Correlation of Aqueous and Lipid Solubilities with Flux for Prodrugs of 5-Fluorouracil, Theophylline, and 6-Mercaptopurine: A Potts–Guy Approach

WILLIAM J. ROBERTS AND KENNETH B. SLOAN*

Contribution from *Department of Medicinal Chemistry, P.O. Box 100485, University of Florida, Gainesville, Florida 32610.*

Received October 23, 1998. Final revised manuscript received February 22, 1999.
Accepted for publication March 1, 1999.

Abstract □ The Potts and Guy equation that has been used to predict permeability coefficients for molecules being delivered from aqueous vehicles has been transformed to accommodate lipid vehicles that are less polar than skin, and polar vehicles that are less polar than water. Solubilities in pH 4.0 aqueous buffer (S_{AQ}), solubilities in isopropyl myristate (S_{IPM}), and molecular weights (MW) of prodrugs of 5-fluorouracil (5-FU), theophylline (Th), and 6-mercaptopurine (6-MP) have been regressed against their fluxes from suspensions in IPM (J_M). Seven series ($n = 39$) of alkylcarbonyloxymethyl (ACOM), alkyloxycarbonyl (AOC), alkylcarbonyl (AC), and alkylaminocarbonyl (AAC) prodrugs were used to determine the best fit to the transformed Potts and Guy equation (eq 6): $\log J_M = x + y \log S_{IPM} + (1 - y)\log S_{AQ} - z$ MW. The estimated values for x, y, and z were –0.193, +0.525, and +0.00364, respectively, with $r^2 = 0.945$ for $n = 39$. Inclusion of a miscellaneous series comprised of the parent drugs and a branched alkyl chain prodrug gave an equally good fit only if 6-MP was excluded from the analysis. The best performer (largest J_M) in each series was usually correctly identified. The values for x, y, and z were consistent with values obtained by Potts and Guy, but the inclusion of the $(1 - y)\log S_{AQ}$ term in eq 6 and the value for y, shows that water solubility is almost as important as lipid solubility in predicting flux. There were no significant changes in predicted $\log J_M$ or x_i for each series if their $\log J_M$ or x_i were calculated using y and z coefficients obtained for solutions to eq 6 from which the data for the series had been excluded. This suggests that the data from all the series is homogeneous. Data from Kasting, Smith, and Cooper for S_{IPM}, S_{PG}, and MW of unrelated molecules were regressed against their fluxes from propylene glycol (PG) using eq 7: $\log J_M = x + y \log S_{IPM} + (1 - y) \log S_{PG} - z$ MW. The estimated values for x, y, and z were –1.673, +0.599, and +0.00595, respectively, with $r^2 = 0.852$ for $n = 28$. These values for x, y, and z are also consistent with those previously reported by Potts and Guy, and, together with the results for fluxes from IPM, show the general utility of the transformed Potts and Guy equation in predicting flux from vehicles other than water and in showing the importance of solubility in a polar solvent as well as a nonpolar solvent in predicting flux.

Introduction

It has become obvious that the water as well as the lipid solubility of a permeant plays an important role in determining the rate of diffusion through biological membranes. Nowhere is this fact more obvious than in the results from diffusion cell experiments where prodrugs designed to enhance topical delivery—or flux—of a parent drug have been evaluated.[1] Examples where different types of promoieties have been used with one parent drug,[2–5] or where one type of promoiety has been used with a number of different parent drugs,[5–8] show that, for an homologous series of more lipid soluble prodrugs, the more water soluble member or members of the series are the more efficient at delivering the parent drug topically. Although the greatest accumulation of data supporting this axiom exists for prodrugs of heterocycles such as a fluorouracil (5-FU),[2–5] theophylline (Th),[8] 6-mercaptopurine (6-MP),[6,7] and arabinofuranosyladenine,[9,10] ample supporting data can also be found from experiments using prodrugs of lipophilic drugs such as levonorgestrel[11] and indomethacin.[12] In one comparison of variables affecting flux, the axiom holds regardless of the polarity of the vehicle used to deliver the prodrug,[6,7] while in another comparison, the axiom holds regardless of the type of skin that is used in the experiments—mouse[2–8] or human skin.[11]

It would be useful to develop a model that could predict the effect of changes in water and lipid solubilities of prodrugs on the topical delivery of their parent drugs. A large portion of the published data on the delivery of parent drugs by prodrugs has been obtained using suspensions of the prodrugs in isopropyl myristate (IPM) as the donor phase where the IPM and aqueous (AQ) solubilities of the prodrugs were variables and flux was measured.[1] On the other hand, many models that have been developed to predict flux actually use measurements of permeability coefficients of drugs obtained using concentrations of drugs in vehicles (usually water) significantly less than saturation as the donor phase, and where the partition coefficient and size of the drug were the variables.[13] In this paper we transform a model that had been developed previously for predicting permeability coefficients of drugs into a model where the aqueous as well as lipid solubilities of prodrugs are variables for predicting the flux of their parent drugs and vehicles other than water can be accommodated.

Development of the Model

Most models used to predict flux or solubility normalized flux—permeability coefficient (P)—have focused on the effects of lipid solubility [either directly as S_{LIPID} or in the form of partition coefficient ($K_{LIPID:AQ}$)] and size [as it affects diffusivity] on flux. Typical of these treatments is eq 1 derived by Kasting, Smith, and Cooper from data developed in their laboratories and published in 1987[14] where J_M is the maximum flux obtained by applying saturated propylene glycol solutions of permeants to the membrane (human skin), S_{MEM} is the solubility of the permeant in the membrane, $D°$ is the diffusivity in the membrane of a

$$\log J_M = \log(D°/L) + \log S_{MEM} - (\beta/2.303)V \quad (1)$$

* To whom correspondence should be addressed. Tel 352-846-1957, fax 352-392-9455, e-mail: sloan@cop.health.ufl.edu.

10.1021/js980419b CCC: $18.00 Published on Web 04/06/1999

hypothetical molecule having zero molecular volume, h (we will use L) is the diffusion path length, V is the van der Waals volume, and β is a constant that is characteristic of the skin.

