Prediction of Transdermal Flux of Prodrugs of 5-Fluorouracil, Theophylline, and 6-Mercaptopurine with a Series/Parallel Model

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ABSTRACT: Multiple regression analysis of fluxes from suspensions in isopropyl myristate (J_M) as a function of molecular weights (MW) and solubilities in isopropyl myristate (S_{IPM}) and water (S_{AQ}) were performed on a data set of 41 compounds ($n = 41$) comprising 39 prodrugs of 5-fluorouracil (5-FU), theophylline (Th), and 6-mercaptopurine (6-MP), in addition to 5-FU and Th, using four models. Two series/parallel models have been developed that allow an aqueous-only path in parallel with a lipid-only path and with a lipid–aqueous series path for the permeation of solutes through skin: $\log J_M = \log \{1/[1/(aS_{LIPID}\ 10^{\Phi MW}) + 1/(bS_{AQ}/MW^{1/2})] + cS_{LIPID}10^{\Phi MW} + dS_{AQ}/MW^{1/2}\}$ where *a, b, c,* and *d* are coefficients for flux through the lipid and aqueous portions of the series path, the lipid-only path, and the aqueous-only path, respectively, and Φ is the dependence of diffusivity in lipid on MW. In the first series/parallel model, S_{LIPID} was predicted by S_{IPM}, and in the second, solvatochromic series/parallel model, S_{LIPID} was predicted by $S_{IPM}^{k\ MW + \Omega i}$ where Ω_i is the sum of the solvatochromic terms α, β, π, and R_2, and k is the coefficient for the dependence of partitioning on MW. Using the $n = 41$ solutions, the coefficients for the aqueous-only path were very small or not different from zero in the two series/parallel models, so only two-path series/parallel models were compared with the solvatochromic and transformed Potts–Guy models where a homogeneous barrier to permeation was assumed. For each model, one compound at a time was omitted from the data set and new parameter estimates were obtained for these 41–1 solutions and used to predict $\log J_M$ for the omitted compound. The average errors of prediction of $\log J_M$ (experimental $\log J_M$ – predicted $\log J_M$) for the four models were 0.134 for the series/parallel ($r^2 = 0.937$), 0.127 for the solvatochromic series/parallel ($r^2 = 0.967$), 0.150 for the solvatochromic ($r^2 = 0.950$), and 0.134 log units for the transformed Potts–Guy model ($r^2 = 0.944$). Thus, the solvatochromic series/parallel model provides fit and predictive ability comparable to or slightly superior to previous models that assumed homogeneity of the diffusional barrier to flux in the rate-determining step, provides further theoretical support against the existence of a high capacity aqueous-only path, and provides further insight into the physicochemical properties that should be incorporated into solutes to optimize their flux. Using the solvatochromic series/parallel model, the parameter estimates for the $n = 41$ solution were used to calculate the flux of each compound through the two paths. For compounds with log partition coefficients ($K_{IPM:AQ}$) of <0.8, permeation was mostly by the lipid–aqueous series path; for compounds with $\log K_{IPM:AQ}$ >1.0, permeation was mostly by the lipid-

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only path; the lipid-aqueous series path exhibited the higher carrying capacity. J Pharm Sci 89: 1415–1431, 2000
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INTRODUCTION

The delivery of drugs into and through skin is an important therapeutic modality in the treatment of not only local but also systemic disease states. The barrier to delivery, that is the resistance of skin to the partitioning of the drug into the skin and its diffusion through the skin, has been shown to reside in the top layers of the epidermis (i.e., the stratum corneum). The stratum corneum is considered to be a lipoidal barrier where diffusion takes place predominantly through the intercellular compartment in which the cells of the stratum corneum—the corneocytes—are embedded.[1] The components of the intercellular compartment, and hence the origin of the contributions to the resistance of the intercellular compartment to diffusion, are derived from lamellar granules comprised of bilamellar disks that have undergone extrusion into the intercellular compartment between the corneocytes and fusion to form sheets.[2] As a consequence, although the lamellar granules are composed of polar lipids in a bilayer configuration, Swartzendruber et al.[3] have shown that the minimum unit of the intercellular sheets is a double bilayer formed from compression of the disks. The composition of the polar lipids is complex, comprising up to 50% of extractable lipids as six different ceramides, up to 25% as cholesterol, 10–12% as mostly long chain (C_{20} to C_{28}) fatty acids, and only 1–2% as triacylglycerols.[4] The diffusion of solutes through the lipid intercellular compartment of the stratum corneum correlates with their lateral diffusion coefficients in stratum corneum lipid bilayers where there is a strong inverse exponential dependence on molecular weight (MW) for smaller solutes (<300 Da) and a weak, nonexponential dependence for larger solutes (>350 Da).[5] Conversely, diffusion correlates directly with lipid (octanol) solubility.[6]

However, although diffusion within the stratum corneum may be directly related to lipid (octanol) solubility, the intercellular compartment is not homogeneous like octanol. The lipid barrier is a heterogeneous mixture of different alkyl chain length components that can form domain mosaics[7] or lipid microdomains. These lateral hydrophobic mismatches[8] cause packing disorder that can allow penetration enhancement, especially at the interfaces bounding the domains, and generally increase bilayer permeability.[9] Further, the lipid barrier was seen by Schatzlein and Cevc to be heterogeneous, with fluorescent planes between stacks of lipid multilamellar structures interspersed with areas of bright fluorescence that filled the intercellular compartment.[10] Some of these hydrophilic areas filling the intercellular compartment may be the result of separation of the bilayers of hydrated skin into lipid-poor (water pools) and lipid-rich phases, as observed by van Hal et al.[11] The existence of less dramatic phase separation and only slightly less effective shortening of diffusion pathways for lipophilic as well as hydrophilic solutes in less highly hydrated skin cannot be discounted. In addition to the existence of water pools, the intercellular lipid bilayers are interspersed periodically with hydrophilic lacunae (lenticular dilations), and the narrow electron lucent lipid bands in the lamella, seen on ruthenium-tetroxide fixing of normal skin, are interrupted by hydrophilic electron-rich fenestrations that bridge the adjacent hydrophilic bands.[12] Thus, interfacial or intramembrane transbilayer transport may not make important contributions to the resistance of the stratum corneum to diffusion of solutes through the lipid bilayers because the lipid bilayers are not "continuous and defect free."[5]

However, regardless of the obvious heterogeneous nature of the stratum corneum and in particular of the intercellular lipid barrier to diffusion, models used to describe the partitioning of solutes into the skin and their diffusion through skin have for the most part assumed that the rate-determining barrier is homogeneous and lipoidal.[5,6,13–19] Although a number of models have described two parallel paths (lipid and aqueous) to accommodate the diffusion of small, polar solutes,[13,15] the consensus interpretation of the relevant data seems to be that inclusion of a term for the dependence of diffusion on solute molecular volume (or weight)[14,16,17] obviates the need for inclusion of a water-solubility-dependent, aqueous-only path. Similarly, the need for a third parallel path of alternating lipophilic and hydrophilic lay-

ers has been discounted because of the insensitivity of the existing permeation data to the inclusion of such a path in the model.[15] However, the logical attractiveness of such a three parallel path model, in view of the complex structure and composition of the rate-determining barrier to diffusion, has inclined some authors to continue to describe solutes as diffusing across numbers of bilayers containing hydrophilic and lipophilic domains.[20,21] On the other hand, the mathematical models[16,17] that were used in one of those same articles[21] discounted the water solubility of the solute as a positive influence on permeation because of its negative influence on partitioning and diffusion.

