Topical Delivery of 5-Fluorouracil and 6-Mercaptopurine by Their Alkylcarbonyloxymethyl Prodrugs from Water: Vehicle Effects on Design of Prodrugs

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Purpose. To determine whether the fluxes through hairless mouse skin for three homologous series of prodrugs of 5-fluorouracil (5-FU, **1**) and 6-mercaptopurine (6-MP, **2**) from saturated aqueous suspensions show dependencies on aqueous (S_{AQ}) and isopropyl myristate (S_{IPM}) solubilities similar to those shown by the identical compounds delivered from IPM.

Methods. Flux through hairless mouse skin from water (J_{MAQ}) and solubility data were measured for a homologous series of six 3-alkylcarbonyloxymethyl (ACOM) prodrugs of 5-FU (3-ACOM-5-FU), and five 6-ACOM-6-MP prodrugs, then combined with literature data for five bis-6,9-ACOM-6-MP prodrugs to give a data base. Multiple linear regression using SPSS 7.5 was performed on log S_{IPM}, log S_{AQ}, molecular weight and log J_{MAQ} data to determine the best fit coefficients to the transformed Potts-Guy equation: log J_{MAQ} = x + y log S_{IPM} + (1 – y) log S_{AQ} + z MW. Permeability coefficients (P_{MAQ}) were calculated from J_{MAQ}/S_{AQ}.

Results. The best fit coefficients for the flux from AQ(J_{MAQ})were x = –1.497, y = 0.660 and z = –0.00469 (r^2 = 0.765) with an average error of prediction equal to 0.193 log units. The best fit coefficients for the flux from IPM (J_{MIPM}) were x = –0.557, y = 0.536 and z = –0.00261 (r^2 = 0.941) with an average error of prediction equal to 0.109 log units. For all three series, log P_{MAQ} increased whereas log P_{MIPM} decreased with increasing alkyl chain lengths in the promoiety and with decreasing solubility parameter values.

Conclusions. The transformed Potts-Guy equation can be used to predict J_{MAQ} but with less certainty than J_{MIPM}. S_{IPM} and S_{AQ} have consistently been shown to have a positive influence on J_{MIPM}, and now on J_{MAQ}, with a balance between the two solubilities being obviously important. The previous observation that log P_{MAQ} increased with lipophilicity is an artifact of normalizing J_{MAQ} by S_{AQ}.

KEY WORDS: water solubility; lipid solubility; diffusion cell experiments; transformed Potts–Guy equation; flux; prodrugs.

INTRODUCTION

The effect of vehicles on the delivery of drugs is an important consideration in the design of topical formulations. Befitting this importance, there are numerous books and reviews written on the effect of vehicles and various excipients, such as penetration enhancers, on topical delivery (1,2). However, there are only a few articles comparing the effect of vehicles on the topical delivery of parent drugs by their prodrugs (3,4), and no reviews. Waranis and Sloan (3) examined the effect of a wide variety of single component vehicles on the delivery of total 6-mercaptopurine (6-MP) species by a homologous series of its bis-6,9-alkylcarbonyloxymethyl-6-MP prodrugs (bis-6,9-ACOM-6-MP) through hairless mouse skin *in vitro*. For each combination of prodrugs with a specific vehicle, the most effective prodrugs at enhancing the delivery of 6-MP species were the more water as well as more lipid soluble acetyl- and propionyloxymethyl (C1 and C2) prodrugs regardless of whether the vehicle was polar and protic (H_2O and propylene glycol), lipophilic and protic (octanol) or lipophilic and aprotic (IPM).

Recently a series of articles by Roberts and Sloan (5,6) reported equations where both lipid and aqueous solubilities were parameters for predicting the delivery of parent drugs by homologous series of prodrugs from a lipid vehicle (isopropyl myristate, IPM) through hairless mouse skin *in vitro*. In the first article (5), a transformation of the Potts and Guy equation (7) was fit to the solubilities of the prodrugs in IPM (log S_{IPM}), their estimated solubilities in pH 4.0 buffer (log S_{AQ}), their molecular weights (MW) and their fluxes (log J_{MIPM}): $\log J_{MIPM} = x + y \log S_{IPM} + (1 - y) \log S_{AQ} - z\,MW$ (Eq. 1). The coefficients for the log S_{IPM} and log S_{AQ} parameters were 0.534 and 0.466, respectively. Data from Wenkers and Lippold (8) for the *in vivo* fluxes of 10 NSAID from mineral oil (MO) through human skin was also fit to the transformed Potts and Guy equation (9): the coefficients and the parameters for solubilities were 0.722 log S_{MO} and 0.278 log S_{AQ}. Thus, delivery from lipid vehicles by series of prodrugs or unrelated drugs, whether *in vitro* or *in vivo*, through hairless mouse skin or human skin are positively dependent on the lipid and aqueous solubilities of the permeants.