Since it is very difficult to measure the solubility of the permeant in the membrane, the authors[14] examined several S_{LIPID} substitutes for S_{MEM} and suggested that S_{OCT} (measured solubility in octanol) gave a better correlation with J_M than S_{IPM} (measured solubility in isopropyl myristate) or S_i (calculated ideal solubility). The assumption was that some sort of lipid solubility alone was sufficient to characterize solubility of permeants in and their flux through the membrane. The other assumption was that J_M was independent of the vehicle because saturated solutions were used as donor phases where the thermodynamic activities of the permeants were the same. This assumed there was no effect of the vehicle on the barrier properties of the skin. Analysis of their unique data set of 36 compounds fitted to eq 1 gave $r^2 = 0.74$ for the correlation of J_M with the model. This data set was unique because propylene glycol, not water, was used as the vehicle or donor phase. Substitution of molecular weight for the molecular volume gave a similar fit.

Subsequently, several groups developed models that were based on permeability coefficients obtained from data from combinations of series from different laboratories[15–17] where water was used as the vehicle. One model frequently referenced is that represented by eq 2 developed by Potts and Guy and published in 1992.[13] In eq 2 K_P (we will use P) is permeability coefficient, $K_{OCT:AQ}$ is the partition coefficient between octanol and water, MW is the molecular weight, $\beta°$ is a constant similar to β in eq 1 but which

$$\log P = \log(D°/L) + f \log K_{OCT:AQ} - \beta° MW \qquad (2)$$

includes a conversion factor for the substitution of MW for molecular volume, and f accounts for the difference between K_m (partitioning between membrane and vehicle) and $K_{OCT:AQ}$ (partitioning between octanol and water): i.e., $K_m = (K_{OCT:AQ})^f$. From the data sets analyzed using eq 2, the values for $D°/L$ and $\beta°$ that were obtained were consistent with physical properties of the skin, and $r^2 = 0.83$ was obtained for the correlation of P with this model for $n = 42$. A somewhat poorer correlation ($r^2 = 0.67$) was obtained using the larger data set ($n = 93$) of Flynn.[18]

Although no positive dependence of log P on S_{AQ} was discussed, an inverse dependence derives from the definition of $K_{OCT:AQ} = C_{OCT}/C_{AQ}$ (where C_{OCT} and C_{AQ} are the equilibrium concentrations of the permeant in octanol and water, respectively), if it is assumed that $K_{OCT:AQ}$ for the permeant is approximately equal to its solubility ratio ($SR_{OCT:AQ}$) in the same solvents (S_{OCT}/S_{AQ}). On the other hand, Potts and Guy[13] discuss that one interpretation of skin transport for molecules of very high lipophilicites (low S_{AQ}) is that the rate-determining step becomes the slow transfer from the lipophilic stratum corneum to the aqueous, viable epidermis and upper dermis, i.e., low water solubility can become rate-determining. Significant conclusions from this analysis were that the limiting barrier, the stratum corneum, could be adequately characterized as a lipid-like barrier alone, and that an aqueous-polar (pore) pathway across the barrier was not necessary to explain the flux of the more water soluble members of the data set.

Improvements in eq 2 have been obtained by a number of groups[19–22] by defining permeant partitioning between membrane/water or organic phase/water from a transfer free energy model where R_2 is molar refractivity, MV is the molar volume, π is the dipolarity/polarizability, and H_d and H_a are the hydrogen bond donor and hydrogen bond acceptor activity, respectively, of the solute. Substitution of eq 3 for $K_{OCT:AQ}$ in eq 2 gives log P values that are independent of the organic phase/water partition coefficients and dependent on the physicochemical properties of the permeant alone. For a monofunctional group subset of their previous data set, Potts and Guy in 1995[20] showed that R_2 and π could be omitted from the analysis giving eq 4 to predict log P with $r^2 = 0.94$. Negative values were

$$\log K_{ORG} = a_1 MV + a_2 \pi + a_3 H_d = a_4 H_a + a_5 R_2 \qquad (3)$$

$$P = (a_1 - \beta)MV + a_3 H_d + a_4 H_a + \log(D°/L) \qquad (4)$$

found for a_3 and a_4 suggesting, for permeants delivered from water, that hydrogen bond donating or accepting abilities exhibited by the permeant were inversely related to stratum corneum (SC) permeation. Hence, water solubility was also inversely related to SC permeation.

Equation 4 or similar models give the best correlation with experimental results but do not offer a mechanism for incorporating water solubility (S_{AQ}) directly as a variable. Similarly, although all of the data in the Kasting, Smith, and Cooper permeation set[14] were from experiments where J_M values were measured, eq 1 does not have S_{AQ} as a variable. On the other hand, eq 2 offers the opportunity to substitute other K values for K_m besides $K_{OCT:AQ}$ and to include the effect of vehicle on flux in the model. Since[23]

$$K_{MEM:IPM} = K_{MEM:AQ}/K_{IPM:AQ}$$

and[24]

$$K_{MEM:AQ} = (K_{IPM:AQ})^f$$

then

$$K_{MEM:IPM} = (K_{IPM:AQ})^f/K_{IPM:AQ} \qquad (5)$$

Substitution of eq 5 into eq 2 for $K_{OCT:AQ}$ gives

$$\log P = \log(D°/L) + f \log S_{IPM} - f \log S_{AQ} - \log S_{IPM} + \log S_{AQ} - \beta° MW$$

or

$$\log P = \log(D°/L) + f \log S_{IPM} - \log S_{IPM} + (1 - f)\log S_{AQ} - \beta° MW$$

Addition of log S_{IPM} to both sides gives

$$\log J = \log(D°/L) + f \log S_{IPM} + (1 - f)\log S_{AQ} - \beta° MW$$

Substitution of x for log $D°/L$, y for f, z for $\beta°$, and assuming that saturated IPM donor phases are used in the diffusion experiments gives

$$\log J_M = x + y \log S_{IPM} + (1 - y) \log S_{AQ} - z\ MW \qquad (6)$$

which is the transformation of the Potts and Guy model, given in eq 2, that will be used in this analysis.

