Use of Theoretical Partition Coefficients Determined From Solubility Parameters to Predict Permeability Coefficients for 5-Fluorouracil*

Elizabeth F. Sherertz, M.D., Kenneth B. Sloan, Ph.D., and Raquel G. McTiernan, B.S.

Department of Medicine (Dermatology), Veterans Administration Medical Center and the University of Florida College of Medicine (EFS), Gainesville, Department of Medicinal Chemistry, University of Florida College of Pharmacy (KBS), Gainesville, and Veterans Administration Medical Center (RGM), Gainesville, Florida, U.S.A.

Values for experimental permeability coefficients of 5-fluorouracil (5-FU) in 7 single- and 4 two-component vehicles were determined from flux measurements through hairless mouse skin in diffusion cells and from solubility data. Theoretical partition coefficients of 5-FU between vehicle and skin were determined from solubility parameters of drug, vehicle, and skin, and from this theoretical permeability coefficients were estimated. Comparison of theoretical with experimental values for the permeability coefficients showed a good correlation for vehicles with solubility parameters between 12–18 $(cal/cm^3)^{\frac{1}{2}}$. For vehicles or mixtures of vehicles with solubility parameters in the range of 8–12 $(cal/cm^3)^{\frac{1}{2}}$, increases in flux and permeability coefficients were seen compared with theoretical predictions, possibly due to the similarity in solubility parameters of the vehicles to that of skin (10 $cal/cm^3)^{\frac{1}{2}}$. There was an inverse relationship between 5-FU solubility in the vehicles and flux or permeability coefficients, with a minimum in flux and permeability coefficient that corresponded approximately to the point where the solubility parameters of drug and vehicle were the same. *J Invest Dermatol 89:147–151, 1987*

In developing drug preparations for topical delivery through the skin, the choice of vehicle formulations for a given drug is important to assure adequate delivery of the drug into the skin. The solubility of a drug in a chosen vehicle is important in determining the rate of delivery into the skin, and this solubility is dependent on physicochemical properties of the drug molecule and of the vehicle. The ability to predict percutaneous penetration of a drug based on these physicochemical characteristics would potentially enhance topical drug development by decreasing the need for in vitro and in vivo animal and human skin penetration studies. Previously, Sloan and associates [1] provided the theoretical basis and experimental evidence to show that the experimentally determined permeability coefficient (Kp) of a drug in a given vehicle should be directly proportional to the product of a theoretically determined partition coefficient (PC) of the drug (between skin and vehicle) and a constant (C). The theoretical equations for this relationship are summarized in Table I.

The calculation of the theoretical PC of the drug between vehicle and skin is determined from the ratio of the reciprocal of the activity coefficient of the drug in the skin to that in the vehicle, which in turn depends on the difference between the solubility parameter of the drug minus that of the vehicle squared, and the solubility parameter of the drug minus that of the skin squared (Eq. 3, Table I). The solubility parameter (δ) is equal to the square root of the cohesive energy (ΔE) divided by the molar volume (V). Further, E and V can be estimated by summing the atomic and group contribution for the energy of vaporization and molar volume, respectively [3,4], so that it is possible to calculate the solubility parameters of chemicals that have not been determined experimentally. The use of solubility parameters to predict the solubility of chemicals has been useful in a wide variety of applications, including the cosmetics industry [5] and the pharmaceutical industry [6].

The antiproliferative agent 5-fluorouracil (5-FU) has been extensively used in topical chemotherapy of cutaneous premalignant and malignant lesions [7]. Hyperkeratotic lesions are particularly refractory to topical 5-FU therapy, and lack of penetration of the drug through the thickened stratum corneum is thought to be the reason for this inefficacy [8]. Thus, it would be helpful to choose a vehicle formulation for 5-FU that would optimize drug delivery in this situation. However, so far there has not been a systematic examination of vehicles to optimize delivery of 5-FU. The current study, then, investigates the flux of 5-FU from nonpolar to very polar vehicles and the use of the calculated PC derived from solubility parameters of 5-FU and different vehicles to attempt to find a vehicle that would maximize delivery of 5-FU and to see whether the results would be predicted from the theoretical relationship outlined in Table I.