It is clear that to design prodrugs that are optimally effective at enhancing the topical delivery of their parent drugs from a lipid vehicle, it is necessary to design the promoiety so that it will optimize the lipid and aqueous solubilities of the prodrugs. A robust model incorporating both lipid and aqueous solubilities as parameters in an equation to predict delivery through hairless mouse skin *in vitro* from a lipid vehicle has been established (5). However, although there are flux data to suggest that the same design considerations should be applied to optimizing topical delivery from an aqueous vehicle, the database is too small to support a model, and an equation from which to derive any conclusions (3). As the first step in developing that data base and a subsequent model, we report here the rates of delivery of total 5-FU and 6-MP species from water through hairless mouse skin *in vitro* using a type of prodrug that is relatively stable in water: the 3- and 6-alkylcarbonyloxymethyl (ACOM) prodrugs, respectively. These results have been combined with previous results, also using an ACOM type prodrug (3), to give a sufficiently large data base that a reasonable fit of the data to the transformed Potts and Guy equation for a polar vehicle (5) has been obtained using multiple regression analysis. Finally, the rates of delivery of 5-FU and 6-MP species by their ACOM prodrugs from water and their dependencies on S_{AQ} and S_{IPM} have been compared to similar data generated when they were delivered from IPM.

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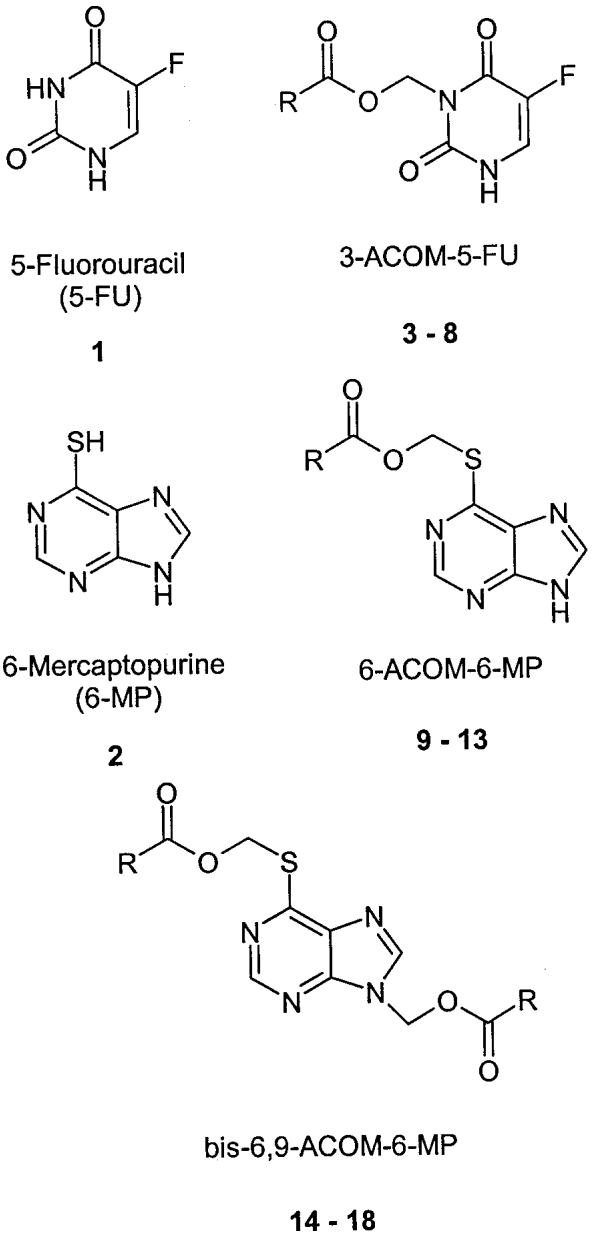
MATERIALS AND METHODS

Melting points were determined with a Meltemp capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 90 MHz on a Varian EM-390 spectrometer. Ultraviolet (UV) spectra were obtained on a Shimadzu UV-265 spectrophotometer. The diffusion cells were from Crown Glass, Somerville, NJ, USA (surface area 4.9 cm^2, 20 mL receptor phase volume). The diffusion cells were maintained at 32°C with a Fisher circulating water bath model 25. TLC were run on Brinkman Polygram Sil G UV 254 plates. IPM was obtained from Givaudan (Clifton, NJ, USA). Theophylline (Th), 5-fluorouracil (5-FU, **1**), and 6-mercaptopurine (6-MP, **2**) were purchased form Sigma Chemical Co.; acid chlorides and all other reagent chemicals for the synthesis of the prodrugs were from Aldrich Chemical Co.; all other solvents were from Fisher. The female hairless mice (25–30 g, 12–16 weeks old, SKH-hr-1) were from Charles River. The animal research adhered to the "Principles of Laboratory Animal Care." The 3-ACOM-5-FU prodrugs (**3** to **8;** Ref. 10) and 6-ACOM-6-MP prodrugs (**9** to **13;** Ref. 4; see Scheme 1) were synthesized as previously described, and were identical with the prodrugs described in the literature by ^{1}H NMR, TLC, and mp.



Scheme 1.