In this paper, a model is developed that allows for the existence of parallel lipid-only, aqueous-only, and alternating lipid and aqueous (series) paths for permeation of the stratum corneum by seven series of prodrugs and their parent drugs from isopropyl myristate (IPM).[19] We have analyzed the various paths in terms of the solubilities of the solute in the phase(s) that comprise those paths. These solubilities are analogous to conductivities in electrical circuits—the reciprocal of resistivity. Thus, the greater the solubility of the solute in the phase(s) that constitute a path, the greater the carrying capacity of that path and the greater the flux through that path. Analysis of the effect of these solubilities (lipid and aqueous) on the extent to which solutes permeate the stratum corneum by each path should give a clearer picture of solute–phase interactions during permeation and allow rational development of drugs that exhibit improved topical delivery.

DEVELOPMENT OF MODELS

Series/Parallel Model

In its simplest form, the rate of mass transfer of a solute across a homogeneous membrane (which provides the resistance to diffusion) is proportional to the concentration gradient of the solute across that membrane,[22] where dM is the amount transferred, dt is the increment of time, dC/dL is the concentration gradient within the membrane, and D is the proportionality coefficient (diffusion coefficient).

$$(\mathrm{d}M/\mathrm{d}t)_{\text{unit area}} = -D(\mathrm{d}C/\mathrm{d}L) \qquad (1)$$

At steady-state, flux (J) is equal to:

$$(\mathrm{d}M/\mathrm{d}t)_{\text{steady state}} = AD(C_1 - C_X)/L = J \qquad (2)$$

where L is the thickness of the homogeneous membrane, A is the area of the membrane, C_1 is the concentration of the solute in the first layer of the membrane, and C_X is the concentration of the solute in the last layer of the membrane. Thus flux is proportional to the concentration drop across a homogeneous membrane in much the same way that an electric current, I, is proportional to the voltage drop, E, across a resistor, R: $I = E\,(1/R)$.

Analogously, the flux of a solute through three parallel paths is equal to the sum of the individual fluxes: $J_T = J_A + J_C + J_D$, where A, C, and D, when used as subscripts, identify a specific path. The flux through each single-phase, parallel path is equal to the product of a coefficient (comprised of the terms AD/L from eq 2) and the concentration gradient within that path. In this context, phase refers to a portion of a nonhomogeneous membrane that exhibits homogeneous properties, where 1 and 2, when used as subscripts, identify a specific phase. Also in the present content, phase 1 refers to a lipid phase and phase 2 refers to an aqueous phase. For the example where the parallel paths C and D are comprised of a single phase, $J_C = c(C_{C1} - C_{C1X})$ and $J_D = d(C_{D2} - C_{D2X})$. It is assumed that the coefficients c and d are defined as $c = A_C D_C/L_C$ and $d = A_D D_D/L_D$; that the concentrations of the solute in the last layer of the phases that comprise paths C and D, C_{C1X} and C_{D2X}, respectively, approach zero in such a single phase path; that C_{C1} and C_{D2} are the concentrations in the first layer of the phases that comprise paths C and D, respectively; and that path C is a lipid-only path and that path D is an aqueous-only path. Under conditions where a saturated solution in equilibrium with the solid phase of the solute is applied and steady-state obtained, C_{C1} and C_{D2} are the saturated solubilities of the solute in those phases; that is, S_{C1} and S_{D2}, respectively.

In the example just presented, where J_C and J_D are fluxes through single-phase, parallel paths, J_A is the flux through a parallel path where the resistance to diffusion is due to two dissimilar phases in series. Again as with electrical circuits, the flux through two phases in series acting as resistors is the same in each phase and equal to the flux through that path: $J_A = J_1 = J_2$. Then $J_1 = a(C_{A1} - C_{A1X})$ and $J_2 = b(C_{A1X} K_{A2:A1} - C_{A2X})$, where $a = A_{A1} D_{A1}/L_{A1}$ and $b = A_{A2} D_{A2}/$

L_{A2}; C_{A1X} and C_{A2X} are the concentrations of the solute in the last layer of the two phases in series that comprise path A; C_{A2X} approaches zero and C_{A1X} is the concentration of the solute in path A, phase 1 that is approaching equilibrium with phase 2; $C_{A1} = S_{A1}$ under conditions where a saturated solution in equilibrium with the solid phase of the solute is applied and steady-state obtained; and $K_{A2:A1}$ is the partition coefficient for the solute in path A between phase 2 and phase 1 that can be approximated by $C_{A2}/C_{A1} = S_{A2}/S_{A1}$, the concentrations and solubilities, respectively, of the solute in the two phases. Solving for C_{A1X} gives:

$$J_1 = a(C_{A1} - C_{A1X}) = a(S_{A1} - C_{A1X}) \quad (3)$$

as $C_{A2X} \rightarrow 0$:

$$J_2 = b(C_{A1X})K_{A2:A1} = b(C_{A1X})(S_{A2}/S_{A1}) \quad (4)$$

Since $J_1 = J_2$, the addition of "a C_{A1X}" to both sides gives:

$$aS_{A1} - aC_{A1X} + aC_{A1X} = bC_{A1X}(S_{A2}/S_{A1}) + aC_{A1X} \quad (5)$$

$$aS_{A1}/[b(S_{A2}/S_{A1}) + a] = C_{A1X} \quad (6)$$

Substituting C_{A1X} into the equation for J_2 as $C_{A2X} \rightarrow 0$ gives:

$$J_A = J_2 = baS_{A1}/[b(S_{A2}/S_{A1}) + a](S_{A2}/S_{A1}) - 0 \quad (7)$$

$$b(S_{A2}/S_{A1}) + a = b(S_{A2}/S_{A1}) + a(S_{A1}/S_{A1}) = (bS_{A2} + aS_{A1})/S_{A1} \quad (8)$$

$$J_2 = [baS_{A1}/(bS_{A2} + aS_{A1})/S_{A1}](S_{A2}/S_{A1}) \quad (9)$$

$$J_2 = baS_{A1}S_{A2}/(bS_{A2} + aS_{A1}) = 1/(1/aS_{A1} + 1/bS_{A2}) \quad (10)$$

$$J_2 = J_A = 1/(1/aS_{A1} + 1/bS_{A2}) \quad (11)$$

Thus, where a saturated solution in equilibrium with a solid phase of the solute is applied and steady-state is obtained, the maximum flux, J_M, is equal to J_T and gives:

$$J_M = 1/(1/aS_{A1} + 1/bS_{A2}) + cS_{C1} + dS_{D2} \quad (12)$$

Assuming that the solubility of the solute in the lipoidal phase 1 or in the aqueous phase 2 is the same regardless of whether that phase is the only phase in a path or is a member of a series gives $S_{A1} = S_{C1} = S_{LIPID}$ and $S_{A2} = S_{D2} = S_{AQ}$. Extracting the associated D for each phase from its coefficient, identifying D specifically, and redefining the coefficients so that they are equal to A/L gives:

$$J_M = 1/(1/aS_{LIPID}D_{LIPID} + 1/bS_{AQ}D_{AQ}) + cS_{LIPID}D_{LIPID} + dS_{AQ}D_{AQ} \quad (13)$$

In the case where the solute is much larger than the molecules that comprise the phase through which the solute is diffusing (e.g., the aqueous phase), flux is expected to be inversely proportional to the square root of the MW.[14] On the other hand, in the case where the solute is smaller than the molecules that comprise the phase through which it is diffusing (e.g., the lipid phase), flux will be proportional to the product of the exponent of some negative parameter Φ and the MW.[14]

$$\log J_M = \log\{1/[1/(aS_{LIPID}10^{\Phi MW}) + 1/(bS_{AQ}/MW^{1/2})] + cS_{LIPID}10^{\Phi MW} + dS_{AQ}/MW^{1/2}\} \quad (14)$$

Although there are differences of opinion,[5,9,23,24] about the ability of water in the stratum corneum, especially that associated with bilayer head groups, to behave like bulk water and solvate polar solutes by the donation and acceptance of hydrogen bonds, the assumption has been made here that the solubility in the aqueous-path phases, S_{AQ}, may be approximated by the solubility of the solute in pH 4.0 buffer. The solubility of the solute in the lipid-path phases was more difficult to approximate. In the simplest form of the series/parallel model, it has been assumed that $S_{LIPID} = S_{IPM}$.

