyl acetate (mean damage ratios of 3.86, 3.07 and 3.60, respectively). The most damaging combination of solvents was propylene carbonate/*n*-butyl lactate/*sec*-butanol with a damage ratio of 3.85.

The mean permeability constants for tritiated water absorption from half-saturated solution in the vehicles and the stratum corneum : vehicle partition coefficients (Table 2) for the same system were used to test the agreement between the experimental results and the theory forming the basis for predictions. Permeability constants and partition coefficients were plotted against the reciprocal of the mole fraction solubility of water in the solvents (Figs. 2 and 3).

As predicted by theory (see Discussion) the graph of permeability constant versus reciprocal solubility closely approaches linearity (correlation coefficient, $r = 0.93$; number of paired values, 28; slope, 0.79×10^{-2} cm $\cdot$ h^{-1}; intercept (1/solubility = 0), -0.46×10^{-2} cm $\cdot$ h^{-1}) and the intercept is close to the origin. Thus the permeability constant

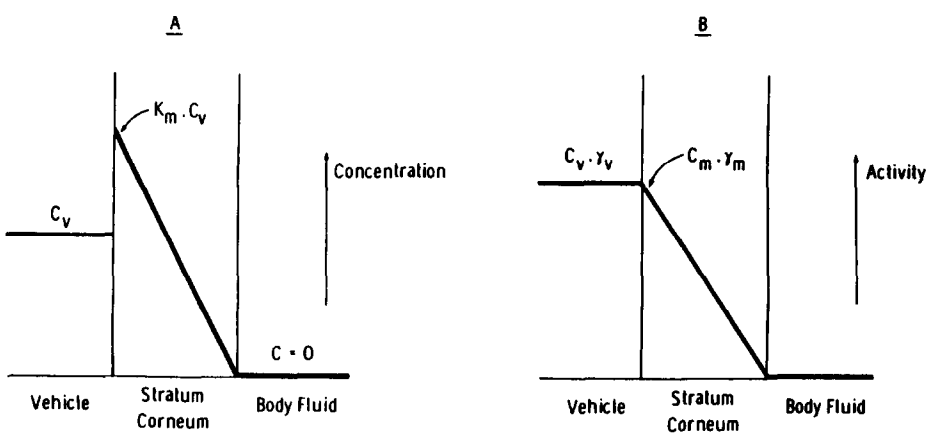

Fig. 1. A: penetrant concentrations profile across stratum corneum during steady-state absorption. C_v = concentration of penetrant in the vehicle; K_m = stratum corneum : vehicle partition coefficient. Thus the concentration difference within the membrane is $K_m \cdot C_v$ if body fluid concentration is effectively zero. B: thermodynamic activity profile of penetrant across stratum corneum during steady-state absorption. γ_v and γ_m are the activity coefficients for the penetrant in vehicle and membrane respectively. C_m is the concentration of penetrant in outer face of stratum corneum. Note that the activity is the same in the vehicle and in the outer face of the stratum corneum where an equilibrium exists. Thus $C_v \cdot \gamma_v = C_m \cdot \gamma_m$ and $K_m = \gamma_v/\gamma_m$ (after Higuchi, 1960).

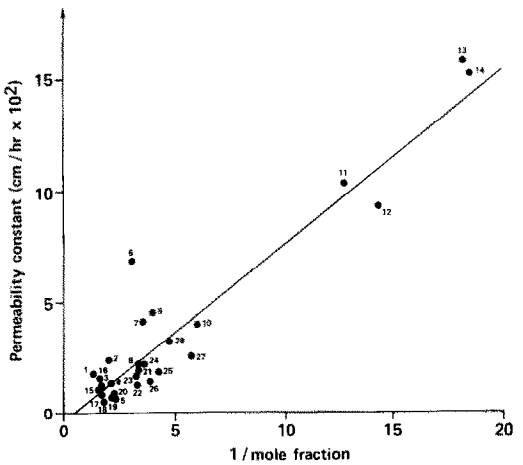

Fig. 2. Graph of permeability constant of tritiated water from half-saturated solution versus the reciprocal of water solubility in the solvent. The line is the regression of permeability constant on reciprocal solubility. Solvents are identified by numbers corresponding to those in Tables 1 and 2.