MATERIALS AND METHODS

Materials The 5-FU was obtained from Sigma (St. Louis, Missouri). The vehicles were obtained from Aldrich; all were 99%

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Reprint requests to: Elizabeth F. Sherertz, M.D., Department of Medicine (Dermatology), Box J-277, JHM Health Center, Gainesville, Florida 32610.

Abbreviations:
δ: solubility parameter
5-FU: 5-fluorouracil
Kp: permeability coefficient
PC: partition coefficient

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Table I. Summary of Theoretical Equations Showing the Relationship of Permeability Coefficient and Partition Coefficient of a Drug in a Vehicle [1]

Permeability Coefficient (Kp) = Partition Coefficient (PC) × Constant (C)

$$\text{then } \log Kp = \log PC + \log C \quad (1)$$

$$\text{where } Kp = \frac{\text{flux of drug through skin}}{\text{solubility of drug in vehicle}} \quad (2)$$

$$\log PC = [(\text{solubility parameter of drug} - \text{solubility parameter of vehicle})^2 - (\text{solubility parameter of drug} - \text{solubility parameter of skin})^2] \times (\text{molar volume of drug})(\text{volume fraction of vehicle})^2/2.3\,RT$$

$$\text{or } \log PC = [(\delta_i - \delta_v)^2 - (\delta_i - \delta_s)^2]\, V_i\Phi^2/2.3\,RT \quad (3)$$

volume fraction of vehicle and skin (Φ) $\cong$ 1

and

$$C = \frac{\text{diffusion coefficient of drug}}{\text{thickness of skin}} = \frac{D}{h_s} \quad (4)$$

Φ = volume fraction; R = 1.98 cal/degree mol; T = 305°K; Solubility parameter of skin (δ_s) = 10 $(cal/cm^3)^2$ [2].

pure and were used as received. The diffusion cells were obtained from Kercso Engineering Consultants, Palo Alto, California, and were 3 cm in diameter (7.06 cm^2 skin surface area) with a 40-ml receptor phase volume. A Labline incubator with Variomag stirrer was used to maintain constant temperature at 32°C and to stir the receptor phases of the cells. Ultraviolet spectra were recorded with a Shimadzu UV-160 spectrophotometer. The 18–22 g female hairless mice (SKH-hr-1) were obtained from Temple University Skin and Cancer Hospital, Philadelphia, Pennsylvania.

Diffusion Cell Studies The suspensions of 5-FU were stirred for 48 h at room temperature before 0.5-ml aliquots were applied to the skin. The 5-FU/vehicle suspensions used are summarized in Table II; the amount of 5-FU used in each was sufficient to assure an excess of 5-FU.

The mouse skin was prepared and diffusion cell sampling was done as previously described [1], with cells run in triplicate for each 5-FU/vehicle suspension. Receptor phase samples for UV spectrophotometric analysis at 265 nm were generally taken at 0, 3, 6, 9, 12, 20, 24, 30, 36, and 48 h after the suspensions were applied. At the end of this 48 h, the donor phase/skin surface was gently washed twice with 10 ml methanol to remove remaining 5-FU. This methanol wash from each diffusion cell was filtered through Whatman #1 filter paper, and analyzed by UV spectroscopy to determine recovery of 5-FU from the donor phase.

Linear regression analysis of cumulative mg of 5-FU in the receptor phase vs time in h gave a slope in mg/h; in all cases the correlation coefficients were at least $r = 0.99$. Fluxes were obtained by dividing these slopes by the skin surface area (7.06 cm^2), and the permeability coefficients (Kp) were then determined by dividing the flux (mg/cm^2 h) by the corresponding solubility of 5-FU (in mg/cm^3 of solution) in that vehicle, as in Eq. 2 of Table I.

