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Transdermal delivery of 5-fluorouracil (5-FU) by 1-alkylcarbonyl-5-FU prodrugs

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Abstract

The members of a series of 1-alkylcarbonyl-5-FU prodrug derivatives have been characterized and evaluated for their abilities to deliver 5-FU into and through skin. There was no correlation of lipid solubility or partition coefficient with relative abilities of the members of the 1-alkylcarbonyl series to deliver 5-FU through skin. However, there was a correlation with water solubility within the series. Although their lipid solubilities and partition coefficient values were greater than those of the 1-alkyloxycarbonyl series, only 1-acetyl-5-FU was more soluble in water, and only 1-acetyl-5-FU delivered more total 5-FU species through the skin than the corresponding member of the 1-alkyloxycarbonyl series. On the other hand, the 1-alkylcarbonyl series was more effective at enhancing the ratio of dermal to transdermal delivery (D/T delivery ratio) than the 1-alkyloxycarbonyl series, presumably because of the rapid hydrolysis of the members of the former series once contact with the aqueous domains of the epidermis had been made. Thus, the hypothesis that enhanced D/T delivery ratio requires rapid hydrolysis of the prodrug after it partitions into the skin is supported. Although the prodrugs hydrolyzed rapidly in water, they were stable in isopropyl myristate (IPM) during their application in IPM to highly hydrated skin. There was also a good correlation of calculated solubility parameters for the prodrugs with their permeability coefficients.

Keywords: 1-alkylcarbonyl-5-FU; Diffusion cell; Water and lipid solubility; Partition coefficients; Flux; Skin accumulation; Solubility parameters

1. Introduction

5-Fluorouracil (**1**, 5-FU) is effective in the topical treatment of a number of disease states that are characterized by uncontrolled proliferation of various skin cell populations. However, in each instance less than optimal delivery of 5-FU using conventional preparations has necessitated the use of more drastic measures to obtain therapeutic results. As examples, light curettage of basal cell carcinomas (BCC), which physically removes the topical barrier to absorption, reduces the 5-year cumulative recurrence rate after topical 5-FU treatment from 21% to a more clinically acceptable 6% (Epstein, 1985). Similarly, topical 5-FU treatment of psoriasis is only effective if applied under occlusion (Tsuji and Sugai, 1972).

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An alternative to using methods such as curettage and occlusion to improve topical delivery is a prodrug approach. In the prodrug approach, the physicochemical properties of the parent drug are transiently modified with a promoiety such that its solubility in the skin, in the case of topical delivery, is improved (Sloan, 1992). A number of prodrug approaches using different types of promoieties to improve the topical delivery of 5-FU have been evaluated recently. Although all of the approaches were effective in increasing transdermal delivery, for most (Mollgaard et al., 1982; Sloan et al., 1988; Sloan et al., 1993) the increase was modest (2- to 5-fold). However, even a modest increase (5-fold) in transdermal delivery of 5-FU by one of the Mannich base prodrugs (Sloan et al., 1988) resulted in a significant reduction in epidermal DNA synthesis compared to that afforded by 5-FU (Sloan et al., 1990).

On the other hand, the best member of the 1-alkyloxycarbonyl type series, 1-ethyloxycarbonyl-5-FU, gave almost a 25-fold increase in transdermal delivery of total 5-FU species (Beall et al., 1994). However, because this type of prodrug was hydrolytically stable ($t_{1/2}$ = 190 to 500 min, pH 7.4, 37°C) (Buur and Bundgaard, 1986), the predominant species delivered by the members of this series was intact prodrug (40% to 90%), and none of the members gave as good a ratio of dermal to transdermal delivery as did 5-FU. It was suggested (Beall et al., 1994) that a type of prodrug which was hydrolytically much less stable than the 1-alkyloxycarbonyl prodrugs, but which retained their solubility properties, was required to selectively improve the dermal delivery of 5-FU.