Solubilities

The directly measured IPM solubilities (S_{IPM}) were taken from the literature for the 3-ACOM-5-FU prodrugs (**3** to **8**). The directly measured S_{IPM} and solubilities in water were taken from the literature for the 6-ACOM-6-MP (**9** to **13**; Ref. 4) and bis-6,9-ACOM-6-MP (**14** to **18**) prodrugs (3). The water solubility for **18** had not been previously reported but was extrapolated from data from the other members of the series.

Direct solubilities in water were measured for **3** to **8**, as previously described (11), by stirring suspensions of **3** to **8** in water at 22 ± 1°C for 60 min, which is the same length of time that suspensions of **3** to **8** and **9** to **13** in water were stirred before they were applied in the diffusion cell experiments. The suspensions were filtered through 0.45-μm nylon filters. The saturated solutions of **3** to **8** were diluted with acetonitrile and quantitated by UV spectrophotometry from their absorbances at 267 nm using their molar absorptivities (ε) in acetonitrile as previously determined (ε = 7153 L mol^{-1}; Ref. 10).

Analysis and Stability

Intact 3-ACOM-5-FU and 5-FU in the receptor phase samples were quantitated by UV, as previously described (12), at 300 and 271 nm, where the molar absorptivities (ε) in the pH 7.1 phosphate buffer containing 0.11% formaldehyde were 476 and 6,570 L mol^{-1}, respectively, for 5-FU and 1,370 and 6,570 L mol^{-1}, respectively, for the 3-ACOM-5-FU prodrugs. The absorbance at 271 nm, the isobestic point for mixtures of 5-FU and its prodrugs, was used to measure the concentrations of total 5-FU species; and a calibration curve, based on the absorbances at 300 nm relative to the absorbances at 271 nm of 10 different ratios of concentrations of 5-FU to its prodrugs, was used to measure the concentrations of intact prodrug at 300 nm. Intact 6-ACOM-6-MP and 6-MP in the receptor phase samples were quantitated by UV spectrophotometry at 321 and 276 nm, where the molar absorptivities (ε) in the pH 7.1 phosphate buffer containing 0.11% formaldehyde were 19,400 and 2,720 L mol^{-1}, respectively, for 6-MP, and were zero and 17,000 L mol^{-1}, respectively, for the 6-ACOM-6-MP prodrugs (4). The absorbance at 321 nm gave the concentration of 6-MP and the total absorbance at 276 nm minus the absorbance at 276 nm because of 6-MP (14% of the absorbance of 6-MP at 321 nm; 2,720/19,400) gave the concentration of the 6-ACOM-6-MP prodrug. The concentrations of both species were combined to give concentrations of total 6-MP species.

Theophylline in the receptor phase samples was quantitated by UV spectrophotometry from its absorbance at 270 nm (ε = 10,020 L mol^{-1}) in pH 7.1 phosphate buffer containing 0.11% formaldehyde.

Donor phases of the prodrugs were analyzed in two ways for stability of the prodrugs. They were filtered and only the

residues were analyzed by mp and ^{1}H NMR spectroscopy, or the entire donor phases were allowed to evaporate in a hood and those residues were analyzed by mp and ^{1}H NMR spectroscopy in DMSO-d_6. For the 3-ACOM-5-FU prodrugs, the absorptions for C^6–*H* were at δ 7.89 for the prodrugs and at δ 7.67 for 5-FU. For the 6-ACOM-6-MP prodrugs, the absorptions for C^2–*H* and C^8–*H* were at δ 8.82 and δ 8.56 for the prodrugs and at δ 8.47 and δ 8.28 for 6-MP.

Diffusion Cell Experiments

The diffusion cell experiments were run in essentially the same way as previously described (13). Briefly, female hairless mice were sacrificed by cervical dislocation. Their skins were removed by blunt dissection and placed epidermal side up in contact with pH 7.1 phosphate buffer (0.05 M, I = 0.11 M, 32°C) containing 0.11% formaldehyde (2.7 mL of 36% aqueous formaldehyde/liter) to prevent microbial growth and to insure the integrity of the mouse skins during the course of the experiment (14). The skins were kept in contact with the buffer for at least 48 h to condition the skins and to allow UV absorbing materials to leach out of the skins; the receptor phases were changed at least three times during this time to facilitate the leaching process. In control experiments, there were no significant differences among the fluxes of a standard solute (theophylline, Th) applied in a standard vehicle (propylene glycol, PG) after 4, 24, 48, or 120 h of contact between the skins and the buffer containing 0.11% formaldehyde (14).

Aliquots (1.0 mL, 0.05–0.40 M) of suspensions of each 3-ACOM-5-FU or 6-ACOM-6-MP prodrug in water were applied to the donor side of each of three diffusion cells and immediately sealed with parafilm. The water suspensions had been stirred for 1 h before they were applied. The first donor phase was removed after 24 h (72 total h) and a second donor phase (1.0 mL) was applied for another 24 h (48 h of initial application, 96 total h), and then removed. The water suspensions for the second donor phase had also been stirred for 1 h before they were applied. Both donor phases were saved, and the solid residues were separated by filtration or the entire donor phases were allowed to evaporate, then all residues were analyzed by ^{1}H NMR spectroscopy as above.