To fit the Kasting, Smith, and Cooper[14] data to the same type of equation, two different substitutions were made. Instead of using the identity $K_{MEM:AQ} = (K_{IPM:AQ})^y$ where IPM has been substituted for MEM, the identity $K_{MEM:AQ} = (K_{IPM:PG})^y$ has been used where PG has been substituted for AQ, and IPM has been substituted for MEM. Then, instead of adding log S_{IPM} to both sides of eq 2, log S_{PG} has been added to both sides of eq 2 to give eq 7 using the same

substitutions as in eq 6. $(K_{OCT:PG})^y$ can also be substituted for $(K_{IPM:PG})^y$ to give a similar equation.

$$\log J_M = x + y \log S_{IPM} + (1 - y) \log S_{PG} - z\,MW \qquad (7)$$

Experimental Section

The methods used to determine the values for flux (J_M), solubilities (S_{IPM}, S_{AQ}), and partition coefficients between IPM and water ($K_{IPM:AQ}$) are described in the original papers for each series of prodrugs: 1-alkylcarbonyloxymethyl-5-FU (ACOM-5-FU),[5] 1-alkyloxycarbonyl-5-FU (AOC-5-FU),[3] 1-alkylcarbonyl-5-FU (AC-5-FU),[4] 1-alkylaminocarbonyl-5-FU (AAC-5-FU),[2] 7-alkylcarbonyloxymethyltheophylline (ACOM-Th),[8] 6-alkylcarbonyloxymethyl-6-MP (6ACOM-6-MP),[7] and 6,9-bis(alkylcarbonyloxymethyl)-6-MP (6,9ACOM-6-MP).[6] In each series only straight chain homologues were completely characterized and evaluated except for the ACOM-5-FU series where one branched chain homologue was characterized and evaluated: 1-pivaloyloxymethyl-5-FU (pivACOM-5-FU). Solubilities (S_{IPM}, S_{AQ}) and partition coefficients ($K_{IPM:AQ}$) are listed in Table 1. S_{AQ} values were calculated from $S_{IPM}/K_{IPM:AQ}$ values where available. Where $K_{IPM:AQ}$ values were not available, directly measured S_{AQ} values were used. In one case where the reported $K_{IPM:AQ}$ value for one member of a series, octylaminocarbonyl-5-FU, was inconsistent with other literature values and did not fit the trend in the remaining data for that series; the literature value,[25] which did fit the trend, was used as well as the corresponding calculated S_{AQ}. The J_M values listed in Table 1 were obtained using female hairless mice (SKH-hr-1) obtained from Temple University Skin and Cancer Hospital or from Charles River. The mice were sacrificed by cervical dislocation. Their skins were removed by blunt dissection and then placed epidermal side up in Franz type diffusion cells thermostated to 32 °C in contact with pH 7.1 phosphate buffer receptor phase. The buffer contained 0.11% formaldehyde as a preservative to prevent microbial growth and maintain the integrity of the skins during the course of the experiment.[8] The surface area of the diffusion cells was 4.9 cm^2, and the receptor phase volume was 20 mL. After contact with the receptor phase for 48 h to condition the skins, aliquots of a suspension of the prodrug in IPM (usually 0.5 mL) were applied to the epidermal side of three skins ($n = 3$) for 48 h. The receptor phases were continuously stirred during the entire experiment and were changed every 3 h during the time when steady-state fluxes were measured which was usually from 19 to 33 h. Variation in flux values was less than 30% except from the 6ACOM-6-MP series where the variation was less than 50%.

The solubilities, partition coefficients, and flux values for the parent drugs (5-FU,[2] Th,[8] 6-MP[6]) and the one branched alkyl chain prodrug (pivACOM-5-FU)[5] are also listed in Table 1 as a separate, miscellaneous series.

The multiple linear regression model depicted in eq 6 was fit to various combinations of the sets of data in Table 1 using the SPSS 7.5 statistical software package.

The J_M values in $\mu g\ cm^{-2}\ h^{-1}$ from Kasting, Smith, and Cooper[14] were converted to $\mu mol\ cm^{-2}\ h^{-1}$ values and the S_{IPM} and S_{PG} (solubilities in propylene glycol) values were converted to millimolar values before converting them to their respective log values and analyzing them using eq 7. The multiple linear regression model depicted in eq 7 was fit to the Kasting, Smith, and Cooper data using the SPSS 7.5 statistical software package. The data for salt forms of amines and for benzyl alcohol were omitted from the analysis to give $n = 28$ instead of $n = 36$.

Results

The log J_M, MW, log S_{IPM}, and log S_{AQ} data for the 39 straight chain alkyl prodrugs from Table 1 comprising seven series of prodrugs ($n = 39$ set) were fit to eq 6 using the SPSS nonlinear function. The parameter estimates for the $n = 39$ set (solution 1) were $x = -0.193$ (± 0.199), $y = +0.525$ (± 0.029), and $z = +0.00364$ (± 0.00084) with $r^2 = 0.945$ (Table 2). Using these estimated values for x, y, and z from solution 1, predicted log J_M values were calculated and are listed in Table 3. The average error or residual for predicting log J_M (experimental log J_M − predicted log J_M = Δ log J_M, data not shown) was 0.126 log units for all log J_M values. The average Δ log J_M value for each series is listed in boldface in the predicted log J_M column in Table 3 and quantitates the variation in Δ log J_M among members of each series and among the different series. The largest Δ log J_M values for members within a series were obtained for the longer alkyl chain members of the ACOM-, AOC-, AC-, and AAC-5-FU series. The largest average error in predicting log J_M values for a series was obtained for the AAC-5-FU series while the smallest was for the 6,9ACOM-6-MP series. The best performing member in each series (highest value for log J_M) was correctly identified in each series except for the 6ACOM-6-MP series, but in that series

Table 1—Molecular Weight (MW), Log Solubilities in Isopropyl Myristate (S_{IPM}), Log Solubilities in pH 4.0 Buffer (S_{AQ}), Log Partition Coefficients between IPM and pH 4.0 Buffer ($K_{IPM:AQ}$), and Log Maximum Flux Values from IPM Donor Phases (J_M)