In order to test this hypothesis, the 1-alkylcarbonyl type of prodrug was chosen for evaluation. The first member of the series (1-acetyl-5-FU, **2**) has been reported to be hydrolytically unstable (pH 7.4, 37°C, $t_{1/2}$ = 6.9 min) (Buur and Bundgaard, 1984); and it was anticipated that the 1-alkylcarbonyl type, like the 1-alkyloxycarbonyl type, would exhibit greater general solubility than 5-FU because one of the N-H groups in 5-FU was masked in the prodrug which would decrease its intermolecular hydrogen bonding capability. In this paper the solubilities of a series of 1-alkylcarbonyl type prodrugs of 5-FU are correlated with their abilities to deliver 5-FU into and through hairless mouse skin.

2. Materials and methods

The diffusion cells were from Crown Glass, Somerville, NJ (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. Isopropyl myristate was obtained from Givaudan, Clifton, NJ. 5-FU was purchased from Sigma Chemical Co. All other reagents were obtained from Aldrich Chemical Co. The female hairless mice (SKH-hr-1) were from Temple University Skin and Cancer Hospital. The 1-alkylcarbonyl-5-FU prodrugs were synthesized by known procedures (Beall et al., 1995).

2.1. Solubilities and partition coefficients

Lipid solubilities (S_{IPM}) were determined using isopropyl myristate (IPM) as the lipid solvent according to previously described procedures (Beall et al., 1993; Sloan et al., 1993; Beall et al., 1994). The partition coefficients (K) were determined using the saturated IPM solutions from the lipid solubility study. For those compounds with large differences in solubility in one phase relative to the other, volume ratios (IPM/buffer) other than 1:1 were necessary, but the ratio never exceeded 1:10. The pH 4.0 buffer solubility (S_{H20}) of each member of the series was then estimated from the mean of its IPM solubility divided by the mean of its corresponding K as previously described (Beall et al., 1993; Sloan et al., 1993; Beall et al., 1994).

2.2. Diffusion cell experiments

The mice were sacrificed by cervical dislocation, their skins were removed immediately by blunt dissection, and the full thickness dorsal sections were mounted in the diffusion cells (Sloan et al., 1993; Beall et al., 1994). The dermal sides of the skins were placed in contact with receptor phase which contained 0.05 M phosphate

buffer (pH = 7.1, I = 0.12 M) with 0.11% formaldehyde as a preservative (Sloan et al., 1991). The receptor phases were stirred continuously and kept at constant temperature (32°C) by a circulating water bath. A preapplication period of 48 h was established to uniformly condition the skins and to remove water-soluble UV-absorbing materials. The receptor phases were changed three times during this period. The epidermal sides of the skins were exposed to the air and were left untreated during this period.

After the preapplication period, 0.5 ml aliquots from suspensions of the prodrugs in IPM were applied to the epidermal sides of the skins (the IPM suspensions were stirred at 22 ± 1°C for 48 h prior to application to ensure that saturation was attained). Total concentrations of the IPM suspensions ranged from 0.6 M to 1.0 M with enough excess solid present to maintain saturation for the duration of the application period (see below). Each drug-vehicle combination was run in triplicate.

Samples were taken from the receptor phases at 4, 8, 12, 21, 24, 27, 30, 33, 36, 45, and 48 h after donor phase application. The receptor phases were changed following removal of each sample so that sink conditions were maintained. Samples were analyzed for total 5-FU species that had diffused by UV spectroscopy (ϵ = 7.13 × 10^3 l/mol at 266 nm). Cumulative amounts of 5-FU in the receptor phase (μmol) were plotted against time (h), and the slopes of the linear, steady-state regions were calculated using linear regression. The slopes divided by 4.9 cm^2 (the area of the donor surface) gave the steady-state fluxes (J, μmol/cm^2/h). Permeability coefficients (P_i) were determined by dividing the values of J_i by the solubility of the corresponding prodrugs in IPM (S_{IPM}).