After the donor phase suspensions were applied, 3-mL samples of the receptor phases were removed, generally at 8, 24, 27, 30, 33, 36, 39, and 48 h. The entire receptor phase was replaced with fresh receptor fluid each time a sample was removed to maintain sink conditions. The amount of 5-FU and its prodrug or of 6-MP and its prodrug in each sample at 27, 30, 33, 36, 39, and 48 h were determined immediately by UV spectrophotometry using the conditions described above to give "initial flux" values, J_{MAQ}, as below.

After the initial application period of 48 h (96 total h), the donor surfaces were quickly washed with 3 × 2-mL portions of methanol to remove any residual prodrug, 5-FU, or 6-MP. After the methanol wash, the skins were kept in contact with fresh receptor fluid for 23–24 h to allow any 5-FU and its prodrugs or 6-MP and its prodrugs to leach out. Samples of the receptor phases were removed and analyzed for total 5-FU or 6-MP species as above. The receptor phases were replaced with fresh receptor fluid, and 0.5 mL aliquots of standard drug/vehicle (Th/PG) suspensions were applied at 120 total h. Samples of the receptor phases (3 mL) from this second application were removed at 4, 8, 12, and 24 h and the amounts of theophylline in the receptor phases were quantitated by UV spectrophotometery as above to give "second flux" values, J_{JAQ}, as below. Each time a sample was removed the entire receptor phase was replaced with fresh receptor fluid.

In all cases the rates of delivery of total 5-FU or 6-MP species (J_{MAQ}) or theophylline (J_{JAQ}) through skin were determined by plotting the cumulative amount (μmol) of total 5-FU or 6-MP species or theophylline measured in the receptor phases against time and dividing the steady-state portions of those plots by the surface area of the diffusion cells. Permeability coefficients (P_{MAQ}) were determined by dividing the J_{MAQ} values by the solubilities of the prodrugs in water (S_{AQ}).

Solubility Parameters

The solubility parameters were obtained using the method of Fedors (15) as illustrated by Martin et al. (16) and Sloan et al. (13).

Statistical Analyses and Regression Analyses

Statistical analysis was accomplished using Student *t* test. Unless otherwise indicated, statistical significance is for $p < 0.05$. Multiple linear regression analysis was accomplished using the SPSS 7.5 statistical software package.

RESULTS AND DISCUSSION

Solubilities

The solubilities (log S_{IPM} and log S_{AQ}) given in Table I were all taken from the literature except for the directly measured solubilities in water for the 3-ACOM-5-FU series. The latter literature values (12) were from $S_{AQ} = S_{IPM}/K_{IPM:AQ}$, where $K_{IPM:AQ}$ was obtained by partitioning the solute between IPM and pH 4.0 buffer (to suppress any ionization) so that S_{AQ} was actually an estimate of pH 4.0 buffer solubility. The directly measured water solubilities for the 3-ACOM-5-FU series were determined here so that all of the S_{AQ} values in this database were measured and their P_{MAQ} values determined in the same way. The S_{AQ} values used here were +28, +5, +14, –4, +8 and +10% greater or lesser than the estimated S_{AQ} values for **3** to **8**, respectively, previously reported (12), and the SD were 3.8, 5.9, 0.8, 4.3, 8.9, and 14% of their S_{AQ}, respectively.

The S_{AQ} value for the C5 member of the bis-6,9-ACOM-6-MP series (**18**) was extrapolated from the average of the log solubility ratios between IPM and water (log *SR*) for the other members of the series(3). The average methylene π value, which is a measure of the fragment effect of a methylene group on partitioning between a lipid and an aqueous phase, was 0.55. This was calculated from (log SR_{n+m} – log SR_n)/m where *SR* is substituted for partition coefficient and where n is the number of methylene units in the promoiety of one prodrug and m is the number of additional methylene units in the promoiety of the prodrug with which it is compared. This gives an extrapolated log *SR* of 4.68 for **18**. The log S_{AQ} for **18** was calculated from log S_{IPM} – log *SR*.

Table I. Solubility and Flux Data for the 5-FU and 6-MP Prodrug Series

Compound	MW	log S_{IPM}[a]	log S_{AQ}[a]	Initial flux log J_{MIPM}[b]	Initial flux log J_{MAQ}[b]
3-ACOM-5-FU					
3 C_1	202	0.09	1.80	–0.22	–1.77
4 C_2	216	1.20	2.25	0.34	–1.41
5 C_3	230	1.42	1.93	0.46	–1.13
6 C_4	244	1.47	1.32	0.12	–1.43
7 C_5	258	1.63	0.92	0.004	–1.41
8 C_7	286	1.60	–0.25	–0.77	–1.85
6-ACOM-6-MP					
9 C_1	224	0.022	0.86	–0.69	–2.55
10 C_2	238	0.36	0.61	–0.67	–2.19
11 C_3	252	0.52	0.31	–0.58	–2.00
12 C_4	266	0.62	–0.10	–0.66	–2.18
13 C_5	280	0.57	–0.63	–1.26	–2.37
bis-6,9-ACOM-6-MP					
14 C_1	296	0.72	0.46	–0.64	–1.98
15 C_2	324	1.53	0.22	–0.63	–1.89
16 C_3	352	1.96	–0.71	–0.85	–2.27
17 C_4	380	2.24	–1.33	–0.99	–2.48
18 C_5	408	1.70	–2.98	–1.94	–3.07
Parent drugs					
1 5-FU	130	–1.31	1.93	–0.62	–1.94
2 6-MP	152	–1.65	0.05	–2.42	–2.62

[a] Units of mM.
[b] Units of μmol $cm^{-2}h^{-1}$.