compounds[a]	MW	log S_{IPM}[b,c]	log S_{AQ}[b,d]	log $K_{IPM:AQ}$	log J_M[e]
ACOM-5-FU					
C_1	202	0.517	2.26	–1.74	0.46
C_2	216	0.993	2.22	–1.23	0.58
C_3	230	1.158	1.63	–0.47	0.41
C_4	244	1.170	1.10	0.08	0.11
C_5	258	1.167	0.35	0.82	–0.25
C_7	286	1.000	–0.77	1.77	–0.92
C_9	314	0.631	–2.51[c]	3.14[f]	–1.82
AOC-5-FU					
C_1	188	0.328	2.05	–1.72	0.42
C_2	202	1.117	2.24	–1.12	0.77
C_3	216	1.182	1.63	–0.45	0.36
C_4	230	1.529	1.37	0.16	0.35
C_6	258	2.186	0.70	1.48	0.19
C_8	286	1.561	–0.89	2.46	–0.53
AC-5-FU					
C_1	172	1.344	2.08	–0.73	0.97
C_2	186	1.561	1.68	–0.12	0.63
C_3	200	1.241	0.81	0.43	0.11
C_4	214	1.593	0.54	1.05	0.00
C_5	228	2.052	0.47	1.58	0.04
C_7	256	2.044	–0.84	2.88	–0.22
AAC-5-FU					
C_1	187	–0.524	0.57	–1.09	–0.68
C_2	201	0.446	0.89	–0.44	–0.22
C_3	215	1.093	0.95	0.14	–0.13
C_4	229	1.391	0.71	0.68	–0.29
C_8	285	1.670	–1.52[g]	3.19[f]	–1.22
ACOM-Th					
C_1	252	0.439	1.29	–0.85	–0.24
C_2	266	0.467	0.67	–0.20	–0.51
C_3	280	1.405	1.02	0.38	0.03
C_4	294	1.643	0.72	0.93	–0.23
C_5	308	1.891	0.44	1.45	–0.33
6ACOM-6-MP					
C_1	224	0.022	0.86[c]	–0.83[f]	–0.69
C_2	238	0.362	0.61[c]	–0.25[f]	–0.67
C_3	252	0.517	0.31[c]	0.21[f]	–0.58
C_4	266	0.624	–0.10[c]	0.73[f]	–0.66
C_5	280	0.566	–0.63[c]	1.19[f]	–1.26
C_7	308	0.618	–1.61[c]	2.23[f]	–1.88
6,9ACOM-6-MP					
C_1	296	0.722	0.46[c]	0.26[f]	–0.64
C_2	324	1.527	0.22[c]	1.30[f]	–0.63
C_3	352	1.959	–0.71[c]	2.67[f]	–0.85
C_4	380	2.241	–1.33[c]	3.57[f]	–0.99
miscellaneous					
5-FU	130	–1.308	1.93[c]	–3.24[f]	–0.62
pivACOM-5-FU	244	0.891	0.90	–0.01	–0.52
Th	180	–0.469	1.66[c]	–2.13[f]	–0.32
6-MP	152	–1.650	0.05[c]	–1.71[f]	–2.42

[a] C_1, C_2, etc., indicate the number of carbons in the alkyl chain. [b] Units of mM. [c] Measured directly. [d] Calculated from $S_{AQ} = S_{IPM}K_{IPM:AQ}$. [e] Units of $\mu mol\ cm^{-2}\ h^{-1}$. [f] Calculated from $K_{IPM:AQ} = S_{IPM}/S_{AQ}$. [g] From reference 25.

Table 2—*x*, *y*, *z*, and Associated r^2 Values for Solutions to Equation 6 and to Equation 7

solution: database	*n*	*x* (± SD)	*y* (± SD)	*z* (± SD)	r^2
1: all n-alkyl prodrugs	39	–0.193 (0.199)	0.525 (0.029)	+0.00364 (0.00084)	0.945
2: $n = 39$ + miscellaneous	43	–0.401 (0.243)	0.530 (0.035)	+0.00293 (0.00103)	0.924
3: $n = 43$ – (6-MP)	42	–0.211 (0.203)	0.534 (0.029)	+0.00364 (0.00086)	0.937
4: $n = 39$ – (ACOM-5-FU)	32	–0.211 (0.193)	0.508 (0.031)	+0.00362 (0.00082)	0.942
5: $n = 39$ – (AOC-5-FU)	33	–0.210 (0.203)	0.523 (0.030)	+0.00359 (0.00084)	0.944
6: $n = 39$ – (AC-5-FU)	33	–0.100 (0.285)	0.532 (0.038)	+0.00400 (0.00116)	0.943
7: $n = 39$ – (AAC-5-FU)	34	–0.081 (0.201)	0.548 (0.029)	+0.00409 (0.00083)	0.955
8: $n = 39$ – (ACOM-Th)	34	–0.260 (0.222)	0.521 (0.033)	+0.00333 (0.00095)	0.950
9: $n = 39$ – (6ACOM-6-MP)	33	–0.198 (0.206)	0.525 (0.030)	+0.00361 (0.00087)	0.933
10: $n = 39$ – (6,9ACOM-6-MP)	35	–0.287 (0.253)	0.518 (0.032)	+0.00322 (0.00108)	0.943
11: all *n*-alkyl prodrugs, $z = +0.00610$	39	0.388 (0.031)	0.590 (0.020)	+0.00610 fixed	0.931
12: $n = 39$ – (AC-5-FU and AAC-5-FU)	28	0.427 (0.325)	0.605 (0.042)	+0.00607 (0.00130)	0.961
13: Kasting et al.	28	–1.673 (0.363)	0.599 (0.126)	+0.00595 (0.00124)	0.852
14: Kasting et al.	28	–1.969 (0.395)	0.849 (0.250)	+0.00673 (0.00146)	0.807

the top four performers were not statistically different from each other.[7] Solution 1 identified the C_2 member of the 6ACOM-6-MP series as the best performer while the C_3 member was actually the best performer experimentally. Using the estimated values for *y* and *z* from solution 1, the values of x_i for the members of each series that were required to give the experimental log J_M values were calculated and are given in Table 3. The average x_i for all members of all series was −0.193 with a standard deviation of ±0.155 log units. The average x_i value and SD for each series of prodrugs are also given in Table 3 and quantitate variations in x_i among the members of each series and among the different series. The largest SD of x_i was seen in the AAC-5-FU series, followed by that in the AOC- and AC-5-FU series. Figure 1 shows a plot of experimental log J_M values versus predicted log J_M values (eq 6) using all 39 prodrugs (solution 1).

Predicted log J_M values and calculated x_i values for the parent drugs and pivACOM-5-FU (miscellaneous series) were determined using the solution 1 fit to eq 6 as above for the $n = 39$ set. Those predicted log J_M and calculated x_i values are given in Table 3. The Δ log J_M value for 6-MP was over twice as large as the next largest Δ log J_M value and almost six times larger than the average for all Δ log J_M values: average Δ log $J_M = 0.146$ log units for all log J_M values, $n = 43$. Similarly, the calculated x_i value for 6-MP was twice as large as any other calculated x_i value. Figure 1 also shows the fit of the members of the miscellaneous series to the solution 1 fit to eq 6. When the log J_M, MW, log S_{IPM}, and log S_{AQ} data for the miscellaneous series were added to the $n = 39$ set to give an $n = 43$ set (solution 2, Table 2) and eq 6 was fit to that data, the correlation coefficient decreased to $r^2 = 0.924$ from $r^2 = 0.945$, and the estimated values for *x*, *y*, and *z* changed to −0.401, +0.530, and +0.00293, respectively. If the data for 6-MP was removed from the set (solution 3, Table 2) the values for *x* and *z* returned to approximately their solution 1 values, and the value for *y* stayed reasonably constant.