Donor phases were changed every twelve h and were set aside for ^{1}H-NMR analysis. Stability of the prodrugs in IPM was determined from the chemical shift of C^6-H. In dimethyl sulfoxide-d_6, the C^6-H signal for 5-FU appears at about δ 7.7 ppm (Beall, 1991). For each of the 1-acyl derivatives, the same signal in dimethyl sulfoxide-d_6 appears at δ > 8.20 ppm. Since this area of the spectrum is free from interference by IPM absorbances, the two signals can be identified and quantified by integration as necessary.

Following removal of the donor phases after the 48-h application period, the epidermal sides of the skins were washed three times with 5 ml portions of methanol to remove all remnants of prodrug and vehicle from the skin surfaces. This was accomplished quickly (< 3 min) to minimize contact time between the skins and methanol. The receptor phases were changed again, and the dermal sides were kept in contact with the fresh buffer for 24 h while the epidermal sides were again left exposed to the air. After this leaching period, another sample was taken from each cell to measure the skin accumulation of total 5-FU species (C_S).

Second applications to the epidermal sides of the skins were made after the leaching period with a standard drug-vehicle suspension. Theophylline in propylene glycol (0.4 M) was applied to assess the damage to the skins from application of the initial drug-vehicle combinations. Samples were taken at 1, 2, 3, 5, 7, 9, and 11 or 12 h after application. The samples were analyzed for theophylline by UV spectroscopy (ϵ = 1.02 × 10^4 l/mol at 271 nm) and second application fluxes (J_j) were determined as described above.

2.3. Solubility parameters

The calculated solubility parameters (δ_i) were obtained using the method of Fedors (1974) as illustrated by Martin et al. (1985) and Sloan et al. (1986).

2.4. Statistical analysis

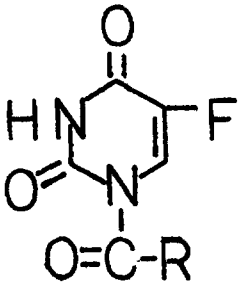
Statistical analysis was accomplished using Student's t-test. Unless otherwise indicated, statistical significance is for P < 0.05.

3. Results and discussion

3.1. Solubility and partition coefficients

The solubilities of the 1-alkylcarbonyl prodrugs in IPM (S_{IPM}), values for partition coefficients

Table 1
Melting points (MP), solubilities in IPM (S_{IPM}), partition coefficients (K), and methylene π values.



Compound R =	MP[a] (°C)	S^{b}_{IPM} (mM)	K^{c} ($\pm$ S.D)	π^{d}
5-FU	280–282	0.049	0.00058	—
2, CH_3	129–130	22.1	0.185 (0.0131)	—
3, C_2H_5	130–131	36.4	0.764 (0.0176)	0.61
4, C_3H_7	145–146	17.4	2.69 (0.215)	0.55
5, C_4H_9	120–121	39.2	11.3 (1.14)	0.62
6, C_5H_{11}	101–102	112.7	38.3 (2.40)	0.53
7, C_7H_{15}	83–84	110.7	759 (94.6)	0.65

[a]From Beall, 1991.
[b]Standard deviations from the mean were within $\pm$ 5%.
[c]Partition coefficient between IPM and pH 4.0 buffer.
[d]$\pi = (\log K_{n+m} - \log K_n)/m$, where n is the number of methylene units in the promoiety of one prodrug and m denotes the number of additional methylene units in the promoiety of the prodrug with which it is compared.

between IPM and pH 4.0 buffer (K), and estimated pH 4.0 buffer solubilities (S_{H20}) have been discussed in a previous paper (Beall et al., 1993). Those values are reproduced here (Table 1 and Table 2) for convenience. As anticipated, all of the members of the series were over two orders of magnitude more soluble in IPM than 5-FU and the 1-acetyl derivative was more soluble in water than 5-FU.