for a given penetrant is inversely proportional to its solubility in a vehicle. Similarly, the stratum corneum : vehicle partition coefficient changes linearly with reciprocal solubility (correlation coefficient, $r = 0.97$; number of paired values, 28; slope, 2.52 K_m units per 1/solubility; intercept (1/solubility = 0), −2.23). The partition coefficient is inversely proportional to the solubility of the penetrant in the vehicle.

Diffusion constants were calculated from measured permeability constants and partition coefficients and an assumed stratum corneum thickness of 40 μm (Table 2). There is no indication of a trend (in the calculated diffusion coefficient, Table 2) which could have given rise to increasing permeability constants with rising reciprocal solubilities. However, there was an apparent slight tendency for the diffusion constant to fall as reciprocal solubility rose.

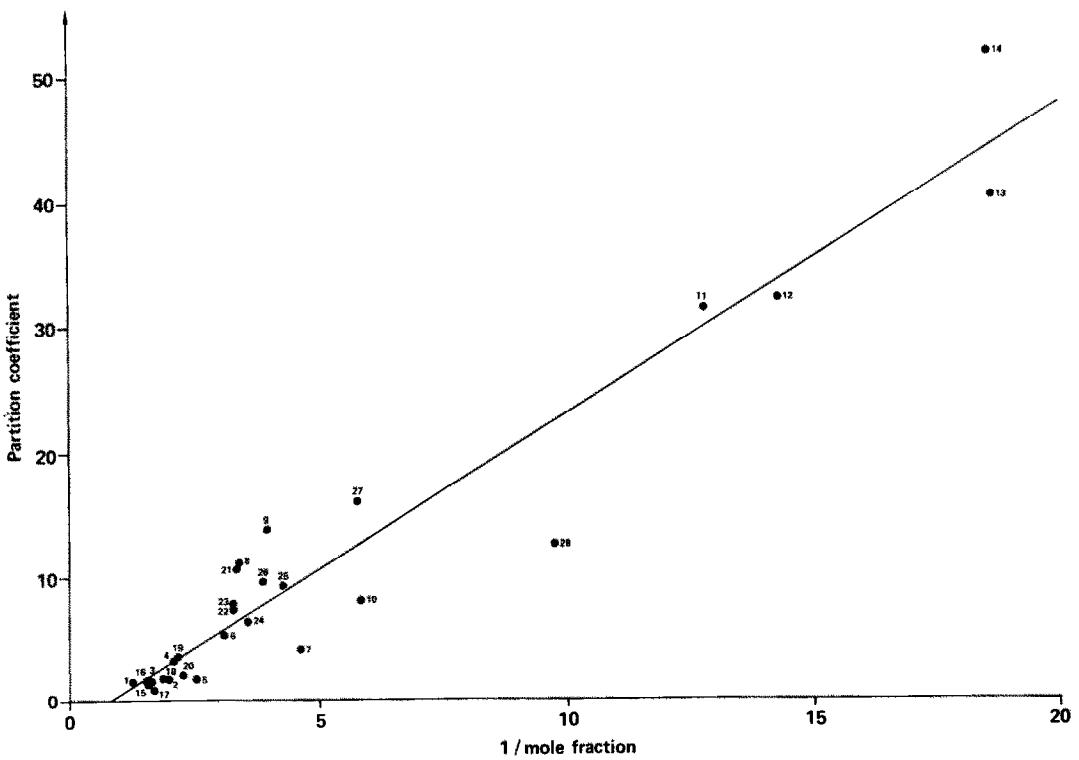

Fig. 3. Graph of stratum corneum : vehicle partition coefficient for tritiated water in half-saturated solution versus reciprocal of water solubility in the solvent. The line is the regression of partition coefficient on reciprocal solubility. Solvents are identified by numbers corresponding to those in Table 1.