Analysis and Stability

The 3-ACOM-5-FU and 6-ACOM-6-MP series of prodrugs were each very stable in the donor phases applied in the diffusion cell experiments. When each of the donor phases was analyzed by ^{1}H NMR spectroscopy after the water had been evaporated at room temperature (usually 1 to 2 days in a hood), only intact prodrug could be seen in their spectra. No C^6-*H* or C^2-*H* and C^8-*H* absorptions because of 5-FU or 6-MP, respectively, were observed and the ratio of C^6-*H* or C^2-*H* and C^8-*H* to N-CH_2-O_2C or S-CH_2-O_2C, respectively, were correct for intact prodrugs. However, because of the inherent imprecision of integrating absorption areas in ^{1}H NMR spectra, the samples could have contained 5% of 5-FU or 6-MP. In all cases where crystals formed on evaporation of the water (C1, C2, C3, and C4 of the 3-ACOM-5-FU and 6-ACOM-6-MP prodrugs), the melting points of several random samples of each batch of crystals were identical with that of intact prodrug.

Diffusion Cell Experiments

There are two sets of "initial flux" values given in Table I. The values for delivery of total 5-FU or 6-MP species from suspensions in IPM (log J_{MIPM}) are taken from the literature (3,4,12). So are the values for the delivery of total 6-MP species from suspensions in water (log J_{MAQ}) by the bis-6,9-ACOM-6-MP series except for the value for C5 (**18**) which had not been previously reported but had been determined in the same way as the other values by the same authors(3). The log J_{MAQ} values for the delivery of total 5-FU and 6-MP species by the 3-ACOM and 6-ACOM prodrugs, respectively, that were determined here are given in Table I. All of the J_{MAQ} values here were well within the expected variation in *J* values (±30%) seen for *in vitro* hairless mouse experiments except those for C1 in the 5-FU series (±73%) and C2 in the 6-MP series (±55%).

The application of a standard solute/vehicle suspension (Th/PG) after the initial application of the prodrug in the vehicle to give "second flux" J_{JAQ} values has been used to measure any irreversible decrease in the ability of the skin to resist permeation caused by application of vehicle (13): this will be referred to as damage. In previous papers these J_{JAQ} were referred to as simply J_j values (11). Although no control experiments were run where water was applied in the initial application, control experiments have been run where nothing was applied in the initial application: $J_J = 0.010 \pm 0.0012$ μmol cm^{-2} h^{-1}(14). The average J_{JAQ} after the application of **3** to **13** for these experiments is 0.0246 ± 0.0063 μmol cm^{-2} h^{-1} or about 2.5 times J_J. The average J_{JIPM} value (12) for the 3-ACOM-5-FU series ($J_{JIPM} = 1.09 \pm 0.11$ μmol cm^{-2} h^{-1}) is usual for the sort of J_{JIPM} values reported elsewhere (11) and for many other series of prodrugs, and is not significantly different from a control value for the initial application of IPM alone: J_{JIPM} value $= 1.02 \pm 0.13$ μmol cm^{-2} h^{-1} (13). The J_{JIPM} values were not determined previously for any of the 6-MP prodrug series. Generally, the J_{JIPM} values are about 50 times greater than the J_{JAQ} values suggesting that IPM causes about 50-times more damage to hairless mouse skin than water, but that water itself is not totally innocuous, causing about 2.5 times more damage than initially applying nothing at all. Most of the differences between J_{MIPM} and J_{MAQ} may therefore be attributed to differences in damage caused by the vehicles since the average of J_{MIPM} / J_{MAQ} is 31 ± 16 and this matches the difference between J_{JIPM} and J_{JAQ} reasonably well.

In a separate set of experiments, the delivery of total 6-MP species by the first two members of the 6-ACOM-6-MP series from water were measured using water instead of buffer (each containing 0.11% formaldehyde) as the receptor phase. The J_{MAQ} for C1 was 20-times and that for C2 was 4-times greater from a water vehicle using only water as the receptor phase than when buffer was used as the receptor phase. Similarly, J_{JAQ} for C1 was 20-times and for C2 it was 8-times greater in the experiments using water as the receptor phase than when buffer was used. Also the % contribution of flux by 6-MP to J_{MAQ} was much less (22% vs. 58% for C1 and 36% vs. 82% for C2) in these separate experiments suggesting that the damage to the skins (based on J_{JAQ} values) not only resulted in increased J_{MAQ} values but also in decreased effectiveness of the enzyme system responsible for hydrolysis of the prodrugs. The J_{JAQ} values in these separate experiments were not quite as large as after the skins had been initially treated with IPM and buffer containing 0.11% formaldehyde had been used in the receptor phase, but in the latter cases (3,4) the conversions of the prodrugs to 6-MP had been essentially complete. Thus, it is essential to use buffer and 0.11% formaldehyde in the receptor phase to insure the viability of the skins.