Although it is not possible to quantitatively compare the solubilities of derivatives in the 1-alkylcarbonyl series with those derivatives of equal alkyl chain length in the 1-alkyloxy- or 1-alkylaminocarbonyl series because of the heteroatom inserted between the carbonyl and the alkyl chain in the latter series, certain qualitative observations can be made. Except for the 1-hexanoyl derivative, **6**, the members of the 1-alkylcarbonyl series are more soluble in IPM (lipid soluble) than the corresponding members of the other two series. This is especially true for the 1-acetyl (methylcarbonyl) derivative **2** which is one order of magnitude more soluble in IPM than the corresponding methyloxycarbonyl derivative (S_{IPM} = 2.13 mM) (Beall et al., 1994) and two orders of magnitude more than the methyl-aminocarbonyl derivative (S_{IPM} = 0.299 mM) (Sloan et al., 1993).

On the other hand, only the first two members of the 1-alkylcarbonyl series are more water soluble than those of the 1-alkylaminocarbonyl series. The next two members of the 1-alkylaminocarbonyl series are more water soluble. Similarly, except for the comparison between the methylcarbonyl derivative **2** and the methyloxycarbonyl derivative (S_{H20} = 111 mM) (Beall et al., 1994), the remaining three of the first four members of the 1-alkyloxycarbonyl series are 4–7 times more soluble in water than the corresponding 1-alkylcarbonyl series (Table 2). The result is that the partition coefficient values for the first four members of the 1-alkylcarbonyl series are 8–10 times greater than those of the corresponding 1-alkyloxycarbonyl series and about 2–2.5 times greater than those of the 1-alkylaminocarbonyl series. Beyond the first four or five members of the series the effect of the alkyl chain on solubilities begins to predominate and the effect of the different

Table 2
Solubilities of prodrugs in water (S_{H20}) and rates of delivery of total 5-FU species by the prodrugs through hairless mouse skin (J_i)

R =	S^a_{H20} (mM)	J_i (±S.D.)/(μmol/cm²/h)	R =	S^c_{H20} (mM)	J^c_i (±S.D.)/(μmol/cm²/h)
5-FU	96.0	0.24 (0.09)			
2,CH_3	120.0	9.3 (0.3)	CH_3O	111	2.6 (0.6)
3,C_2H_5	47.6	4.3 (0.1)	C_2H_5O	174	5.9 (1.3)
4,C_3H_7	6.50	1.3 (0.2)	C_3H_7O	42.6	2.3 (0.2)
5,C_4H_9	3.48	1.0 (0.1)	C_4H_9O	23.3	2.2 (0.1)
6,C_5H_{11}	2.94[b]	1.1 (0.0)	$C_6H_{13}O$	5.04	1.5 (0.1)
7,C_7H_{15}	0.146[b]	0.60 (0.01)	$C_8H_{17}O$	0.13	0.3 (0.02)

[a]Determined from solubility ratio: $S_{H20} = S_{IPM}/K$.
[b]IPM/buffer phase volume ratio used to determine K was 1:10.
[c]From Beall et al., 1994: converted from mg/ml and mg/cm²/h, respectively.

enabling functional groups in the different types of prodrugs on solubilities is minimized.

The mean methylene π values ± standard deviations for the 1-alkylcarbonyl series calculated from their log K values is 0.59 ± 0.05. This mean π value for the methylene group is consistent with those for methylene groups from the other series of N-acyl derivatives (0.61 ± 0.06 for the 1-alkyloxycarbonyl series (Beall et al., 1994) and 0.60 ± 0.05 for the 1-alkylaminocarbonyl series (Sloan et al., 1993)). The only unusual solubility behavior was exhibited by the 1-butyryl derivative, **4**, which is higher melting and less lipid soluble than either **3** or **5**. The water solubility of **4** must be commensurately lower than expected for its place in the series as well, since the π values derived from the comparison of log K values of **3** with **4** (0.55) and of **4** with **5** (0.62) are well within one standard deviation of the average.