Solvatochromic Series/Parallel Model

In this model, S_{LIPID} has been calculated from S_{IPM} data using the general solvatochromic equation:[17]

$$\log SP = \text{constant} + h_1R_2 + h_2\pi_2 + h_3\Sigma\alpha_2 + h_4\Sigma\beta_2 + h_5V_X \quad (15)$$

where SP is some property of various solutes in a given solvent system and where $h_1, \ldots h_5$ are the

values of the coefficients for R_2 (solute excess molar refraction), π_2 (solute dipolarity/polarizability), α_2 (solute hydrogen-bond acidity), β_2 (solute hydrogen-bond basicity), and V_X (McGowan characteristic volume), respectively. Because experimental values for the solvatochromic terms were not readily available, the assumption was made that the sum of all the terms, except the molecular volume (MV)-dependent term, were equal within acceptable error for all of the prodrugs within each homologous series. The sum of those terms, however, would be different from series to series. The observation of the lack of variation in the solvatochromic terms, especially $\Sigma\alpha_2$, $\Sigma\beta_2$, and π_2, for congeneric series was previously made by Abraham et al.[17] The assumption has also been made that MW can be substituted for MV. Thus, for SP = $K_{LIPID:IPM}$:

$$\log K_{LIPID:IPM} = k\mathrm{MW} + \Omega_i \tag{16}$$

where Ω_i is the sum of the $\Sigma\alpha_2$, $\Sigma\beta_2$, π_2, and R_2 solvatochromic terms for each of the series to be determined by regression analysis using a different index number, *i,* for each series, and where k gives the dependence of partitioning between lipid and the donor phase, IPM, on MW. Because:

$$S_{LIPID} = (K_{LIPID:IPM})(S_{IPM}) \tag{17}$$

then:

$$S_{LIPID} = S_{IPM}\ 10^{(k\mathrm{MW}+\Omega i)} \tag{18}$$

Substitution of eq 18 into eq 14, $10^{\log\ a}$ for a, and rearranging slightly gives:

$$\begin{aligned}\log J_M = \log\{1/[1/(S_{IPM}10^{\Phi\mathrm{MW}}\ 10^{k\mathrm{MW}+\Omega i+\log a}) \\ + 1/(bS_{AQ}/\mathrm{MW}^{1/2})] \\ + c/aS_{IPM}10^{\Phi\mathrm{MW}}\ 10^{k\mathrm{MW}+\Omega i+\log a} \\ + dS_{AQ}/\mathrm{MW}^{1/2}\}\end{aligned} \tag{19}$$

Because it is impossible for regression to distinguish between exponential change in partitioning due to change in MW (or MV) and exponential change in diffusivity due to change in MW, as has been noted previously by Potts and Guy,[16] values for Φ and k cannot be determined individually by regression; only their sum, which will be designated as η, can be determined. Also, whether a change in carrying capacity of a lipid phase is due to a change in path length, a change in cross-sectional area, or a change in partitioning into the lipid phase from the donor phase cannot be answered by regression. Thus, although the individual magnitudes of the log a and Ω_i terms cannot be determined by regression because they are both multipliers of S_{IPM}, the sum of their values, X_i, can be determined for each homologous series. Substitution of $\eta = \Phi + k$ and $X_i = \Omega_i + \log a$ in eq 19 gives the solvatochromic series/parallel model:

$$\begin{aligned}\log J_M = \log\{1/[1/(S_{IPM}10^{\eta\mathrm{MW}+Xi}) \\ + 1/(bS_{AQ}/\mathrm{MW}^{1/2})] + c/aS_{IPM}\ 10^{\eta\mathrm{MW}+Xi} \\ + dS_{AQ}/\mathrm{MW}^{1/2}\}\end{aligned} \tag{20}$$

Solvatochromic Method

The solvatochromic series/parallel model is compared with a simple solvatochromic model that assumes a homogeneous barrier. An important part of the solvatochromic series/parallel model is the use of the solvatochromic equation to derive S_{LIPID} from S_{IPM} and $K_{LIPID:IPM}$. Previously, the solvatochromic equation has been used to derive K_m (partitioning between membrane and applied aqueous phase) from K_{ORG} (partitioning between an organic phase and water) to predict permeability in homogeneous membrane barrier models such as the 1995 Potts and Guy model.[25] Following the example of Potts and Guy, but using the designations already presented gives:

$$\begin{aligned}\log K_{LIPID:IPM} = h_1R_2 + h_2\pi_2 + h_3\Sigma\alpha_2 + h_4\Sigma\beta_2 \\ + h_5V_X\end{aligned} \tag{21}$$

Substitution of $\log K_{LIPID:IPM}$ for $\alpha\log K_{ORG}$ in $\log P = \alpha\log K_{ORG} - B\mathrm{MV} + \log D_0/L$ gives:

$$\begin{aligned}\log P = h_1R_2 + h_2\pi_2 + h_3\Sigma\alpha_2 + h_4\Sigma\beta_2 + h_5V_X \\ - B\mathrm{MV} + \log D_0/L\end{aligned} \tag{22}$$

Then, making the substitution of Ω_i for the solvatochromic terms π_2, $\Sigma\alpha_2$, $\Sigma\beta_2$, and R_2, k for h_5 and MW for V_X and MV gives:

$$\log P = k\ \mathrm{MW} + \Omega_i + \log D_o/L - B'\mathrm{MW} \tag{23}$$

Adding $\log S_{IPM}$ to both sides of eq 23 gives:

$$\begin{aligned}\log P + \log S_{IPM} = k\ \mathrm{MW} + \Omega_i + \log D_o/L - B'\mathrm{MW} \\ + \log S_{IPM} = \log J_M\end{aligned} \tag{24}$$

Using the same arguments as in the discussion of the solvatochromic series/parallel model, the k

and B' terms have been combined to give η' and the Ω_i and D_o/L terms have been combined to give X_i'. These combinations give the solvatochromic model:

$$\log J_M = \eta' MW + X_i' + \log S_{IPM} \quad (25)$$

Transformed Potts–Guy Model

The solvatochromic series/parallel model is also compared with the transformed Potts–Guy model,[19] which had previously been used to analyze the same data.

$$\log J_M = x + y \log S_{IPM} + (1 - y) \log S_{AQ} - zMW \quad (26)$$

EXPERIMENTAL SECTION

The methods used to determine the values for flux (J_M), solubilities (S_{IPM}, S_{AQ}), and partition coefficients between IPM and pH 4.0 buffer ($K_{IPM:AQ}$) are described in the original papers for each series of prodrugs:1-alkylcarbonyloxymethyl-5-fluorouracil (1-ACOM-5-FU),[26] 1-alkyloxycarbonyl-5-FU (1-AOC-5-FU),[27] 1-alkylcarbonyl-5-FU (1-AC-5-FU),[28] 1-alkylaminocarbonyl-5-FU (1-AAC-5-FU),[29] 7-alkylcarbonyloxymethyltheophylline (7-ACOM-Th),[30] 6-alkylcarbonyloxymethyl-6-mercaptopurine (6-ACOM-6-MP),[31] and 6,9-alkylcarbonyloxymethyl-6-MP (6,9-ACOM-6-MP).[32] In each series, only straight-chain homologues were completely characterized and evaluated. Solubilities (S_{IPM}, S_{AQ}), MW, and partition coefficients ($K_{IPM:AQ}$) are listed in Table 1. The 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, 1-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,[33] 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.[30] 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 <30% except from the 6-ACOM-6-MP series, where the variation was <50%.

The solubilities, partition coefficients, and flux values for two of the parent drugs (5-FU[29] and Th[30]) are also listed in Table 1. This data set of 39 prodrugs and two parent drugs has been presented previously[19] and is reproduced here for the convenience of the reader.