The effect of the solubilities (S_{IPM} and S_{AQ}) on flux can be seen in Fig. 1, where log S_{IPM}, log S_{AQ}, log J_{MIPM} and log J_{MAQ} have been plotted against the alkyl chain length of each of the prodrugs. What one sees first is that the log J_{MIPM} and

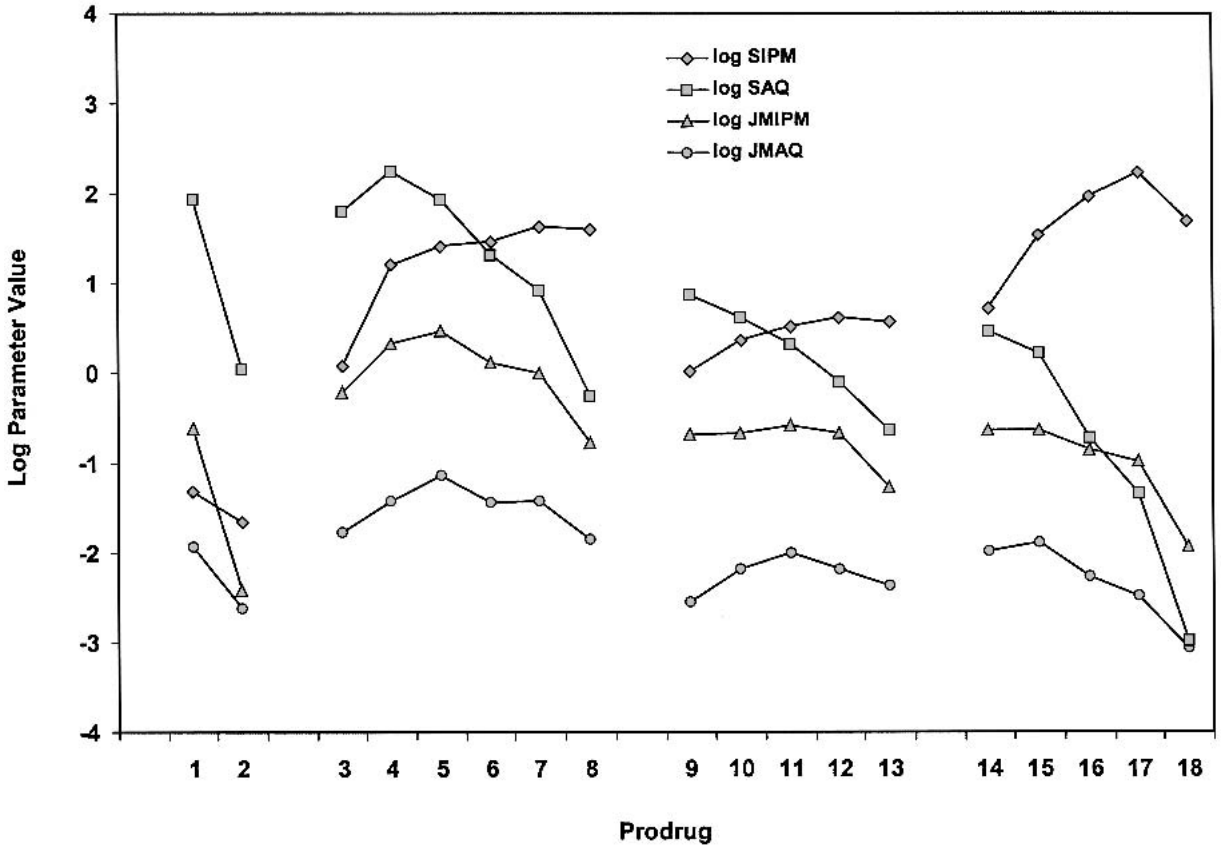


Fig. 1. Log solubility and log flux values for the three homologous 3-alkylcarbonyloxymethyl prodrug series vs. alkyl chain length.