Solubility Determinations The solubility of 5-FU in each vehicle was determined in triplicate by stirring an excess of 5-FU (240 mg 5-FU/3 ml vehicle or mixture of vehicles except for 400 mg 5-FU/3 ml dimethylformamide) in each vehicle in sealed flasks for 48 h at room temperature (23 ± 1°C). This time period was adequate to insure a saturated solution [9,10]. The resulting suspensions were allowed to sit at room temperature for 24 h and then were filtered by gravity through Whatman #1 filter paper. Aliquots of the filtrates were diluted with methanol for measurement of 5-FU concentration by UV spectroscopy at 265 nm (extinction coefficient 5-FU = 7.13×10^3 liters/mol).

Solubility Parameter and PC Calculations The calculated solubility parameters (δ_i) were obtained using the method of Fedors [4], as demonstrated previously [1,11]. For mixed vehicle systems, it was assumed that there was no significant change of volume on mixing, and $\delta_{v(1+2)}$ was calculated as the sum of the products of the volume fraction and solubility parameter for each vehicle [9].

RESULTS

The vehicles used in the diffusion cell experiments cover a large range of solubility parameters; some represent vehicles that could be used in therapeutic formulations (e.g., isopropyl myristate, propylene glycol). For the diffusion experiments, saturated solutions of 5-FU were maintained by using suspensions of 5-FU in each vehicle. This assumes that dissolution of 5-FU in the vehicles did not become the rate-limiting step for diffusion. The values for the experimental fluxes, solubility of 5-FU in the vehicles, and experimental permeability coefficient (Kp, calculated from Eq. 2 in Table I) are summarized in Table II. The value for flux of 5-FU from 5% Efudex (Roche, Nutley, New Jersey) solution, which contains propylene glycol, is included for comparison. The values for the flux of 5-FU from single vehicles are all significantly different from each other at the $p < 0.05$ level by two-sample t-test [12], except for the values of isopropyl myristate vs dimethylformamide. The permeability coefficients of 5-FU from single vehicles are also significantly different from each

Table II. Experimental Fluxes, Solubilities, and Permeability Coefficients for the Steady-State Diffusion of 5-Fluorouracil Through Hairless Mouse Skin From the Vehicles.

Vehicles[a]	Flux ± SD[b] (mg/cm^2h)	Solubility (mg/cm^3)	Permeability Coefficient[c] (Kp)	× Intercept (h)
Oleic acid (OA)	0.1 ± 0.012	0.74	0.15 ± 0.016	14.2
Isopropyl myristate (IPM)	0.028 ± 0.002	0.0051	5.4 ± 0.39	3.2
Octanol (Oct)	0.44 ± 0.014	0.60	0.73 ± 0.023	2.3
Dimethylformamide (DMF)	0.025 ± 0.002	62.3	0.00041 ± 0.00003	0.0
Propylene glycol (PG)	0.0016 ± 0.00	16.5	0.000097 ± 0.000061	0.1
Ethylene glycol (EG)	0.0047 ± 0.0013	19.6	0.00024 ± 0.000066	1.1
Formamide (Form)	0.015 ± 0.00	13.7	0.0011 ± 0.00010	3.8
OA/PG (1:1)	0.050 ± 0.012	0.98	0.051 ± 0.012	2.3
OA/PG (1:3)	0.050 ± 0.002	4.3	0.012 ± 0.00047	1.7
OA/PG (1:14.5)	0.088 ± 0.005	11.1	0.0079 ± 0.00045	2.3
OCT/PG (1:1)	0.53 ± 0.32	3.6	0.15 ± 0.089	0.2
Efudex 5% solution	0.006 ± 0.002			1.9

[a]For diffusion cell studies, 200 mg 5-FU was used in 5 ml IPM or PG, 800 mg in 5 ml DMF, and 400 mg/5 ml of remaining vehicles.
[b]Fluxes are significantly different from each other $p < 0.05$ except IPM vs DMF and OA:PG(1:1 vs 1:3) by two-sample t-test.
[c]Permeability coefficients are significantly different from each other $p < 0.05$.

other. For the mixed vehicles, there is no significant difference in the fluxes of 5-FU from 1:1 or 1:3 mixtures of oleic acid/propylene glycol but the remainder are different from each other. Thus, the flux of 5-FU from vehicles in this study is not thermodynamically controlled [10].