Equation 6 was then fit to the log J_M, MW, log S_{IPM}, and log S_{AQ} data for the seven series of straight chain alkyl prodrugs using the SPSS nonlinear function, but using only six of the series in each fitting. This systematically excluded a different series each time to give a total of seven sets of parameter estimates for eq 6 (solutions 4−10). This was done to correct for overly optimistic measures of fit which result from using the same data to both calibrate the model (estimate its parameters) and assess the error of prediction. The estimates for *x*, *y*, *z*, and associated r^2 values for these seven sets are given in Table 2. Using these estimated values for *x*, *y*, and *z* for solutions 4−10, predicted log J_M values were calculated for each member of the series that had been excluded from determining that solution to eq 6. Those predicted log J_M values for solutions 4−10 are given in Table 3. The average error for predicting log J_M (Δ log J_M, data not shown) was 0.132 log units for all log J_M values, $n = 39$. The average Δ log J_M value for each series is listed in boldface in the predicted log J_M column in Table 3. The largest average error in predicting log J_M values for the series excluded from obtaining the solution to eq 6 was for the AAC-5-FU series. Using the estimated values for *y* and *z* for each of the seven solutions to eq 6 generated by excluding the data from one series of prodrugs, values for x_i which were required to give the experimental log J_M values were calculated for each member of the series that had been excluded. These calculated x_i values for solutions 4−10 are given in Table 3. The average x_i for all members of all series was −0.193 with a standard deviation of ±0.173 which was essentially identical with the average x_i value and standard deviation from solution 1. The results in Table 2 show that the estimated *x*, *y*, and *z* values from solution 7 (exclusion of the AAC-5-FU series) exhibited the largest differences from the estimated *x*, *y*, and *z* values from solution 1. The estimated value for *z* from solutions 4−10 are all quite close to the estimated values of *z* from solution 1 and to several of those reported by Potts and Guy[13] for fits to data from combinations of series from different laboratories (+0.0042 ± 0.0001, $n = 19$; +0.0050 ± 0.0003, $n = 42$; +0.0061 ± 0.0006, $n = 93$).

Using the Potts and Guy value that is most frequently quoted for *z* of +0.0061, a solution to eq 6 was obtained using the $n = 39$ set: solution 11 Table 2, $x = +0.388$, $y = +0.590$. Using the estimated values for *x* and *y* from solution 11 and *z* fixed at 0.0061, predicted log J_M values were calculated and are listed in Table 3. The average error for predicting log J_M (Δ log J_M, data not shown) was 0.141 log units for all log J_M values, $n = 39$. The average Δ log J_M value for each series is listed in boldface in the predicted log J_M column in Table 3. The predicted log J_M values for the miscellaneous series were also calculated using the coefficients from solution 11. Figure 2 shows the fit of the $n = 39$ prodrug set and the members of the miscellaneous series to a plot of experimental log J_M versus predicted log J_M based on solution 11. Using the estimated value for *y* and the fixed value for *z*, values for x_i which were required to give the experimental log J_M values were calculated for all the members of all the series. Those x_i values are given in Table 3. The average x_i for all members of all series was +0.413 with a standard deviation of ±0.187 log units. Excluding the data for the AC- and AAC-5-FU series, the solution 12 fit to eq 6 gave estimated values for *x*, *y*, and *z* (no longer fixed) which are given in Table 2.

Equation 7 was fit to the log J_M, MW, log S_{IPM}, and log S_{PG} data for the 28 molecules comprising the Kasting, Smith, and Cooper[14] data set (with the amine salts and

Table 3—Predicted log J_M and Calculated x_i Values for Calculated Solutions to Equation 6

	pred[a] log J_M	calcd[b] x_i	pred[a] log J_M	calcd[b] x_i	pred[a] log J_M	calcd[b] x_i
ACOM-5-FU	sol 1[c]		sol 4[c]		sol 11[c]	
C_1	0.41	–0.15	0.43	–0.18	0.38	0.46
C_2	0.60	–0.21	0.60	–0.23	0.57	0.40
C_3	0.35	–0.13	0.35	–0.15	0.33	0.46
C_4	0.05	–0.13	0.04	–0.14	0.04	0.46
C_5	–0.36	–0.09	–0.38	–0.08	–0.36	0.49
C_7	–1.08	–0.04	–1.12	–0.02	–1.08	0.55
C_9	–2.20	0.19	–2.26	–0.24	–2.19	0.75
average	**0.12**[d]	–0.08	**0.14**[d]	–0.08	**0.13**[d]	0.51
SD		0.13		0.16		0.12
AOC-5-FU	sol 1[c]		sol 5[c]		so1 1[c]	
C_1	0.26	–0.04	0.26	–0.04	0.27	0.53
C_2	0.72	–0.14	0.72	–0.14	0.73	0.43
C_3	0.41	–0.24	0.41	–0.24	0.43	0.32
C_4	0.42	–0.27	0.42	–0.27	0.45	0.29
C_6	0.35	–0.35	0.34	–0.35	0.39	0.19
C_8	–0.84	0.11	–0.85	0.11	–0.80	0.66
average	**0.13**[d]	–0. 16	**0.13**[d]	–0.16	**0.14**[d]	0.40
SD		0.17		0.17		0.17
AC-5-FU	sol 1[c]		sol 6[c]		sol 11[c]	
C_1	0.87	–0.10	0.90	–0.03	0.98	0.37
C_2	0.75	–0.31	0.77	–0.24	0.86	0.16
C_3	0.11	–0.19	0.14	–0.12	0.23	0.27
C_4	0.12	–0.31	0.14	–0.24	0.24	0.14
C_5	0.28	–0.43	0.30	–0.36	0.40	0.03
C_7	–0.45	0.04	–0.43	0.11	–0.31	0.48
average	**0.14**[d]	–0.22	**0.14**[d]	–0.14	**0.18**[d]	0.24
SD		0.17		0.17		0.16
AAC-5-FU	sol 1[c]		sol 7[c]		sol 11[c]	
C_1	–0.88	0.00	–0.88	0.11	–0.83	0.54
C_2	–0.27	–0.15	–0.26	–0.05	–0.21	0.38
C_3	0.05	–0.37	0.07	–0.28	0.11	0.15
C_4	0.04	–0.52	0.06	–0.43	0.10	0.00
C_8	–1.08	–0.34	–1.02	–0.28	–0.99	0.16
average	**0.18**[d]	–0.27	**0.20**[d]	–0.19	**0.20**[d]	0.24
SD		0.20		0.21		0.21
ACOM-Th	sol 1[c]		sol 8[c]		sol 11[c]	
C_1	–0.27	–0.16	–0.25	–0.24	–0.36	0.51
C_2	–0.60	–0.10	–0.59	–0.18	–0.69	0.57
C_3	0.01	–0.18	0.03	–0.26	–0.07	0.49
C_4	–0.06	–0.36	–0.04	–0.45	–0.14	0.30
C_5	–0.11	–0.41	–0.09	–0.50	–0.19	0.25
average	**0.11**[d]	–0.24	**0.10**[d]	–0.33	**0.13**[d]	0.42
SD		0.13		0.14		0.14
6ACOM-6-MP	sol 1[c]		sol 9[c]		so1 1[c]	
C_1	–0.59	–0.30	–0.59	–0.31	–0.61	0.30
C_2	–0.58	–0.28	–0.58	–0.29	–0.60	0.32
C_3	–0.70	–0.08	–0.69	–0.09	–0.72	0.53
C_4	–0.88	0.03	–0.88	0.03	–0.91	0.64
C_5	–1.21	–0.25	–1.21	–0.25	–1.24	0.37
C_7	–1.73	–0.34	–1.73	–0.35	–1.77	0.27
average	**0.12**[d]	–0.20	**0.12**[d]	0.21	**0.11**[d]	0.41
SD		0.15		0.15		0.15
6,9ACOM-6-MP	sol 1[c]		sol 10[c]		sol 11[c]	
C_1	–0.67	–0.16	–0.65	–0.29	–0.81	0.55
C_2	–0.47	–0.36	–0.44	–0.48	–0.60	0.36
C_3	–0.78	–0.26	–0.75	–0.39	–0.90	0.43
C_4	–1.03	–0.15	–0.99	–0.29	–1.16	0.55
average	**0.08**[d]	–0.23	**0.08**[d]	–0.36	**0.11**[d]	0.47
SD		0.10		0.10		0.10
miscellaneous	sol 1[c]				sol 11[c]	
5-FU	–0.44	–0.38			–0.39	0.15
pivACOM-5-FU	–0.19	–0.53			–0.21	0.07
Th	–0.30	–0.21			–0.31	0.37
6-MP	–1.59	–1.01			–1.50	–0.52