log J_{MAQ} values follow the same trend; log J_{MIPM}–log J_{MAQ} is reasonably constant (1.44 ± 0.22, n = 16), illustrating the fact that the trend in flux values are nearly the same regardless of the vehicle. It is important to note that, although each prodrug applied as a suspension is at saturation in a particular vehicle and exhibits its maximum chemical potential because its activity is one when the solution is in equilibrium with its pure solid (which by definition has an activity of one), the chemical potential for each prodrug in a series is different because each is in equilibrium with a different pure solid (17). Thus, the flux for each prodrug in a series from its suspension in a vehicle such as water will be different. However, the flux of each prodrug from a suspension in a different vehicle, in this case IPM, should be the same as from the water vehicle (18) unless one of the vehicles interacts with the skin to reduce the barrier to permeation (13). In this comparison, IPM interacts with the skin to reduce the barrier to permeation as can be seen from the second application fluxes where J_{JIPM} values are about 50 times higher than J_{JAQ}. Thus, the fluxes from IPM and water for each prodrug are different but the effect of each vehicle on the skin should be the same regardless of the solute and log J_{MIPM}–log J_{MAQ} should be relatively constant as shown above. This phenomenon had been noted before for one series of homologous prodrugs (3), but these results suggest that it may be a more general phenomenon. The second thing that one sees is that J_{MIPM} or J_{MAQ} in most cases decrease whereas S_{IPM} values continue to increase: S_{IPM} alone is not a good predictor of J_{MIPM} or J_{MAQ}. Instead, it is a combination of S_{IPM} and S_{AQ}, which is a good predictor of J_M because the skin presents a lipid–aqueous biphasic barrier to permeation as a result of the multilamellar bilayer nature of the intercellular components of the stratum corneum (19, 20).

When the MW, log S_{IPM}, log S_{AQ}, and log J_{MAQ} for the prodrugs and 5-FU (Table I) were fit to the transformed Potts and Guy Eq. (1) (see above) using the SPSS 7.5 statistical software package, the parameter estimates were x = –1.497, y = 0.660 and z = –0.00469 (r^2 = 0.765) with an average error of prediction ref (5) equal to 0.193 log units (Fig. 2). For comparison purposes, when the same data but using the corresponding J_{MIPM} values were fit to the transformed Potts and Guy equation, the parameter estimates were x = –0.557, y = 0.536 and z = –0.00261 (r^2 = 0.941) with an average error of prediction of 0.109 log units (Fig. 3). The latter results were consistent with the results from analysis of the original data base(5) (n = 42) where the parameter estimates were x = –0.211, y = 0.534, and z = –0.00364 with an average error of prediction of 0.126 log units (r^2 = 0.937). In all cases the data for 6-MP itself was deleted from the data base used for determining the best fit to the transformed Potts and Guy equation, but are included in Figs. 2 and 3.

Although the subset of J_{MIPM} data for the prodrugs in this study fits the transformed Potts and Guy equation as well as the entire database, the J_{MAQ} do not fit as well based on a smaller r^2 value (0.765 vs. 0.941) and a larger average error of prediction value (0.193 vs. 0.109 log units). However, these results show that S_{AQ} values are important in predicting J_{MAQ} values just as they are in predicting J_{MIPM} and that both J_{MIPM} and J_{MAQ} can be modeled by the same equation but with different values for x, y, and z. The difference in "x" is at

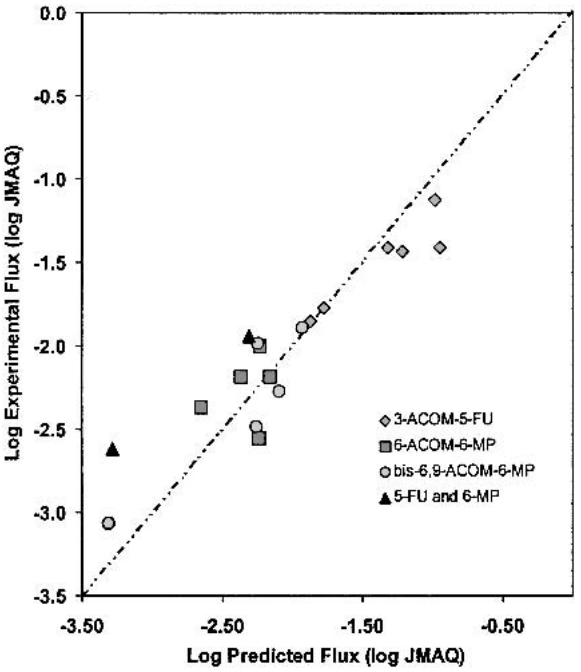


Fig. 2. Log-predicted flux vs. log experimental flux using an aqueous vehicle.

least partly the result of differences in vehicle effects on the resistance of the skin to permeation because "x" = log (D_O/L) where D_O is the diffusivity in the membrane of a hypothetical molecule having zero molecular volume and L is the diffusion path length (7). Finally, S_{IPM} is not the only model for S_{LIPID} that could have been used to predict J_{MAQ}. S_{OCT} could have been used if they had been available. However, S_{IPM} values were available from the literature and S_{IPM} had been shown to be reasonable model for S_{LIPID} (5).