The physical properties of the vehicles, mole fraction solubilities of 5-FU in vehicles, and calculated PC are summarized in Table III. Based on the mole fraction solubilities of 5-FU in the vehicles, the peak solubility of 5-FU would be in a vehicle exhibiting a δ_v between 14.8–16.1 $(cal/cm^3)^{\frac{1}{2}}$ if dimethylformamide is excluded [13]. The calculated solubility parameter (δ) for 5-FU of 15 $(cal/cm^3)^{\frac{1}{2}}$ (Table IV) fits well in this range. The log PC was calculated from Eq. 3 in Table I, using the δ_v for vehicles obtained from the literature [3] and δ for 5-FU of 15 $(cal/cm^3)^{\frac{1}{2}}$. A solubility parameter of 10 $(cal/cm^3)^{\frac{1}{2}}$ was used for the skin [2], and the skin thickness was considered to be constant within the range of biologic variability. These log theoretical PC values are shown in Table III.

Figure 1 shows the plot of the log of the experimental permeability coefficients (Kp) vs the solubility parameters of the single component vehicles. In the same figure the log calculated PC for the same vehicles are plotted against the solubility parameters. If the assumption made that the vehicles are not causing any changes in the diffusion coefficient is applicable [14,15], and if the log PC values derived from regular solution theory realistically describe the partitioning process in this diffusion cell system, then the difference between each of the log calculated PC and the log experimental Kp should be a constant that corresponds to $C = D/h_s$ in Eq. 4 in Table I. The average difference between the log calculated PC and log experimental Kp for 5-FU in oleic acid, dimethylformamide, propylene glycol, ethylene glycol, and formamide is 2.454 ± 0.24, which would give a value for $C = 2.88 \times 10^{-3}$ cm/h. Using this value for the constant, and assuming that the stratum corneum thickness provides the main barrier to penetration by polar solutes and that this thickness (h_s) for hairless mouse skin is about 0.0009 cm [16], then the diffusion coefficient (D) for 5-FU through skin would be about 7.2×10^{-10} cm^2/s. This value is in the expected range for the diffusion coefficient for a molecule such as 5-FU [17].

The value for the constant noted above excluded the values for the log theoretical PC minus log experimental Kp for isopropyl myristate and octanol. Previous studies of the delivery of theophylline [1] or 6-mercaptopurine (unpublished) from isopropyl myristate and octanol have shown that these vehicles, having solubility parameters close to the value of 10 $(cal/cm^3)^{\frac{1}{2}}$ for (porcine) skin [2], appear to have a destructive effect on the barrier function of the skin and thus their values for flux and permeability coefficient do not tend to fit the predicted relationship. The broken line in Fig 1 represents the log theoretical Kp values calculated from the log theoretical PC minus 2.454. The log experimental Kp values for the single component vehicles, other than isopropyl myristate and octanol, approximate this theoretical curve.