[a] Units of μmol cm^{-2} h^{-1}. [b] Units of cm h^{-1}. [c] Solutions from Table 2. [d] Average $\triangle$ log J_M for series.

benzyl alcohol data deleted) using the SPSS nonlinear function. The solution 13 for the fit to eq 7 gave $x = -1.673 \pm 0.363$, $y = +0.599 \pm 0.236$, $z = +0.00595 \pm 0.00124$, and $r^2 = 0.852$. If log S_{OCT} was substituted for log S_{IPM}, solution 14 was obtained which gave a poorer fit ($r^2 = 0.807$), although z stayed relatively constant. Figure 3 shows the fit of the $n = 28$ data set from Kasting, Smith, and Cooper[14] to eq 7 solution 13.

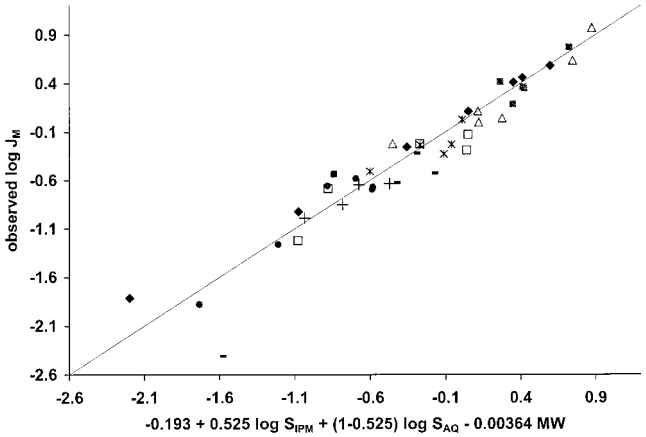

Figure 1—Fit of 39 prodrugs and the miscellaneous series to solution 1: ACOM-5-FU (◆), AOC-5-FU (■), AC-5-FU (△). AAC-5-FU (□), ACOM-Th (∗), 6ACOM-6-MP (●), 6,9ACOM-5-FU (+), miscellaneous (–).

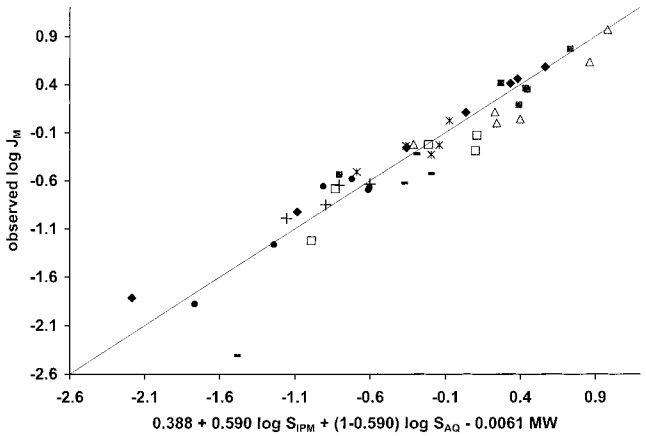

Figure 2—Fit of 39 prodrugs and the miscellaneous series to solution 11: ACOM-5-FU (◆), AOC-5-FU (■), AC-5-FU (Δ). AAC-5-FU (□), ACOM-Th (∗), 6ACOM-6-MP (●), 6,9ACOM-5-FU (+), MISCELLANEOUS (–).

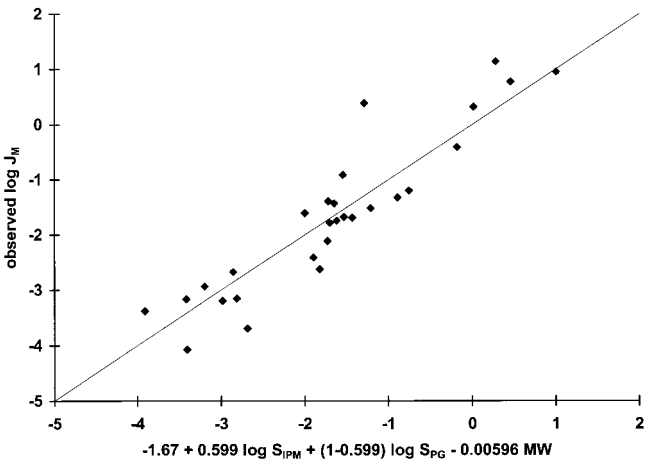

Figure 3—Prediction of log J_M from Kasting, Smith, and Cooper data, solution 13.