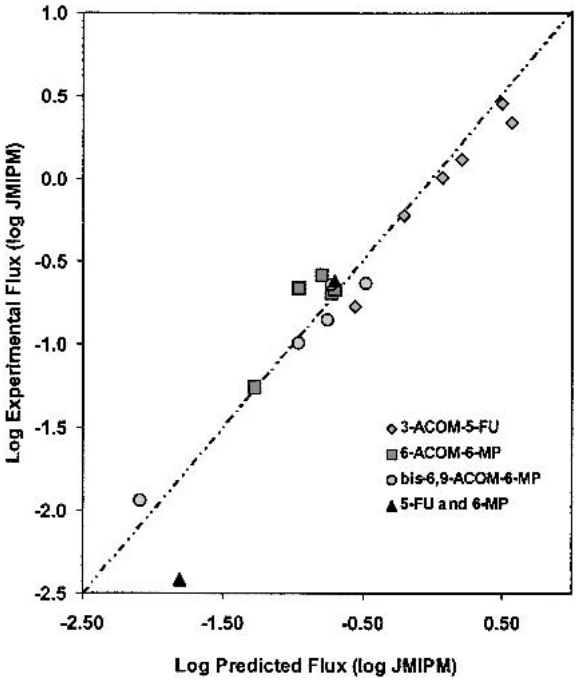


Fig. 3. Log-predicted flux vs. log experimental flux using an IPM vehicle.

When the J_{MIPM} and J_{MAQ} values were divided by their corresponding S_{IPM} and S_{AQ} values, values for their corresponding permeability coefficients (P_{MIPM} and P_{MAQ}, respectively) were obtained. The log P_{MIPM} and log P_{MAQ} are given in Table II. When the log P_{MIPM} values for the 3-ACOM-5-FU prodrugs (**3** to **8**), the 6-ACOM-6-MP prodrugs (**9** to **13**) and the bis-6,9-ACOM-6-MP prodrugs (**14** to **18**) were plotted against their corresponding calculated solubility parameters, positive slopes were obtained: +1.109 (r = 0.977), +0.608 (r = 0.935) and +1.330 (r = 0.998), respectively. When the log P_{MAQ} values were similarly plotted, negative slopes were obtained: –1.190 (r = 0.953), –1.021 (r = 0.993), and –1.287 (r = 0.948), respectively.

The trends in P_M values with increasing alkyl chain length can be seen quite clearly. If the vehicle is IPM the log P_{MIPM} values become increasing smaller with increasing chain length while the opposite is true if the vehicle is water. Although this dichotomy has been noted before for one homologous series of prodrugs (3), these results with three series suggest that such a dichotomy may in fact be a general result and that it should not be surprising. As S_{IPM} increases and J_{MIPM} decreases with increasing alkyl chain length, P_{MIPM} obviously decreases. However, S_{AQ} decreases faster than J_{MAQ} decreases with increasing alkyl chain length so that P_{MAQ} increases. Because J_{MIPM} and J_{MAQ} are following the same trend and log J_{MIPM}–log J_{MAQ} is reasonably constant (see above), subtracting increasingly larger log S_{IPM} from log J_{MIPM} will lead to increasingly smaller log P_{MIPM} and subtracting increasingly smaller log S_{AQ} from log J_{MAQ} will lead to increasingly larger log P_{MAQ} (3).

CONCLUSIONS

The data for the delivery of total 5-FU and 6-MP species by ACOM prodrugs from water, when fit to the transformed Potts and Guy equation, show that there is a positive dependence of flux on S_{AQ} similar to that shown by the same series of prodrugs when delivering total 5-FU and 6-MP species

Table II. Log Permeability and Solubility Parameter Values

Compound	log P_{MIPM}[a]	log P_{MAQ}[a]	Delta[b]
3 C_1	–0.31	–3.57	13.06
4 C_2	–0.86	–3.66	12.63
5 C_3	–0.96	–3.06	12.28
6 C_4	–1.35	–2.75	11.95
7 C_5	–1.63	–2.33	11.73
8 C_7	–2.37	–1.60	11.33
9 C_1	–0.71	–3.41	14.40
10 C_2	–1.03	–2.80	13.90
11 C_3	–1.10	–2.31	13.50
12 C_4	–1.28	–2.08	13.10
13 C_5	–1.83	–1.74	12.80
14 C_1	–1.36	–2.44	13.30
15 C_2	–2.16	–2.11	12.75
16 C_3	–2.81	–1.56	12.30
17 C_4	–3.23	–1.15	11.90
18 C_5	–3.64	–0.09	11.60
5-FU	0.69	–3.87	14.99
6-MP	–0.77	–2.67	14.40

[a] Units of cm h^{-1}.
[b] Solubility parameter, units of $cal^{1/2}$ $cm^{-3/2}$.

from IPM. Thus, the design of prodrugs for the delivery of parent drugs from water as well as lipid vehicles should include approaches that maximize S_{AQ} as well as S_{IPM}.

In addition, these results suggest that for these prodrugs, flux from water mirrors flux from IPM. The best prodrugs for delivering a parent drug from IPM will probably be the best for delivering a parent drug from water. The big difference between the two vehicles is the amount of apparent damage done by the respective vehicle where IPM is apparently 50 times more damaging than water. Finally, the fact that P_{MAQ} increases with the increasing alkyl chain length of a homologous series of prodrugs whereas J_{MAQ} decreases is merely an artifact of S_{AQ} decreasing faster than J_{MAQ} decreases.

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