Two two-component vehicle systems were investigated in the diffusion cell studies to determine whether the relationship between theoretical PC and permeability coefficient would apply in this setting. Of particular interest to us was the effect of mixed vehicles using the lipid, oleic acid, mixed with the polar solvent,

Table III. Physical Properties of Vehicles and Calculated Partition Coefficients of 5-Fluorouracil in Vehicles

Vehicles	Solubility Parameter[a] δ_v $(cal/cm^3)^{\frac{1}{2}}$	Mole Fraction Solubility[b] $X_i^{V(n)}$	Theoretical[c] log $PC_i^{s,v(n)}$
Oleic acid (OA)	7.6	1.8×10^{-3}	1.35
Isopropyl myristate (IPM)	8.5	0.0013×10^{-3}	0.78
Octanol (Oct)	10.3	0.73×10^{-3}	−0.13
Dimethylformamide (DMF)	12.1	70.0×10^{-3}	−0.75
Propylene glycol (PG)	14.8	6.1×10^{-3}	−1.13
Ethylene glycol (EG)	16.1	8.5×10^{-3}	−1.08
Formamide (Form)	17.9	4.6×10^{-3}	−0.75
OA/PG(1:1)	9.3[d]	1.5×10^{-3}	0.52
OA/PG(1:3)	10.6[d]	4.5×10^{-3}	0.27
OA/PG(1:14.5)	13.5[d]	7.5×10^{-3}	−0.98
Oct/PG(1:1)	11.7[d]	3.2×10^{-3}	−0.65

[a]From [3], solubility parameter of vehicle = δ_v.
[b]Calculated from mg/cm³ solubility in Table II and M_r and density of vehicle. Mole fraction solubility of 5-fluorouracil (i) in a vehicle [v(n)] = $X_i^{v(n)}$.
[c]Partition coefficient for distribution of 5-fluorouracil between skin and vehicle is $PC_i^{s,v(n)}$
[d]Calculated using equation described in text [4,10]

Table IV. Group Contribution Method for Calculating Molar Volume and Solubility Parameter (δ) of 5-Fluorouracil [3]

Atom or Group	Number of Groups	Energy of Vaporization (ΔE, cal/mol)	Molar Volume (ΔV, cm^3/mol)
Ring closure	1	250	16.
Double bond	1	400	−2.2
CH=	1	1030	13.5
C=	1	1030	−5.5
F (attached to C atom with double bond)	1	800 (1000 × 0.8)	18.0
C=0	2	8300	21.6
NH	2	4000	9.0
		$\Sigma\Delta E$ = 15810	$\Sigma\Delta V$ = 70.4

$\delta = (\Sigma\delta E/\Sigma\Delta V) = (15810/70.4)^{\frac{1}{2}} = 15(cal/cm^3)^{\frac{1}{2}}$

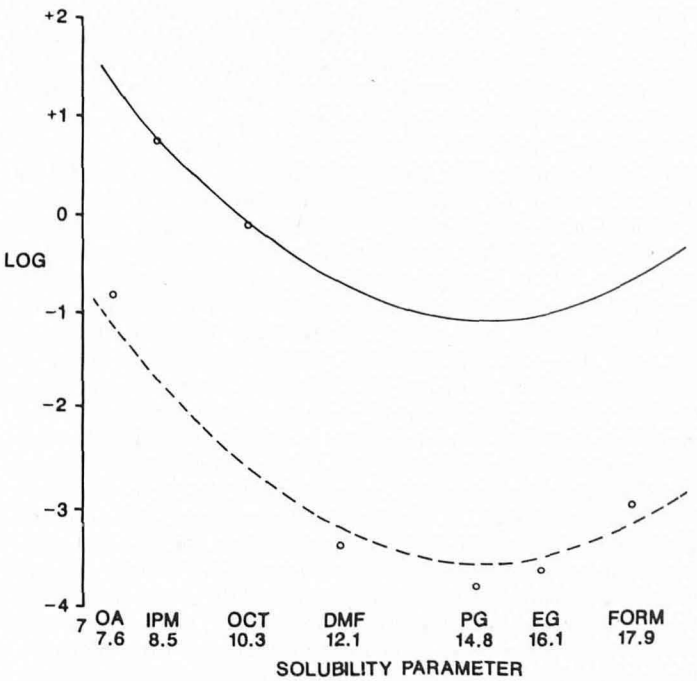

Figure 1. 5-Fluorouracil in single vehicles. Plot of the log of the theoretical partition coefficients (*solid line*) and permeability coefficients (*broken line*) vs solubility parameters of the vehicles. Experimental values for log Kp are shown as individual *open circles*. *OA* = oleic acid; *IPM* = isopropyl myristate; *OCT* = octanol; *DMF* = dimethylformamide; *PG* = propylene glycol; *EG* = ethylene glycol; *FORM* = formamide.