Discussion

Transformation of the Potts and Guy model[13] was done not only to include S_{AQ} as a variable in predicting flux but

also to accommodate donor phases other than water in the model. One of the key features of the Potts and Guy model is the substitution of $(K_{OCT:AQ})^f$ for K_m where K_m is the partition coefficient between the biological membrane, skin, and water. A more specific representation of K_m would be $K_{MEM:AQ} = (K_{LIPID:AQ})^f$ where water (AQ) is defined as the polar phase, and lipids, which can be different from octanol, are defined as appropriate nonpolar phase substitutes for skin (MEM). However, since $K_m D°/L$ is equal to the permeability coefficient (P), in the Potts and Guy model the polar phase is also the donor phase in the diffusion cell experiments which measure flux. This presents a significant limitation to the extension of the Potts and Guy model to predict P (or J) where the donor phase is a lipid or a polar phase other than water. The key substitution cannot be made if the donor phase is also a lipid such as isopropyl myristate (IPM) or even octanol. Taking the example where IPM is used as the donor phase, K_m is the partition coefficient between skin and IPM and a lipid/aqueous partition coefficient cannot be substituted for K_m.

There are three important features of the transformation of the Potts and Guy model into the model represented by eq 6. The first feature is the use of the identity of $K_{MEM:IPM}$ with $K_{MEM:AQ}/K_{IPM:AQ}$ which had previously been established by Surber et al.[23] Use of this identity allows substitution of the experimental partition coefficient, $K_{MEM:IPM}$, by the partition coefficient used by Potts and Guy in developing their model, $K_{MEM:AQ}$, and by a partition coefficient, $K_{IPM:AQ}$, containing two variables available from the published data on the prodrugs: S_{AQ} and S_{IPM}. This assumes that the solubility ratio, $SR_{IPM:AQ} = S_{IPM}/S_{AQ}$, can be substituted for partition coefficient, K. The second feature is the use of the identity of $K_{MEM:AQ}$ with $(K_{LIPID:AQ})^f$ where the membrane phase cannot only be replaced by another lipid phase such as octanol, which is similar in polarity, but also by lipids such as ether,[17] or in this case IPM, which are much less polar than skin or octanol. In this case $K_{MEM:AQ} = (K_{IPM:AQ})^f$. The coefficient f is used to account for the difference between the partitioning domain presented by IPM and that presented by the permeation limiting barrier in the skin: the stratum corneum. The third feature is the use of saturated solutions of the permeants in the donor phases. This allows all of the prodrugs to be evaluated at the same thermodynamic activity.

The estimated values for x, y, and z obtained for solution 1 to eq 6 using data from the seven series of straight chain alkyl prodrugs are consistent with the values obtained by Potts and Guy.[13] The value for y is 0.525 ± 0.029 which is consistent with the f value of 0.48 ± 0.05 obtained by Potts and Guy when they performed multiple linear regression of log P (K_P) values upon log $K_{ETHER:AQ}$ and MW from the data of Ackerman et al.[17] A y value of 1.0 would indicate that IPM is a good substitute for the partitioning domain of the stratum corneum (SC) lipids. On the other hand, the y values when IPM or ether is used are significantly less than 1.0, which suggests that they are both much less polar than the partitioning domain of the SC and in fact are less polar than octanol for which y (f) values of from 0.82 to 0.70 were obtained.[13] This order of polarity follows from the solubility parameters of ether, IPM, skin, and octanol: 7.4,[26] 8.5,[26] 10.0,[27] and 10.3[26] $(cal/cm^3)^{1/2}$, respectively. Since ether and IPM exhibit similar solubility parameter values, one would expect them to behave similarly and to be significantly less polar than octanol or skin.

Cohen and co-workers[27] have estimated a macroscopic value of $\delta = 9.7-10.0$ $(cal/cm^3)^{1/2}$ for the solubility parameter of porcine skin. However, the fact that the y value for octanol as the SC substitute is less than 1.0 suggests that the SC is more polar than $\delta = 9.7-10.0$ $(cal/cm^3)^{1/2}$ and may be as large as 12 $(cal/cm^3)^{1/2}$.

The value for z of $+0.00364 \pm 0.00084$ is also consistent with the $\beta°$ value of $+0.0019 \pm 0.0008$ obtained by Potts and Guy[13] in their analysis of the Ackerman et al. data,[17] where mouse skin was used as the diffusion cell membrane and $K_{ETHER:AQ}$ was used instead of $K_{OCT:AQ}$. It is also consistent with the $\beta°$ value of $+0.0050 \pm 0.0003$ obtained by Potts and Guy for the $n = 42$ combined data from Schuplein and Blank[15] and Roberts et al.[16] Although the value for z most often quoted from the paper of Potts and Guy is the value of $+0.0061 \pm 0.0006$ obtained using the data collected by Flynn,[18] it was obtained from a regression analysis that only yielded an $r^2 = 0.67$.

Although the estimated values for y and z from the prodrug data set are consistent with those previously obtained by Potts and Guy data from combinations of series from different laboratories, the value for x obtained here is different from that obtained by Potts and Guy by a factor of approximately 10^6. This difference can be attributed to differences in the way the flux data was obtained and the units used to present the data. The prodrug J_M data has been presented in units of μmol cm^{-2} h^{-1} instead of units of μmol cm^{-2} s^{-1}. This introduces a factor of 3.6×10^3. In addition, since x defines D, any experimental difference that affects D will result in differences in x. The prodrug J_M data were obtained using hairless mouse skin instead of using human skin. Hairless mouse skin may be as much as 10 times more permeable than human skin,[28] using experimental conditions similar to the ones used to collect the prodrug flux data. Finally, isopropyl myristate (IPM) was used as the vehicle (donor phase) in the diffusion cell experiments used to obtain the prodrug J_M values. IPM has been shown[29−31] to irreversibly change hairless mouse skin so that it is 50 to 100 times more permeable than it would be if there were no interactions between the skin and vehicle. Taking all three factors into account gives an x value of the same order of magnitude as that obtained by Potts and Guy. Considering all the differences in the experimental details between the way the data in the two data sets were obtained, this is a good agreement.