3.2. Diffusion cell experiments

The results from the diffusion cell experiments are given in Tables 2 and 3. IPM, a nonprotic solvent, was used as the vehicle for the 1-alkylcarbonyl derivatives in all the diffusion cell experiments because of the instability of the derivatives in protic solvents (Beall, 1991). Only intact prodrug was observed in the donor phases by ^{1}H-NMR during the course of the experiments. The very short half-lives (3–5 min in pH 7.1 buffer at 32°C) (Beall et al., 1995) and the relatively long lag times (6–13 h) for development of steady-state flux insured that only 5-FU was observed in the receptor phase (Beall, 1991; Beall et al., 1995).

All of the 1-alkylcarbonyl derivatives are more effective (3–40 times) than 5-FU in IPM at delivering 5-FU through hairless mouse skin. However, although all of the 1-alkylcarbonyl derivatives are much more soluble in IPM than 5-FU, there is no direct correlation between the rates of delivery (flux) of 5-FU and their solubilities in IPM (lipid solubility) or their partition coefficient values. One of the least lipid soluble derivatives, **2**, gives almost an order of magnitude greater flux of 5-FU than all the other derivatives except for **3**, while the more lipid soluble derivatives, **6** and **7**, give significantly lower flux values than **2** and **3** give.

On the other hand, there is a correlation of the relative water solubilities of the members of the 1-alkylcarbonyl series of prodrugs of 5-FU with their relative abilities to deliver 5-FU through hairless mouse skin. The more water soluble members are the more effective at delivering 5-FU. This same correlation was observed for the two other series of N-acyl derivatives that have been evaluated (Sloan et al., 1993; Beall et al., 1994). Thus, in order to optimize transdermal delivery of 5-FU by one type of prodrug, the more water soluble member of the series needs to be identified.

In order to optimize transdermal delivery by different types of prodrugs, water solubility remains an important criterion for selecting the best type. However, the comparison is not straightforward because of the nonlinear effects that alkyl chain length in different types of promoieties have

Table 3
Rates of delivery of theophylline (J_j) through hairless mouse skin, log permeability coefficients for delivery of 5-FU by 1-alkylcarbonyl prodrugs (log P_i), solubility parameters of prodrugs (δ_i), amounts of 5-FU species retained in skin (C_S) and dermal/transdermal (D/T) delivery ratios (n = 3)

Compound (δ_i)[a]	J_j(± S.D) (μmol/cm^2/h)	C_S(± S.D) (μmol)	Log P_i[b] (cm/h)	D/T[c]	D/T[c,d]
5-FU (15.0)	1.2 (0.2)	3.7 (0.9)	0.69	0.131	
2 (14.09)	1.6 (0.0)	68 (10)	−0.38	0.062	0.027
3 (13.45)	1.2 (0.2)	69 (10)	−0.93	0.136	0.026
4 (12.96)	1.0 (0.0)	8.2 (2.7)	−1.13	0.054	0.019
5 (12.56)	0.80 (0.03)	16 (4)	−1.59	0.136	0.016
6 (12.23)	0.47 (0.02)	11 (3)	−2.01	0.085	0.062
7 (11.71)	0.72 (0.11)	12 (3)	−2.27	0.170	0.094

[a]Units of (cal/cm^3)$^{1/2}$.
[b]Calculated from J_i/S_{IPM}.
[c]Calculated from $[C_S/(4.9\ cm^2\ 24\ h)]/J_i$ to give a dimensionless ratio.
[d]Values from Beall et al. (1994) for $R = CH_30$ to $R = C_8H_{17}0$ corresponding to the J_i values in Table 2.

on the lipid-water solubility balance. Since the 1-alkyloxycarbonyl series have been reported to be more effective than the 1-alkylaminocarbonyl series at delivering 5-FU species into and through skin (Beall et al., 1993), the 1-alkylcarbonyl series will be compared to the former series (Table 2). Except for the first member of the series (1-methylcarbonyl-5-FU, **2**), which is 10% more soluble in water than 1-methyloxycarbonyl-5-FU, the remaining three of the first four members of the 1-alkyloxycarbonyl series are significantly more water soluble and they deliver significantly more total 5-FU species through hairless mouse skin than the corresponding members of the 1-alkylcarbonyl series. Hence, although the partition coefficient values and the lipid solubilities of the members of the 1-alkylcarbonyl series are all greater than those of the corresponding 1-alkyloxycarbonyl series, the members of the more water soluble 1-alkyloxycarbonyl series deliver more 5-FU. The more water soluble type of derivative is the more effective type at enhancing transdermal delivery (Sloan, 1992), but not all the members of one series may be more water soluble than the corresponding members of another series and hence more effective.