The multiple linear regression models depicted in eqs 14, 20, 25, and 26 were fit to various combinations of the sets of data in Table 1 using the SPSS 7.5 statistical software package. Each model (series/parallel, solvatochromic series/parallel, solvatochromic, and transformed Potts–Guy) was tested in three ways: for fit, for predictive ability, and for stability of the models to omission of compounds or series from the data set. In the test for fit, regression was performed on the entire $n = 41$ data set of 39 prodrugs and two parent drugs (5-FU and Th), a solution was obtained for the parameters of the equation tested, and error of fit (experimental log J_M – calculated log J_M = Δlog J_M), r^2 and adjusted r^2 values were obtained. Adjusted r^2 accounts for the inherent ability of added parameters (p) to improve fit and compensates for this by penalizing equations according to the number of parameters. It is computed as: adjusted $r^2 = 1 - (1 - r^2)(n - 1)/(n - p)$. In the tests for predictive ability of each model, solutions were obtained for the 41 possible data sets, each omitting one compound (referred to as 41 – 1 solutions). In each case, a predicted log J_M value for the omitted compound was calculated from the solution obtained using all other compounds, and the error of prediction (experimental log J_M – predicted log J_M – Δlog J_M') was assessed. Averages of Δlog J_M and Δlog J_M' are absolute averages. To evaluate stability of each model to omission of compounds from the data

Table 1. Molecular Weights (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 Flux Values from Saturated IPM Donor Phases (J_M)

Compound[a]	MW	Log S_{IPM}[b,c]	Log S_{AQ}[b,d]	Log $K_{IPM:AQ}$	Log J_M[e]
1-ACOM-5-FU					
C1	202	0.52	2.25	–1.73	0.46
C2	216	0.99	2.22	–1.23	0.58
C3	230	1.16	1.63	–0.47	0.41
C4	244	1.17	1.09	0.08	0.11
C5	258	1.17	0.35	0.82	–0.26
C7	286	1.00	–0.77	1.77	–0.92
C9	314	0.63	–2.51[c]	3.14[f]	–1.82
1-AOC-5-FU					
C1	188	0.33	2.04	–1.71	0.42
C2	202	1.12	2.24	–1.12	0.77
C3	216	1.18	1.63	–0.45	0.36
C4	230	1.53	1.37	0.16	0.35
C6	258	2.19	0.70	1.48	0.19
C8	286	1.56	–0.89	2.45	–0.53
1-AC-5-FU					
C1	172	1.34	2.08	–0.73	0.97
C2	186	1.56	1.68	–0.12	0.63
C3	200	1.24	0.81	0.43	0.11
C4	214	1.59	0.54	1.05	0.00
C5	228	2.05	0.47	1.58	0.04
C7	256	2.04	–0.84	2.88	–0.22
1-AAC-5-FU					
C1	187	–0.52	0.57	–1.09	–0.68
C2	201	0.44	0.89	–0.44	–0.22
C3	215	1.09	0.95	0.14	–0.13
C4	229	1.39	0.71	0.68	–0.29
C8	285	1.67	–1.52[g]	3.19[f]	–1.22
7-ACOM-Th					
C1	252	0.44	1.29	–0.85	–0.24
C2	266	0.47	0.66	–0.20	–0.51
C3	280	1.40	1.02	0.38	0.03
C4	294	1.64	0.72	0.93	–0.23
C5	308	1.89	0.44	1.45	–0.33
6-ACOM-6-MP					
C1	224	0.03	0.86[c]	–0.83[f]	–0.69
C2	238	0.36	0.61[c]	–0.24[f]	–0.67
C3	252	0.52	0.31[c]	0.21[f]	–0.58
C4	266	0.62	–0.10[c]	0.73[f]	–0.66
C5	280	0.57	–0.62[c]	1.19[f]	–1.26
C7	308	0.62	–1.61[c]	2.23[f]	–1.88
6,9-ACOM-6-MP					
C1	296	0.72	0.46[c]	0.26[f]	–0.64
C2	324	1.53	0.22[c]	1.30[f]	–0.63
C3	352	1.96	–0.71[c]	2.66[f]	–0.85
C4	380	2.24	–1.33[c]	3.57[f]	–0.99
5-FU	130	–1.31	1.93[c]	–3.24[f]	–0.62
Th	180	–0.47	1.66[c]	–2.13[f]	–0.32

[a] C1, C2. . . 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 μmol cm^{-2} h^{-1}. [f]Calculated from $K_{IPM:AQ} = S_{IPM}/S_{AQ}$. [g]From ref. 33.

set, the changes in parameter estimates upon such omission for each of the 41 – 1 solutions were tabulated and analyzed. Likewise, to evaluate stability of each model with respect to omission of entire series, the changes in parameter estimates on each omission were obtained for each of the 7 – 1 solutions; that is, solutions to each of the seven possible sets of six series of compounds each omitting one series.

RESULTS AND DISCUSSION

Series/Parallel Model

When the experimental log J_M, MW, log S_{IPM}, and log S_{AQ} data in Table 1 for the 39 straight-chain alkyl group prodrugs and two of their parent drugs (5-FU and Th) were fit to the three-path series/parallel model (eq 14) to give the $n = 41$ solution, the parameter estimates were $a = 18.7 \pm 11.3$, $b = 1.83 \pm 0.29$, $c = 0.49 \pm 0.39$, $d = 0.024 \pm 0.016$, $\Phi = -.0074 \pm 0.0011$, and $r^2 = 0.942$. The value for the coefficient d (aqueous-only, path D) was very small, and the flux of most solutes through this path, calculated with these coefficients, was much <3% of their experimental flux (data not shown). However, 75% of 5-FU and 17% of Th flux could be attributed to the D path. In addition, ~5% of C1 1-ACOM-Th, C1 6-ACOM-6-MP, and C2 1-AOC-5-FU; ~7% of C1 1-AOC-5-FU and C2 1-ACOM-5-FU; and ~10% of C1 1-ACOM-5-FU flux could be attributed to the D path. All eight of these solutes exhibited low log $K_{IPM:AQ}$ values of <–0.8. Thus, the data are consistent with the existence of a very low capacity, aqueous-only path for solutes exhibiting low log $K_{IPM:AQ}$ values, which is similar in concept to the aqueous pore suggested to accommodate the permeation of polar solutes.[34] However, such a path is not necessary to adequately explain the data (vide infra). No attempt has been made to fit any data sets used to support the existence of an aqueous pore[34] to the series/parallel model because those data sets lacked the necessary S_{LIPID} and S_{AQ} values.

When the data in Table 1 were fit to the series/parallel model as before, but excluding path D (a two-path model), the parameter estimates for the $n = 41$ solution were $a = 37.8 \pm 17.9$, $b = 1.62 \pm 0.24$, $c = 0.90 \pm 0.62$, $\Phi = -0.0082 \pm 0.0010$, $r^2 = 0.937$. These coefficients were used to give calculated log J_M values (data not shown). The average error of fit (from $\Delta\log J_M$ values, Table 2) was only 0.119 ± 0.108 log units. The average $\Delta\log J_M$ for the eight solutes exhibiting log $K_{IPM:AQ}$ values <–0.8 was less than that of the whole data set: 0.11 ± 0.06 log units. Thus, the two-path series/parallel model adequately explains the data even for those solutes exhibiting low log $K_{IPM:AQ}$ values. In addition, the average error of prediction improved when the D path was omitted (vide infra). The $\Delta\log J_M$ values, the flux values for the parallel lipid–aqueous series path, J_A, the flux values for the parallel lipid-only path, J_C, and the ratios J_A/J_C for this two-path model are given in Table 2.