Under similar experimental conditions as used in this study, we have measured the absorption of [^{3}H]water from aqueous solution to be approximately 1.3 $\mu l/cm^2/h$. This value is in close agreement with other workers (e.g. Scheuplein, 1965). This value can be considered to be the absorption rate of water from a saturated solution of water in water. We have measured the rates from half-saturated solutions of water in solvent vehicles (Table 2). In such circumstances, if theory is obeyed, the predicted rate of absorption of water will be approximately 0.65 $\mu l/cm^2/h$. 28 vehicles were used in this study and the absorption rate of water from 23 of the vehicles were within a factor of 2 of the predicted value.

Discussion

For a particular vehicle, assuming Fick's Law of Diffusion, the steady-state absorption rate of a penetrant, is proportional to the concentration difference across the stratum corneum. Thus

$$J_s = k_p \cdot \Delta C_s \tag{1}$$

where J_s is the flux, the absorption rate per unit area of skin, ΔC_s is the difference in concentration across the stratum corneum and k_p is the permeability constant which is a proportionality constant ideally independent of concentration. The permeability constant has been expanded (Scheuplein, 1965) to indicate the factors controlling the absorption rate:

$$k_p = \frac{K_m \cdot D_m}{\delta} \tag{2}$$

and this by substitution:

$$J_s = \frac{K_m \cdot D_m \cdot \Delta C_s}{\delta} \tag{3}$$

where δ is the thickness of the stratum corneum, D_m is the diffusion constant of the penetrant in the stratum corneum and is a measure of the mobility of molecules, K_m is the membrane : vehicle partition coefficient.

The physical significance of the partition coefficient is illustrated in Fig. 1A and it is important because the driving force for net movement of molecules across the stratum corneum is the difference in concentration within the stratum corneum. Thus the concentration of penetrant within the outer region of the membrane rapidly equilibrates with the external solution (concentration C_v) and is given by the product $K_m \cdot C_v$ (Fig. 1A). In most experimental and practical situations the concentration of penetrant at the inner face of the stratum corneum is effectively zero.

A saturated solution of a penetrant in a vehicle establishes a saturated solution in the outer region of the stratum corneum (Dugard, 1983) to give the maximum possible concentration (activity) gradient within the stratum corneum (Fig. 1B). If S_m is the solubility of the penetrant in the stratum corneum and S_{v_1} the solubility of the penetrant in vehicle 1 then

$$K_{m_1} = \frac{S_m}{S_{v_1}} \tag{4}$$

where K_{m_1} is the penetrant partition coefficient between the stratum corneum and vehicle 1.
If S_m and δ are assumed constant despite changing the vehicles, then from Eqn. 2 we see that:

$$K_p \propto K_m \propto \frac{1}{S_v} \tag{5}$$

In this study, the relationship presented in Eqn. 5 has been experimentally examined.

The results of this study show that, for the system tested, predictions of absorption rates from vehicle to vehicle can be made using solubility information. This is possible because, in accord with theory as stated in Eqn. 5, the permeability constant for water was inversely proportional to the solubility of water in the vehicle. Thus the graph of permeability constant versus the reciprocal of water solubility (mole fraction) in the vehicle (Fig. 2) was linear and passed through the origin. Also in agreement with theory, the variation in permeability constant from vehicle to vehicle was due to a change in partition coefficient which was itself shown to be inversely proportional to solubility (as in Eqn. 5). The diffusion constant played

no part in the regular changes in permeability constant.