A plot of experimental log J_M values versus predicted log J_M values from solution 1 for the prodrug series is shown in Figure 1. The largest differences between experimental and calculated values for log J_M (Δ log J_M) were found for the C_9 member of the ACOM-5-FU, the C_8 member of AOC-5-FU, and the C_4 member of AAC-5-FU series: Δ log $J_M = 0.31$ to 0.38 log units. Inclusion of the fit of the data from the miscellaneous series to solution 1 in Figure 1 shows that 6-MP is an obvious outlier (Δ log $J_M = 0.83$) to solution 1 and that pivACOM-5-FU (Δ log $J_M = 0.33$) is only predicted as well as the worst predicted members of the straight chain alkyl series. When the data from the miscellaneous series was included in the data used to determine a solution (solution 2, Table 2) to eq 6 the fit was worse ($r^2 = 0.924$) and x and z changed substantially from their solution 1 values. Exclusion of the data for 6-MP from the solution to eq 6 gave estimated values for x, y, and z (solution 3, Table 2) which were consistent with those from solution 1. Thus, there is no reason to exclude parent drugs (except for 6-MP) or branched alkyl chain prodrugs from analysis of the data for the straight alkyl chain prodrugs using eq 6.

To determine if any of the data from individual series were inconsistent with the remaining data set, solutions 4−10 to eq 6 were obtained in which each series was individually excluded from the entire data set one series at a time. Using solutions 4−10 from Table 2, predicted log J_M and x_i values were calculated for the excluded series and compared with the predicted log J_M and x_i values calculated from solution 1 for the excluded series (Table 3). There was no substantial change in the differences

between the experimental log J_M and predicted log J_M values calculated from solution 1 and predicted log J_M calculated from solutions 4−10. Also there were no significant differences between the average x_i values calculated for each of the individual series using solution 1 compared to the average x_i values calculated using solutions 4−10. Thus, the data from each of the series is consistent with the remaining series.

When the Potts and Guy value for z was used to obtain a solution (solution 11, Table 2) for the $n = 39$ data set fit to eq 6, there were significant changes in the average x_i value for all the series and the AC- and AAC-5-FU series together gave average x_i values that were significantly different ($p < 0.01$) from the average of all the other series (Table 3). If the data from AC- and AAC-5-FU series were excluded from the $n = 39$ data set and a solution (solution 12, Table 2) was obtained for the fit of that $n = 28$ data set to eq 6, the estimated values for x, y, and z were consistent with those from solution 11. The value for z remained the same even though it was not fixed in solution 12 and was free to optimize. Solution 12 gave the best fit to the data ($r^2 = 0.961$) but at the expense of excluding the AC- and AAC-5-FU data and possibly biasing estimation of x, y, and z to give values that are not representative of all the prodrugs. Thus, the best solution to eq 6 for all the data is solution 1 or 3.

To determine if the data from diffusion cell experiments where donor phases other than IPM and membranes other than hairless mouse skin were used could be analyzed by a transformation of the Potts and Guy model, eq 7 was fit to the data from Kasting, Smith, and Cooper to give solution 13 in Table 2. The value for z obtained (+0.00595) is consistent with the previous values obtained when water or IPM were the donor phases. Thus, the dependency (z) of diffusivity on molecular weight (size) of the solute is not changed by properties of the vehicle or the membrane used. The value for y obtained by substitution of $(K_{IPM:PG})^y$ for $K_{MEM:AQ}$ is consistent with the value of y obtained when $(K_{IPM:AQ})^y$ was substituted for $K_{MEM:AQ}$. Thus PG does not behave significantly differently from AQ as a donor phase. Finally, the value for x estimated from the Kasting, Smith, and Cooper data is about 2 orders of magnitude more negative than that from the IPM data. Since human skin was used in the Kasting, Smith, and Cooper diffusion cell experiments and PG, which does not irreversibly change the skin, was used as the donor phase, there could be as much as 3 orders of magnitude difference between the IPM and PG data. Thus, the x value from solution 13, where PG was the donor phase, is also consistent with those where IPM or AQ were the donor phases.

It is probable that some error is introduced into the model as a result of hydrolysis of the prodrugs to parent drug during their diffusion through the skin. Partial hydrolysis would tend to give increased values of experimental total flux compared to predicted values of flux because two species (parent drug and intact prodrug) would be diffusing independently. In this analysis no attempt was made to account for hydrolysis since rates for the hydrolyses of the prodrugs in skin homogenates were not available. However, neglect of hydrolysis has resulted in a good fit and a simple equation with good predictive value.

The results presented here show for the first time that S_{AQ} is an important variable to incorporate into a model that is to be used to predict the topical delivery of drugs and prodrugs. In addition, the importance of S_{AQ} in determining the best correlation between permeation of 5-FU and its prodrugs in Caco-2 cells and various physicochemical parameters has also recently been identified.[32] Thus, S_{AQ} is an important physicochemical parameter for predicting flux not only through skin but also membrane models for intestinal absorption.

Conclusion

Transformation of the Potts and Guy equation gives an eq 6 that can accommodate vehicles as donor phases that are less polar than skin and that can predict maximum flux values from aqueous and lipid solubilities (instead of partition coefficients) and molecular weights. The values for the coefficients estimated by fitting eq 6 to the values of fluxes from IPM through hairless mouse skin, solubilities in IPM and AQ and molecular weights from the prodrug literature were consistent with the values previously reported by Potts and Guy. In addition, the value for the coefficient defining the contribution of IPM and AQ solubilities to predictions of flux showed that water solubility was almost as important as IPM or lipid solubility. The Potts and Guy equation was also transformed into eq 7 to accommodate a vehicle that was more polar than skin but not as polar as water and a membrane other than hairless mouse skin, i.e., human skin. The values for the coefficients estimated by fitting eq 7 to the values of fluxes from PG through human skin, solubilities in IPM and PG and molecular weights from the data set of Kasting, Smith, and Cooper were also consistent with the values previously reported by Potts and Guy. These results support the conclusion that the coefficients have physical meaning in the diffusion process and that equations of the type developed by Potts and Guy have general utility in predicting flux when suitably transformed.

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Acknowledgments

These studies were supported by NIH grant R15 CA67230. Dr. Jane Pendergast of the University of Florida was consulted on the statistical analyses.

JS980419B