The data in Table 2 show that the greatest flux generated from members in each series of prodrugs through either path in the two-path series/parallel model is through the lipid–aqueous series path. For some series of prodrugs, the flux through the lipid-only path can be quite high for some of the more lipophilic members of the series, but even then the flux generated by some of the more hydrophilic members of the series was much higher through the lipid–aqueous series path where hydrophilicity as well as lipophilicity are important. For example, the flux of total 5-FU species generated by the C6 1-AOC-5-FU prodrug through the lipid-only path is 1.043 μmol cm^{-2} h^{-1}, which is >5 times the total flux generated by the application of 5-FU itself under the same conditions and >2 times that generated through the lipid–aqueous series path by C6 1-AOC-5-FU. However, in the 1-AOC-5-FU series, the flux of total 5-FU species generated by the C2 1-AOC-5-FU prodrug through the lipid–aqueous series path is 7.009 μmol cm^{-2} h^{-1}, which is >28 times the total flux generated by the application of 5-FU and >7 times the flux generated through the lipid-only path by the C2 1-AOC-5-FU prodrug. Thus, the lipid–aqueous series path A has a much greater potential carrying capacity for solute than does the lipid-only path C in the two-path series/parallel model. The same qualitative result was observed for the three-path model as well.

When one solute at a time was omitted from the data set and the data in Table 1 were fit to the two-path series/parallel model as above, new values for *a, b, c,* and Φ were calculated (data not shown) from the data for the remaining solutes to give 41 – 1 solutions. Predicted values for J_M for the omitted solutes (data not shown) were then obtained using the new values for *a, b, c,* and Φ. The average error or residual for predicting log J_M (from $\Delta\log J_M'$ values, Table 2) was 0.134 ± 0.122 log units, which is somewhat smaller than the corresponding average $\Delta\log J_M'$ obtained us-

Table 2. Two-Path Series/Parallel Model: Flux through Lipid–Aqueous Series Path (J_A), Flux through Lipid-Only Path (J_C), the Ratio J_A/J_C, Average Error of Fit ($\Delta\text{Log } J_M$) to $n = 41$ Solution, and Average Error of Prediction ($\Delta\text{Log } J_M'$) from 41 – 1 Solutions

Compound	$\Delta\text{Log } J_M$[a]	J_A[a]	J_C[a]	J_A/J_C	$\Delta\text{Log } J_M'$[a]
1-ACOM-5-FU					
C1	0.07	2.40	0.06	37	0.08
C2	–0.10	4.65	0.15	31	–0.11
C3	–0.06	2.75	0.17	17	–0.06
C4	0.04	1.04	0.13	8.0	0.04
C5	0.25	0.21	0.10	2.1	0.27
C7	0.33	0.02	0.04	0.40	0.35
C9	0.17	0.00	0.01	0.03	0.20
1-AOC-5-FU					
C1	0.11	1.95	0.05	36	0.13
C2	–0.09	7.01	0.26	27	–0.10
C3	–0.17	3.15	0.23	14	–0.17
C4	–0.06	2.17	0.39	5.6	–0.06
C6	0.00	0.50	1.04	0.48	0.00
C8	0.27	0.01	0.15	0.08	0.30
1-AC-5-FU					
C1	–0.07	10.10	0.77	13	–0.07
C2	–0.14	4.96	0.97	5.1	–0.15
C3	0.09	0.70	0.35	2.0	0.10
C4	0.00	0.38	0.61	0.62	0.00
C5	–0.18	0.31	1.35	0.23	–0.22
C7	–0.12	0.01	0.78	0.02	–0.15
1-AAC-5-FU					
C1	0.03	0.19	0.01	24	0.03
C2	–0.06	0.64	0.06	12	–0.07
C3	–0.16	0.88	0.19	4.6	–0.17
C4	–0.20	0.52	0.29	1.8	–0.21
C8	–0.51	0.00	0.19	0.02	–0.59
7-ACOM-Th					
C1	–0.04	0.61	0.02	29	–0.04
C2	0.02	0.28	0.02	16	0.02
C3	0.05	0.84	0.11	7.4	0.05
C4	–0.01	0.46	0.15	3.0	–0.01
C5	0.01	0.25	0.21	1.2	0.02
6-ACOM-6-MP					
C1	–0.23	0.33	0.01	24	–0.25
C2	–0.17	0.29	0.02	13	–0.18
C3	0.12	0.17	0.03	6.9	0.13
C4	0.35	0.07	0.02	3.0	0.38
C5	0.15	0.02	0.02	1.4	0.15
C7	0.00	0.00	0.01	0.20	0.00
6,9-ACOM-6-MP					
C1	0.02	0.20	0.02	11	0.02
C2	0.05	0.14	0.07	2.2	0.05
C3	0.07	0.02	0.10	0.16	0.08
C4	–0.07	0.00	0.12	0.03	–0.12
5-FU	0.17	0.16	0.00	42	0.26
Th	0.07	0.40	0.01	39	0.09

[a] Units of μmol cm^{-2} h^{-1}.

ing the three-path model (0.143 ± 0.151 log units). Moreover, the standard deviation (SD) values for the coefficients for the 41 – 1 solutions were small (a = 37.7 ± 2.6, b = 1.62 ± 0.05, c = 0.90 ± 0.10, and Φ = –0.0082 ± 0.0001), which gives confidence that the log J_M values for additional members of these series of prodrugs could be accurately predicted using this model.

Similarly, when one series of prodrugs at a time was omitted from the data set and the data in Table 1 were fit to the two-path series/parallel model as before, new values for *a, b, c,* and Φ were calculated (data not shown) from the data for the remaining series to give 7 – 1 solutions. The SD values for the coefficients for the 7 – 1 solutions were small (a = 41.0 ± 0.76, b = 1.61 ± 0.10, c = 1.04 ± 0.44 and Φ = –0.0083 ± 0.0004), which gives confidence that the log J_M values for additional series of prodrugs of 5-FU, Th, and 6-MP could be accurately predicted using this model.

Using the two-path series/parallel model (and the other models discussed later), the member of each series giving the highest flux was correctly identified except in the 6-ACOM-6-MP series. The member of that series giving the highest flux was also not correctly identified by the transformed Potts–Guy model.[19] This result has been attributed to the fact that the experimental fluxes from the first four members of the series are not statistically different from each other.[19]

Solvatochromic Series/Parallel Model

When the data in Table 1 were fit to the three-path solvatochromic series/parallel model (eq 20) to give the n = 41 solution, a value of 0.0000 was obtained for coefficient d. Thus, regression showed that no flux should occur through the parallel aqueous-only path D. This result is different from that for the three-path series/parallel model (eq 14) where the possibility of a low-capacity, aqueous-only path was observed for solutes exhibiting low values of log $K_{IPM:AQ}$. Fit of the data to a two-path solvatochromic series/parallel model n = 41 solution gave parameter estimates for X_i, *b, c/a,* and η; that were identical to those obtained for the three-path model: b = 1.41 ± 0.35, c/a = 0.100 ± 0.064; η = –0.0136 ± 0.0028, r^2 = 0.967. Parameter estimates for X_i for each series, calculated flux values for the parallel lipid–aqueous series path, J_A, for the parallel lipid-only path, J_C, and the ratios J_A/J_C are also given in Table 3. The average error of fit (from Δlog J_M values, Table 3) was only 0.093 ± 0.070 log units. The ratio J_A/J_C declined steadily in each series as the length of the alkyl chain increased and as $K_{IPM:AQ}$ increased in each series as in the series/parallel model. A plot of experimental log $K_{IPM:AQ}$ versus the log ratio J_A/J_C is shown in Figure 1. At that point where flux through the series path is predicted to be equal to flux through the lipid-only path, log $K_{IPM:AQ}$ is ~1. Compounds with log $K_{IPM:AQ}$ $\lesssim$0.8 are delivered mostly through the lipid–aqueous series path, but compounds with log $K_{IPM:AQ}$ >1.0 are delivered mostly through the lipid-only path. However, as in the two-path series/parallel model, the lipid–aqueous series path A in the two-path solvatochromic series/parallel model has a much greater potential carrying capacity for solute than the lipid-only path C. The obvious difference in a comparison of the two models in Tables 2 and 3, respectively, is that flux through path C is generally greater and hence ratios J_A/J_C are smaller in the latter model. This result is expected because the more realistic treatment of S_{LIPID} in the solvatochromic model will give a somewhat more polar phase than that represented by S_{IPM}.