propylene glycol, since studies by Cooper had suggested such a mixed system could enhance skin permeability for lipophilic molecules such as salicylic acid [18] and polar molecules such as acyclovir [19]. Since the highest flux of 5-FU from any single component vehicle was realized from octanol, the effect of a mixture of octanol and propylene glycol (1:1) on flux of 5-FU was also examined. The data for the experimental flux, solubility and permeability coefficient for each of these mixed vehicles are included in Table II, and the calculated solubility parameters and log partition coefficients are shown in Table III. It is notable that the addition of oleic acid to propylene glycol in the vehicle does moderately increase the flux of 5-FU through skin in the diffusion cell system compared with propylene glycol alone but not to oleic acid alone. This increased flux from the 2-component vehicle is associated with a decreased solubility of 5-FU in the mixed vehicle as more oleic acid is added compared with 5-FU in propylene glycol. The flux of 5-FU from oleic acid:propylene glycol (1:14.5), δ = 13.5 $(cal/cm^3)^{\frac{1}{2}}$, and from octanol:propylene glycol (1:1), δ = 11.7 $(cal/cm^3)^{\frac{1}{2}}$ was much greater than the flux of 5-FU from a single component vehicle at a similar δ value [dimethylformamide, δ = 12.1 $(cal/cm^3)^{\frac{1}{2}}$]. This difference may be due to the very high solubility of 5-FU in the dimethylformamide. On the other hand, there was a clear inverse relation between Kp and solubility which numerous investigators have shown before [1,20].

DISCUSSION

Previous studies by Sloan et al [1,11] on theophylline and salicylic acid had shown that from knowledge of the solubility parameters of vehicles, drug, and skin, theoretical PC of drug between vehicle and skin could be calculated and that from these PC values it was possible to predict values for permeability coefficients of the drug. Using this predicted Kp value and the solubility of the drug in the vehicle, the flux of the drug through the skin also could be predicted. The goal in the current study was to determine, using this same theoretical relationship, whether one could predict which vehicle would give maximum delivery of 5-FU.

For single-component vehicles exhibiting a solubility parameter range of 7.6–18 $(cal/cm^3)^{\frac{1}{2}}$, the theoretical Kp values for 5-FU obtained from Eq. 1 generally correlate well with the experimental Kp values obtained from diffusion cell experiments and the determined solubilities. The exception to this is for those vehicles, isopropyl myristate (δ = 8.5) and octanol [δ = 10.3, $(cal/cm^3)^{\frac{1}{2}}$], which have solubility parameters similar to that of skin [2]. For these two vehicles, the experimental flux and Kp were much higher than would be expected. This is similar to what is seen for the diffusion of theophylline [1] and 6-mercaptopurine but not salicylic acid [11] from these vehicles. This result has also been seen previously for the effect of octanol on butyric acid flux [21]. It is thought that this enhanced flux is due to irreversible damage by isopropyl myristate and octanol to the lipids in the stratum corneum, thus altering the barrier function for polar drugs [22]. A scanning electron microscopic study of the treated stratum corneum may help clarify the destructive effect of such vehicles, and this work is planned. A second application of a polar drug such as theophylline to skin in diffusion cells after they had been pretreated with 5-FU, 6-mercaptopurine (unpublished data) theophylline [1], or salicylic acid [11] in isopropyl myristate or octanol, or these two vehicles alone, demonstrates much higher flux of theophylline than would be expected, also supporting the idea that isopropyl myristate and octanol are permanently altering the permeability barrier of the skin toward polar drugs. It has been suggested by Sloan et al [11] that salicylic acid behaves like a nonpolar drug in these (octanol, isopropyl myristate, oleic acid) lipid-like vehicles. If the lipid vehicles damage the barrier to absorption of polar drugs by leaching the lipid part of the barrier leaving a more polar barrier, then salicylic acid absorption would not be enhanced and in fact should be retarded [11].