All of the 1-alkylcarbonyl derivatives of 5-FU are much more effective than 5-FU at causing accumulation of 5-FU in skin as determined by the C_S values listed in Table 3. Derivatives **2** and **3** are the best by this criterion, causing almost 20 times more 5-FU to accumulate in the skin than 5-FU causes. The 1-alkylcarbonyl derivatives are also more effective than the 1-alkyloxycarbonyl derivatives (Beall et al., 1994) at causing accumulation of 5-FU in skin. Even the best 1-alkyloxycarbonyl derivative, 1-ethyloxycarbonyl (C_S = 18 μmol), is only about one-fourth as effective as the corresponding 1-alkylcarbonyl derivative. Thus, rapid hydrolysis (Beall et al., 1995) of the more lipid soluble 1-alkylcarbonyl derivatives, to highly polar 5-FU, as they partition into the skin results in 5-FU being effectively locked into the remaining lipid domains of the skin and giving relatively higher skin accumulation values of 5-FU than the lipid soluble but more stable 1-alkyloxycarbonyl derivatives or 5-FU give.

The D/T delivery ratios (Table 3) for the 1-alkylcarbonyl derivatives are also from 2 to 8 times greater than the corresponding D/T delivery ratios for the 1-alkyloxycarbonyl derivatives (Beall et al., 1994) which are reproduced in Table 3 for convenience. However, the D/T delivery ratios for the 1-alkylcarbonyl derivatives are not as great or are not substantially greater than the D/T delivery ratio for 5-FU. Although significantly greater amounts of 5-FU are accumulated in the skin from the application of the 1-alkylcarbonyl derivatives than from 5-FU, this is balanced by even greater values for the flux of 5-FU generated from the derivatives. Thus, the D/T delivery ratios for this series suggest that **7** is the best derivative with which to enhance dermal delivery without unduly enhanc-

ing transdermal delivery even though its skin accumulation value is lower than those of **2** or **3**.

For the members of the 1-alkylcarbonyl series there is a regular decrease in flux and skin accumulation values with increasing chain length, similar to that observed for the 1-alkyloxycarbonyl series. On the other hand, the flux value and especially the skin accumulation value for the 1-butyryl derivative, **4**, are lower than expected for its position in the series. However, the low flux and C_S values of **4** are consistent with the lower than expected S_{H20} and S_{IPM} values. Thus, although the partition coefficient value for **4** appears to be normal relative to those for **3** and **5**, flux and C_S values are more sensitive to S_{H20} and S_{IPM} values while partition coefficient values can be misleading.

The differences in delivery of 5-FU observed for the members of the 1-alkylcarbonyl-5-FU type of derivative do not appear to be due to differences in damage to the skin caused by the application of the derivative in IPM. In control experiments, the application of IPM alone in place of the derivatives in IPM using the same protocol as the latter experiments gave a J_j value of 1.7 μmol/cm^2/h. Thus, using J_j values as one measure of damage caused by the application of the derivatives in IPM (Sloan, 1992), the derivatives in IPM generally caused less damage than IPM or 5-FU in IPM. Although there are significant differences in J_j values caused by the different 1-alkylcarbonyl derivatives in IPM, normalized J_i values obtained from J_i/J_j (data not shown), give the same trends in J_i observed before normalization.