When regression on the n = 41 data set was performed, parameter estimates for individual X_i were obtained for each of the prodrug series, for 5-FU, and for Th simultaneously, where X_i for 5-FU and Th were defined as X1 – (X7 – X6) and X5 – (X7 – X6), respectively. For example, the X_i value for 5-FU was obtained from the X_i value for the 1-ACOM-5-FU series (X1) minus the X_i value for an ACOM group, which in turn was obtained from the X_i value for 6,9-ACOM-6-MP (X7) minus the X_i value for 6-ACOM-6-MP (X6). Notice that X7 – X6 gives an X_i value for an ACOM group attached to a nitrogen. A similar indirect calculation of X_i for 6-MP is not possible from the X_i values for the various series that are available because they all contain a masked acidic SH group instead of the necessary masked acidic NH group from the N=C–SH $\leftrightharpoons$ HN–C=S tautomeric forms that contribute to the structure of 6-MP. To calculate the X_i value for 6-MP, solubility and flux data for the 1-ACOM-6-MP series, where the ACOM group is attached to the nitrogen in HN–C=S, would be necessary. Similarly, no X_i value for the 1-pivaloyloxymethyl-5-FU prodrug, analyzed in the previous study of this data set,[19] could be calculated because solubility and flux data for a homologous series of similar branched chain alkyl prodrugs are not available. Thus, the data set studied here was limited to n = 41 instead of the n = 43 data set previously studied.

Table 3. Solvatochromic Series/Parallel Model: Flux through Lipid–Aqueous Series Path (J_A), Flux through Lipid-Only Path (J_C), the Ratio of J_A/J_C, Average Error of Fit (ΔLog J_M) to $n = 41$ Solution, and Average Error of Prediction (ΔLog J_M') from 41 – 1 Solutions

Compound	X_i	ΔLog J_M[a]	J_A[a]	J_C[a]	J_A/J_C	ΔLog J_M'[a]
1-ACOM-5-FU	2.756					
C1		–0.04	2.829	0.337	8.41	–0.06
C2		–0.14	4.616	0.648	7.12	–0.17
C3		–0.07	2.406	0.613	3.93	–0.08
C4		0.00	0.879	0.406	2.16	0.00
C5		0.10	0.181	0.260	0.70	0.12
C7		0.13	0.014	0.074	0.19	0.17
C9		0.06	0.000	0.013	0.02	0.10
1-AOC-5-FU	2.569					
C1		0.10	1.842	0.220	8.37	0.15
C2		–0.05	5.806	0.873	6.65	–0.07
C3		–0.14	2.512	0.653	3.85	–0.16
C4		–0.08	1.769	0.937	1.89	–0.10
C6		–0.15	0.431	1.769	0.24	–0.22
C8		0.20	0.011	0.174	0.06	0.31
1-AC-5-FU	2.141					
C1		0.06	6.706	1.404	4.78	0.07
C2		–0.08	3.701	1.491	2.48	–0.10
C3		0.10	0.565	0.460	1.23	0.11
C4		0.01	0.318	0.668	0.48	0.01
C5		–0.14	0.269	1.238	0.22	–0.19
C7		0.06	0.013	0.506	0.03	0.11
1-AAC-5-FU	2.173					
C1		0.28	0.096	0.013	7.49	0.42
C2		0.11	0.384	0.077	5.00	0.14
C3		–0.05	0.618	0.221	2.80	–0.06
C4		–0.13	0.408	0.282	1.45	–0.16
C8		–0.20	0.003	0.093	0.03	–0.41
7-ACOM-Th	2.839					
C1		0.00	0.507	0.072	7.08	0.00
C2		0.06	0.220	0.049	4.48	0.07
C3		0.05	0.671	0.275	2.44	0.06
C4		–0.06	0.377	0.307	1.23	–0.08
C5		–0.08	0.210	0.351	0.60	–0.10
6-ACOM-6-MP	2.672					
C1		–0.20	0.271	0.045	5.99	–0.23
C2		–0.14	0.232	0.063	3.69	–0.16
C3		0.13	0.137	0.058	2.36	0.15
C4		0.31	0.060	0.048	1.25	0.35
C5		0.07	0.019	0.027	0.69	0.09
C7		–0.04	0.002	0.013	0.15	–0.07
6,9-ACOM-6-MP	2.952					
C1		0.06	0.155	0.045	3.47	0.07
C2		–0.01	0.118	0.118	1.00	–0.01
C3		–0.02	0.015	0.133	0.11	–0.04
C4		–0.03	0.003	0.106	0.03	–0.05
5-FU	2.476	–0.06	0.246	0.025	9.77	–0.13
Th	2.559	0.03	0.404	0.044	9.17	0.06

[a] Units of μmol cm^{-2} h^{-1}.

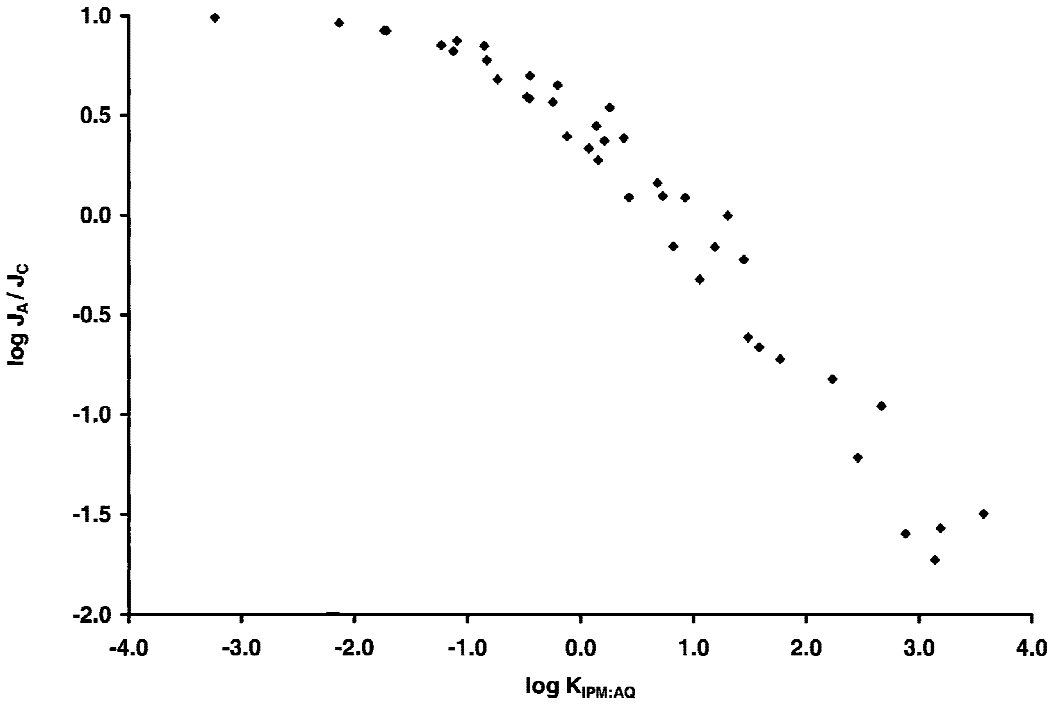

Figure 1. Plot of log $K_{IPM:AQ}$ versus log ratio J_A/J_C for the two-path solvatochromic series/parallel model.