As the solubility parameter of the vehicle approaches that of 5-FU (δ = 15 $(cal/cm^3)^{\frac{1}{2}}$, Table IV), the solubility of 5-FU in that vehicle is increased so that flux and subsequently the permeability coefficient (Kp) decrease to a minimum (Table II). Maximum solubility for 5-FU was actually seen with dimethylformamide [δ_v = 12.1 $(cal/cm^3)^{\frac{1}{2}}$] but dimethylformamide is such a good solvent because it forms strong solvates and complexes with solutes that it does not fit the relationship between solubility and solubility parameters of the vehicles [13].

The axis of the parabola obtained by plotting the log theoretical PC of 5-FU in the vehicles vs solubility parameter (Fig 1) is δ_i = 15$(cal/cm^3)^{\frac{1}{2}}$ since this was the δ_i used for 5-FU. The axis for the experimental Kp is also approximately 15 $(cal/cm^3)^{\frac{1}{2}}$, suggesting that this calculated δ_i for 5-FU approaches a reasonable value. This finding of increased solubility and decreased flux of a drug when its solubility parameter is close to that of the vehicle has been seen previously by our group and others [1,11,23]. It suggests that the solubility parameters of drug and vehicle must be sufficiently different to allow ready release of drug from the vehicle for efficient percutaneous penetration [6]. These findings also show the utility of using solubility parameters in describing the partitioning process of 5-FU from vehicles with widely different properties. The fairly constant relationship between the theoretical PC calculated from activity coefficients and the experimental permeability coefficients also suggests that assumptions made about the diffusion coefficient are justified, except when the solubility parameter of the vehicle is close to that of skin.

There are other theoretical methods that have been put forth to predict skin permeability. Osborne [24] recently reviewed 4 such models and compared their predictive value with experimental flux values for 10 different drugs. Osborne found that models using water solubility, molecular weight, and PC data put forth by Berner and Cooper [25], Michaels and colleagues [26], and Albery and Hadgraft [27,28] were all useful in predicting flux through the skin barrier, but all had some limitations. Dugard and Scott [20] recently described a method of predicting percutaneous absorption rates in various vehicles based on mole fraction solubility of the penetrant in a given vehicle. Generally, our results follow the same trend as Dugard and Scott put forth with permeability coefficient being inversely proportional to the solubility of 5-FU in the vehicle; the exceptions being dimethylformamide (in which 5-FU is more soluble than expected based on its solubility parameter), and isopropyl myristate and octanol (from which 5-FU exhibits higher than expected Kp values).

In summary, solubility parameters of a drug such as 5-FU and vehicle can be used to calculate a theoretical PC which, in turn, can be used to estimate a theoretical permeability coefficient. With this theoretical permeability coefficient and the experimentally determined solubility of 5-FU in a given vehicle, a reasonable determination of flux can be calculated. This computational method for predicting skin permeability compares favorably, in our experience, with other methods recently reviewed [20,24], and may offer the potential advantage of decreasing the need for determining experimental PC or for in vitro animal skin experiments to determine flux of investigational drugs through skin. The highest flux of 5-FU from any vehicle was realized with octanol. Although octanol has been found to compromise the skin's barrier to permeation [1], other vehicles exhibiting similar physical properties (i.e., solubility parameters close to that of skin) may be found that are not as damaging as octanol yet retain the ability to enhance penetration like octanol.

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