The 1-alkylcarbonyl-5-FU prodrugs also give results that are similar to those of the previously studied prodrugs when their calculated solubility parameters (δ_i) are plotted against the corresponding log permeability coefficients (log P_i) (Sloan et al., 1993; Beall et al., 1994). These results and those of these previous two studies are plotted in Fig. 1. It is apparent in all three series that as the members of the series became more lipophilic (decreasing absolute δ_i value) they become less efficient at delivering the parent drug from a lipoidal vehicle (decreasing log P_i value). It is also apparent from Fig. 1 that the sensitivity of log P_i to δ_i for the 1-alkylcarbonyl derivatives (slope = 0.89, r = 0.99) is essentially the same as that for the 1-alkyloxycarbonyl derivatives (slope = 0.86, r = 0.99). On the other hand, log P_i values for the 1-alkylaminocarbonyl derivatives are somewhat more sensitive to δ_i (slope = 1.09, r = 0.99). For a given δ_i value, log P_i will be largest for the member of the 1-alkyloxycarbonyl series and smallest for the member of the 1-alkylaminocarbonyl series.

4. Conclusion

The solubility and diffusion cell results for the members of the 1-alkylcarbonyl-5-FU series of prodrugs show that they behave very similarly to the corresponding members of the previously reported 1-alkyloxycarbonyl-5-FU series. However, in comparisons between the corresponding members of the two series, the more water soluble member of the two lipophilic series was the more effective at increasing transdermal delivery. Thus,

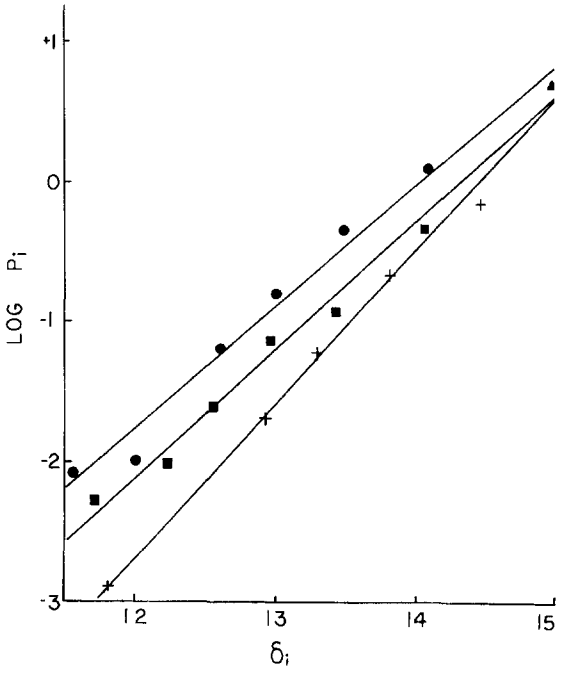


Fig. 1. Plots of experimental log permeability coefficients (P_i) versus solubility parameters for the 1-alkylcarbonyl-5-FU prodrugs (δ_i) for the delivery of 5-FU through hairless mouse skin (■) and plots of the same data for the 1-alkyloxycarbonyl-5-FU prodrugs (●) and the 1-alkylaminocarbonyl-5-FU prodrugs (+). Line plots through each set of data include 5-FU (▲).

the members of the 1-alkyloxycarbonyl series, which were usually the more water soluble, were generally also more effective at increasing transdermal delivery. On the other hand, the members of that 1-alkylcarbonyl series were much more labile than those of the 1-alkyloxycarbonyl series. Hence, the former were much more effective at increasing 5-FU accumulation in the skin. This led to much better D/T delivery ratios (2–8 times) by members of the 1-alkylcarbonyl series. Although there was no inverse relationship between J_i values and the corresponding values for D/T delivery ratio, the largest D/T delivery ratio for both the 1-alkylcarbonyl and 1-alkyloxycarbonyl series was achieved by the longest alkyl chain member of each series, which was also the member that gave the smallest J_i value. Thus, selective dermal delivery may be expected with the longer alkyl chain members of other homologous series that are capable of rapid bioconversion to their parent drug.

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References

Beall, H.D., *Bioreversible Derivatives of 5-Fluorouracil (5-FU): Improving Dermal and Transdermal Delivery with Prodrugs*, Ph.D. dissertation, University of Florida, Gainesville, Dec. 1991.