When one prodrug at a time was omitted from the data set to give 41 – 1 solutions of fit to the two-path solvatochromic series/parallel model, values for X_i, *b, c/a,* and η were generated for each omitted solute (data not shown). The average for the X_i parameter estimates for the members in each series was only slightly different from the X_i parameter estimates for that series given in Table 3 for the $n = 41$ solution: <1% variation for X_i except for X4 = 4%. The values for the other parameter estimates for each solute varied at most 11% from the $n = 41$ solution and most varied <5%. This result gives confidence that if an additional prodrug was added to the series, X_i would not change substantially and that its log J_M value could be accurately predicted using this model. The average error for predicting log J_M (from Δlog J_M' values, Table 3) was 0.127 ± 0.101 log units. The largest average Δlog J_M' is for the 1-AAC-5-FU series and the smallest is for the 6,9-ACOM-6-MP series. A plot of experimental log J_M versus predicted log J_M is shown in Figure 2.

When one series of prodrugs at a time was omitted from the data set to give 7 – 1 solutions of fit to the two-path solvatochromic series/parallel model, values for X_i, *b, c/a,* and η were generated for each omitted series. Those values and those for the $n = 41$ solution are given in Table 4. The average of the parameter estimate for 7 – 1 solutions are very close to the parameter estimates for the $n = 41$ solution (<6% variation in X_i), which gives confidence that the addition of another series to the data set would not significantly change the $n = 41$ parameter estimates for *b, c/a,* and η. Finally, the values for X_i for individual series relative to each other were consistent. This consistency can be seen in Table 5, which shows the results of subtracting X1 from each of the other X_i values. Even though the absolute values of X_i for omitting the 1-AAC-5-FU series are significantly lower than the average X_i for all 6 sets of series in Table 4, the differences between X1 and the other X_i values in Table 5 are stable (< 0.03 log units SD) except for X7 – X1, where the SD is 0.08 log units.

Solvatochromic Model

When the data in Table 1 were fit to the solvatochromic model (eq 25) to give the $n = 41$ solution, values for X_i' and η′ were generated which are given in Table 6. The values for X1′ . . . X7′ in Table 6 for the $n = 41$ solution are quite a bit larger than the comparable values for the fit of the data to eq 20 given in Table 3. This difference is because, when using the solvatochromic equa-

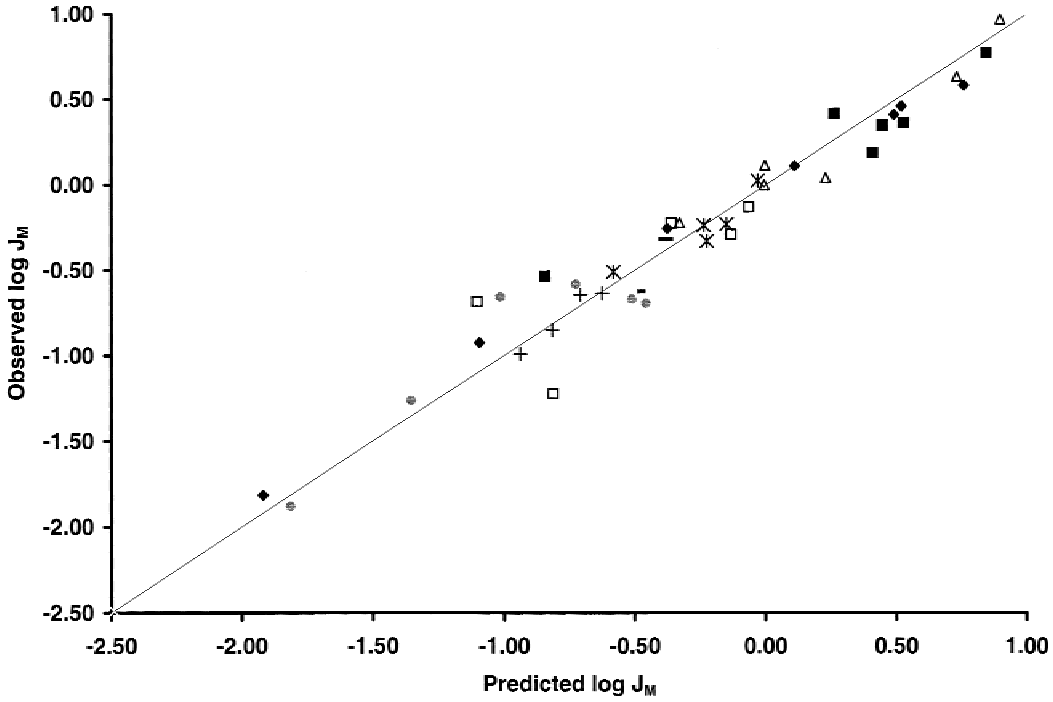

Figure 2. Plot of observed log J_M for 39 prodrugs, Th, and 5-FU versus predicted log J_M from 41 – 1 solutions to eq 20, the two-path solvatochromic series/parallel model: 1-ACOM-5-FU (◇), 1-AOC-5-FU (■), 1-AC-5-FU (△), 1-AAC-5-FU (□), 7-ACOM-Th (*), 6-ACOM-6-MP (●), 6,9-ACOM-6-MP (+), Th and 5-FU (–).

tion to model flux, the ability of the skin to solvate a solute depends on the interaction of the solute with only one hypothetical phase, whereas in the two-path solvatochromic series/parallel model, it depends on the interaction of the solute with two hypothetical phases of dissimilar solubilizing abilities (lipid and aqueous), only one of which (the lipid phase) is characterized by the solvatochromic equation and by the solvatochromic descriptors. Thus, the solvatochromic descriptors used in the solvatochromic model describe the interaction of a solute with a phase that is a blend

Table 4. Solvatochromic Series/Parallel Model: Parameter Estimates for $n = 41$ Solution to Two-Path Version of Model and Parameter Estimates for 7 – 1 Solutions Omitting One Series at a Time

	Data Set									
Parameter	X1	X2	X3	X4	X5	X6	X7	b	c/a	η
$n = 41$	2.76	2.57	2.14	2.17	2.84	2.67	2.95	1.41	0.100	–0.0136
Standard error	0.57	0.53	0.43	0.53	0.68	0.59	0.79	0.35	0.064	0.0028
Series omitted from $n = 41$										
1-ACOM-5-FU + 5-FU	n/a	2.76	2.34	2.35	3.02	2.91	3.21	1.29	0.080	–0.0140
1-AOC-5-FU	2.84	n/a	2.19	2.25	2.94	2.75	3.06	1.58	0.115	–0.0141
1-AC-5-FU	2.91	2.71	n/a	2.31	3.02	2.84	3.17	1.33	0.121	–0.0144
1-AAC-5-FU	2.46	2.29	1.87	n/a	2.51	2.36	2.52	1.56	0.104	–0.0125
7-ACOM-Th + Th	2.85	2.65	2.20	2.26	n/a	2.76	3.09	1.39	0.120	–0.0141
6-ACOM-6-MP + 5-FU + Th	2.79	2.59	2.20	2.19	2.84	n/a	2.95	1.23	0.076	–0.0133
6,9-ACOM-6-MP + 5-FU + Th	3.05	2.82	2.36	2.42	3.16	3.00	n/a	1.16	0.124	–0.0148
Average of sets omitting one series	2.82	2.64	2.19	2.30	2.92	2.77	3.00	1.36	0.106	–0.0139
SD	0.20	0.19	0.18	0.09	0.22	0.22	0.25	0.16	0.020	0.0008

Table 5. Solvatochromic Series/Parallel Model: Relative Differences in Estimates of Solvatochromic Terms for Each of Six Series Relative to 1-ACOM-5-FU Series, Using Two-Path Version of Model and Omitting One Series at a Time

	Data Set					
Parameter	X2–X1[a]	X3–X1[a]	X4–X1[a]	X5–X1[a]	X6–X1[a]	X7–X1[a]
Series omitted from $n = 41$						
1-AOC-5-FU	n/a	–0.65	–0.59	0.10	–0.09	0.22
1-AC-5-FU	–0.20	n/a	–0.60	0.11	–0.07	0.26
1-AAC-5-FU	–0.17	–0.59	n/a	0.05	–0.10	0.06
7-ACOM-Th + Th	–0.20	–0.65	–0.60	n/a	–0.09	0.23
6-ACOM-6-MP + 5-FU + Th	–0.20	–0.60	–0.60	0.05	n/a	0.16
6,9-ACOM-6-MP + 5-FU + Th	–0.23	–0.69	–0.63	0.11	–0.05	n/a
Average of sets omitting one series	–0.20	–0.64	–0.60	0.08	–0.08	0.19
SD	0.02	0.02	0.01	0.03	0.02	0.08

[a] Values for X1 . . . X7 from Table 4.

of properties, whereas in the two-path solvatochromic series/parallel model, they describe an interaction with a phase that can be more purely lipoidal.