There are two methods of calculating permeability constants from vehicle to vehicle from determinations of permeability constants and solubility data. The first method is graphical and experimental measurements of permeability constants for several vehicles must be made. Thus a line such as that in Fig. 2, derived statistically or drawn by eye and forced through the origin, would provide a sound means of predicting the rate of water absorption from an untested vehicle in which the solubility of water was known. In a practical situation, a graph such as that in Fig. 2 might be based on measurements for four vehicles providing that vehicles in which the penetrant has a moderately low solubility are included and that an acceptable degree of linearity is displayed. In the second method of calculating permeability constants from vehicle to vehicle the permeability constant for the penetrant in only one vehicle is measured. Because the permeability constant is proportional to solubility:

$$k_{p_2} = k_{p_1} \frac{S_{v_1}}{S_{v_2}} \qquad (6)$$

where k_{p_2} is the permeability constant to be predicted, k_{p_1} has been measured and S_{v_1} and S_{v_2} are the solubilities of the penetrant in vehicles 1 and 2. Graphically this is equivalent to constructing the line in Fig. 2 by connecting a single point to the origin and extrapolating without limit. Using the results of this study, predictions for other solvents from the permeability constant for each solvent singly would have worked well in most cases. Because large inter-subject variations in skin permeability properties exist, predictions of absorption rates to within a factor of two would be adequate for most practical purposes. Predictions of this type should be as successful whether based on in vivo or in vitro permeability measurements.

Of the 28 vehicles used, the absorption rate of water from each was within a factor of two of the expected value, from 23 of the vehicles. This we believe is a satisfactory degree of success. Characteristically, the vehicles for which results deviated from the theory had a high percentage of water or were the more membrane damaging vehicles.

Damage to the epidermal membrane, following solvent contact, does enhance the permeability to water (Scott et al., 1982). The breakdown of the theory at high penetrant concentration in the vehicle perhaps indicates that theory will be better obeyed at lower (infinite) dilution. However, many pharmaceutical topical preparations and other formulations such as those to be sprayed on crops, do not contain penetrants at infinite dilution. Exploration using vehicles containing the range of penetrant concentration as used here can be related to the everyday practical case.

The combination of tritiated water at half-saturation in individual pure solvents and solvent combinations was chosen to give a single state of stratum corneum hydration in all experiments. Practically, it is unlikely that stratum corneum hydration would be the same from vehicle to vehicle. Since the degree of hydration of stratum corneum may influence the diffusion constant in, and thickness of, the stratum corneum, the simple predictive scheme may be perturbed to a greater or lesser extent.

A further factor capable of perturbing predictions is the entry of vehicle into the stratum corneum to an extent sufficient to alter significantly the diffusion constant or solubility of the penetrant within the stratum corneum. Only the attempted use of prediction will show whether the frequency of occurrence and the magnitude of the effects produced by the above factors are sufficiently great to prevent accurate results from being obtained.

The importance of considering the thermodynamic activity and not simply the concentration of a skin penetrant in the vehicle is apparent when comparing the calculated (Eqn. 1) absorption rates from a 0.5% solution of water in for example *sec*-butanol, 8.6×10^{-2} mg/cm^2/h, and from the same concentration in amyl acetate, 76.5×10^{-2} mg/cm^2/h; a 10-fold difference in absorption rate from the same concentration. The factor of difference would probably be greater in practice because of the hydration effect. The findings of this study are in agreement with those of others (Flynn and Smith, 1972; Hadgraft et al., 1973) that the absorption rates from solutions of the same ther-

modynamic activity are equal.

Emphasis has been placed on solubility comparisons as a means of relating thermodynamic activity in different vehicles. Other ways of relating activities in different systems depend on knowledge of equilibrium states where activities in two phases must be equal. Thus the partitioning of a penetrant between vehicles and a common solvent or measurement of vapour–solution equilibria provide potential methods of relating activities without requiring a limiting solubility and these are under investigation at present.

Yalkowsky et al. (1972) have suggested a method for predicting solubility of a solute in mixtures of two polar solvents if the solubilities of the solute in the individual solvents are known. This type of prediction increases the scope of skin absorption rate predictions for two component vehicles by rendering solubility determination unnecessary.

The results of this study demonstrate that, in agreement with theory, the percutaneous absorption rate of a penetrant depends directly upon its thermodynamic activity in a vehicle. The solubility of the penetrant in different vehicles provides a means of relating the activity of the penetrant in the vehicles since the permeability constant, which is used to calculate absorption (Eqn. 1), is inversely proportional to solubility. The suggested scheme for absorption rate predictions should now be tested in more complex practical situations.

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