Beall, H.D., Getz, J.J. and Sloan, K.B., The estimation of relative water solubility for prodrugs that are unstable in water. *Int. J. Pharm.*, 93 (1993) 37–47.

Beall, H., Prankerd, R. and Sloan, K.B., Transdermal delivery of 5-fluorouracil (5-FU) through hairless mouse skin by 1-alkyloxycarbonyl-5-FU prodrugs: physicochemical characterization of prodrugs and correlations with transdermal delivery. *Int. J. Pharm.*, 111 (1994) 223–233.

Beall, H., Prankerd, R. and Sloan, K.B., 1-Alkylcarbonyl-5-fluorouracil prodrugs: synthesis, thermal and hydrolytic stability. *Drug Dev. Ind. Pharm.*, 22 (1996) 85–90.

Buur, A. and Bundgaard, H., Prodrugs of 5-fluorouracil. I. Hydrolysis kinetics and physicochemical properties of various *N*-acyl derivatives of 5-fluorouracil. *Int. J. Pharm.*, 21 (1984) 349–364.

Buur, A. and Bundgaard, H., Prodrugs of 5-fluorouracil. V. 1-Alkyloxycarbonyl derivatives as potential prodrug forms for improved rectal or oral delivery of 5-fluorouracil. *J. Pharm. Sci.*, 74 (1986) 522–527.

Epstein, E., Fluorouracil paste treatment of thin basal cell carcinomas. *Arch. Dermatol.*, 121 (1985) 207–213.

Fedors, R.F., A method for estimating both the solubility parameters and molar volumes of liquids. *Polym. Eng. Sci.*, 14 (1974) 147–154.

Martin, A., Wu, P.L. and Velasquez, T., Extended Hildebrand solubility approach: sulfonamides in binary and ternary solvents. *J. Pharm. Sci.*, 74 (1985) 277–282.

Mollgaard, B., Hoelgaard, A. and Bundgaard, H., Pro-drugs as drug delivery systems. XXIII. Improved dermal delivery of 5-fluorouracil through human skin via *N*-acyloxymethyl pro-drug derivatives. *Int. J. Pharm.*, 12 (1982) 153–162.

Sloan, K.B., Koch, S.A.M., Siver, K.G. and Flowers, F.P., The use of solubility parameters of drug and vehicle to predict flux. *J. Invest. Dermatol.*, 87 (1986) 244–252.

Sloan, K.B., Sherertz, E.F. and McTiernan, R.G., The effect of structure of Mannich base prodrugs on their ability to deliver theophylline and 5-fluorouracil through hairless mouse skin. *Int. J. Pharm.*, 44 (1988) 87–96.

Sloan, K.B., Sherertz, E.F. and McTiernan, R.G., The effect of 5-fluorouracil on inhibition of epidermal DNA synthesis in vivo: a comparison of the effect of formulations and a prodrug of 5-FU. *Arch. Dermatol. Res.*, 282 (1990) 484–486.

Sloan, K.B., Beall, H.D., Weimar, W.R. and Villaneuva, R., The effect of receptor phase composition on the permeability of hairless mouse skin in diffusion cell experiments. *Int. J. Pharm.*, 73 (1991) 97–104.

Sloan, K.B., Functional group considerations in the development of prodrug approaches to solving topical delivery problems. In Sloan, K.B. (Ed.), *Prodrugs: Topical and Ocular Drug Delivery*, Marcel Dekker, New York, NY, 1992, pp. 17–116.

Sloan, K.B., Getz, J.J., Beall, H.D. and Prankerd, R.J., Transdermal delivery of 5-fluorouracil (5-FU) through hairless mouse skin by 1-alkylaminocarbonyl-5-FU prodrugs: physicochemical characterization of prodrugs and correlations with transdermal delivery. *Int. J. Pharm.*, 93 (1993) 27–36.

Tsuji, T. and Sugai, T., Topically administered fluorouracil in psoriasis. *Arch. Dermatol.*, 105 (1972) 208–212.