When one prodrug at a time was omitted from the data set to give 41 – 1 solutions of fit to the solvatochromic model, values for X_i' and η' were generated for each omitted solute (data not shown). The average for the X_i' and η' parameter estimates for the 41 – 1 solutions are identical with the $n = 41$ parameter estimates given in Table 6, and the SD are smaller. The average error for predicting log J_M (average $\Delta\log J_M'$) was significantly larger using the solvatochromic model (eq 25) than using the two-path solvatochromic series/parallel model (eq 14): average $\Delta\log J_M' = 0.150$ and 0.127 log units, respectively. When one series of prodrugs at a time was omitted from the data set to give 7 – 1 solutions of fit to the solvatochromic model, values for X_i' and η' were generated for each omitted series and are given in Table 6. The variation in X_i' as the individual series were omitted was <5% of the average value of X_i' for the $n = 41$ solution.

Transformed Potts–Guy Model

To obtain a better comparison between the two-path solvatochromic series/parallel model and the

Table 6. Solvatochromic Model: Parameter Estimates for $n = 41$ Solution to Model Compared with Parameter Estimates for 7 – 1 Solutions Omitting One Series At a Time

	Data Set							
Parameter	X1′	X2′	X3′	X4′	X5′	X6′	X7′	η'
$n = 41$	4.62	4.26	3.46	3.85	5.06	4.63	5.44	–0.0231
Standard error	0.21	0.20	0.18	0.19	0.24	0.22	0.29	0.0008
Series omitted from $n = 41$								
1-ACOM-5-FU + 5-FU	n/a	4.44	3.62	4.02	5.27	4.84	5.69	–0.0239
1-AOC-5-FU	4.60	n/a	3.45	3.84	5.05	4.62	5.42	–0.0231
1-AC-5-FU	4.63	4.27	n/a	3.86	5.08	4.64	5.46	–0.0232
1-AAC-5-FU	4.43	4.09	3.31	n/a	4.86	4.44	5.18	–0.0224
7-ACOM-Th + Th	4.54	4.19	3.40	3.78	n/a	4.54	5.35	–0.0228
6-ACOM-6-MP + 5-FU + Th	4.74	4.36	3.55	3.94	5.17	n/a	5.57	–0.0235
6,9-ACOM-6-MP + 5-FU + Th	4.68	4.31	3.50	3.89	5.11	4.69	n/a	–0.0233
Average of sets omitting one series	4.60	4.28	3.47	3.89	5.09	4.63	5.45	–0.0232
SD	0.11	0.12	0.11	0.09	0.14	0.14	0.18	0.0005

transformed Potts–Guy model that had previously been used to analyze this data,[19] one compound at a time was omitted from the $n = 41$ data set, and 41 – 1 solutions to eq 26 were generated. The average $\Delta\log J_M'$ was 0.134 log units, which is identical to the value previously obtained from the $n = 39$ set (solution 1)[19] after averaging in the $\Delta\log J_M'$ for 5-FU and Th.

CONCLUSIONS

Results from the fit of the flux data from seven series of prodrugs to the series/parallel models, where permeation was allowed to follow combinations of three parallel paths (a lipid-only, aqueous-only, and a lipid–aqueous series), suggest that little, if any, permeation follows the aqueous-only path even though the possibility of such a path is explicitly allowed. These results support the contention of Potts and Guy[16] and Abraham et al.[17] that the extent of flux of small, hydrophilic solutes does not have to be explained by an "aqueous pore" path; that is, that the inclusion of a term for the effect of molecular weight on flux (or permeability) can account for the differences in permeability coefficients of groups of molecules of dissimilar size.[14,16,17] On the other hand, the observation that for a homologous series of more lipophilic prodrugs, which do not differ greatly in size, the largest flux is obtained from the more water-soluble members of the series[35] strongly suggests that some dependence of flux on water solubility exists. In the series/parallel models, these seemingly contradictory conclusions can be accommodated by the extent of flux through the lipid–aqueous series path. No aqueous-only path is necessary, the dependence of flux on water solubility results from the conductivity of the aqueous part of a series path, and the existence of lipid and aqueous phases in the lipid–aqueous series path more accurately reflects the complex nature of the barrier presented by the skin to permeation. This lipid–aqueous series path also has the potential to be a high-capacity path capable of carrying or conducting much more solute than the lipid-only path.

The results in Table 7 show r^2 and r^2 adjusted for number of parameters for fitting $\log J_M$, and average $\Delta\log J_M'$ obtained for predicting $\log J_M$ from the four models. For comparison, r^2 values for fitting $\log P$ using the same models are included. The two-path solvatochromic series/parallel model gives the best r^2 value regardless of whether values for flux or permeability coefficient are being compared. All four models give reasonably small errors in predicting $\log J_M$, but the two-path solvatochromic series/parallel model gives the smallest error. In that model, only four prodrugs gave predicted fluxes that were as much as twice or as little as half the experimental values, and the average was 34% variation, which is comparable to the average of the variation in the experimental flux values for individual compounds.

For dissimilar solutes, where the solvatochromic descriptors cannot be determined by regression analysis of a homologous series, the solvatochromic descriptors may not be available or it may be too time consuming to generate them for the constituent functional groups. Then, the two-path series/parallel model can still be employed to predict J_M, using S_{IPM} instead of $S_{IPM}\ 10^{k^{MW+\Omega i}}$ for S_{LIPID} in eq 14, and give reasonable results.

In addition, although the data set used in this analysis is comprised only of results from *in vitro*

Table 7. Comparison of the Four Models

Measure of Goodness of Fit	Two-Path Series/parallel	Two-Path Solvatochromic Series/Parallel	Solvatochromic	Transformed Potts–Guy
$n = 41$ solution for $\log J_M$				
r^2	0.937	0.967	0.950	0.944
Adjusted[a] r^2	0.932	0.957	0.940	0.941
Average $\Delta\log J_M$	0.119	0.093	0.107	0.124
Predicting $\log J_M$ from 41 – 1 solutions				
Average $\Delta\log J_M'$	0.134	0.127	0.150	0.134
$n = 41$ solution for $\log P$				
r^2	0.967	0.983	0.974	0.971

[a] Adjusted $r^2 = 1 - (1 - r^2)\,(n - 1)/(n - p)$, where p is the number of parameters.

experiments using hairless mouse skin, the two-path series/parallel model can also be used to analyze data from *in vivo* experiments using human skin. Fit of the *in vivo* human skin permeation data from Wenkers and Lippold[36] to eq 14 gave $r^2 = 0.918$ versus $r^2 = 0.934$ using the transformed Potts–Guy model.[37] Thus, the two-path series/parallel model works well regardless of whether the data is *in vitro* or *in vivo*, hairless mouse skin or human skin.

Finally, although the transformed Potts–Guy model[19] does a reasonably adequate job of predicting log J_M without having to incorporate the solvatochromic equation or parallel paths, it does not give a significantly better fit to this data than does the two-path series/parallel model (Table 7). However, for solutes exhibiting markedly different physicochemical properties (such as $K_{IPM:AQ}$ and MW) than those studied here, the transformed Potts–Guy model should give substantially different predictions than series/parallel models regardless of whether the solvatochromic equation is used to predict S_{LIPID} from S_{IPM} because the latter allows a lipid-only path. Further research should be done to determine the flux of such solutes and to determine if series/parallel models are the best predictor of their fluxes.

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