

Selection of a Proper Prodrug for Penetration Enhancement

10

Kenneth B. Sloan, Jennifer Synovec,
and Scott C. Wasdo

Contents

10.1	Introduction	137
10.1.1	Push Versus Pull Mechanisms for Penetration Enhancers	137
10.2	Basis for Prodrugs as Penetration Enhancers	138
10.3	Acyl Versus Soft Alkyl Promoieties	139
10.4	Mechanisms for Penetration Enhancement	140
10.4.1	Decrease Crystal Lattice Energy by Masking Hydrogen Bond Donor Functional Groups	140
10.4.2	Incorporation of Water Solubility Enhancing Functional Groups into Promoieties	144
	Conclusion	149
	References	149

10.1 Introduction

10.1.1 Push Versus Pull Mechanisms for Penetration Enhancers

From a mechanistic point of view, there are two general ways to accomplish the task of improving topical delivery using a chemical-based approach. The first approach is to increase the “push” of the vehicle components on the drug to drive it into the skin (Kadir et al. 1987). One way to increase the “push” of the vehicle is to use vehicle components in which the drug is more soluble but which are more volatile than the other components. Evaporation of the volatile components after application of the drug-vehicle combination leaves a supersaturated solution of the drug in a state of heightened thermodynamic activity in the vehicle (α_{VEH}) (Coldman et al. 1969), that is, α_{VEH} greater than one. The second approach is to increase the “pull” on the drug into the skin by components of the vehicle that have permeated the skin and have decreased the resistance of the skin to permeation by the drug (Kadir et al. 1987) or increased the solubility of the drug in the skin, S_{MI} : these components interact with the skin. Such components of the vehicle do not have to permeate the skin faster than the drug. However, another way to increase the “pull” on the drug by components of the vehicle is to use components that do permeate the skin faster than the drug and pull the drug along with them – a “drag” effect (Friend and Smedley 1993).

K.B. Sloan (✉) • J. Synovec
Department of Medicinal Chemistry,
College of Pharmacy, University of Florida,
Gainesville, FL, USA
e-mail: sloan@cop.ufl.edu

S.C. Wasdo
Department of Anesthesiology, College of Medicine,
University of Florida, Gainesville, FL, USA

The basis for the two chemical-based approaches to enhancing topical delivery (decreasing the solubility of the drug in the vehicle and increasing its solubility in the skin; “push” and “pull,” respectively) lies in the form of the equation that describes flux. The flux, J , of the drug through skin is directly related to the concentration of the drug in the first layer of the skin, C_{M1} , from Fick’s Law: $J=(C_{M1} - C_{Mn}) D/L$ where C_{Mn} is the concentration of the drug in the last layer of skin (and is assumed to approach zero at steady-state), D is the diffusion coefficient of the drug in the skin, and L is the thickness of the membrane. The concentration of the drug in the skin, C_{M1} , is generated from its equilibrium with the concentration of the drug in the vehicle, C_{VEH} , through the product of its partition coefficient between the two phases $K_{M1:VEH}$ and C_{VEH} . The concentration of the drug in the skin approaches its saturated solubility in the skin, S_{M1} , and a thermodynamic activity (α_{M1}) of one when C_{VEH} approaches the saturated solubility of the drug in a noninteractive vehicle, S_{VEH} ; that is, α_{VEH} also is one. The flux J is now the maximum possible flux from noninteractive vehicles, J_M , and Fick’s law can be written as Eq. 10.1. Regardless of the value for S_{VEH} , the highest concentration of drug in the skin that is possible from a drug applied in a noninteractive vehicle is S_{M1} . As S_{VEH} increases $K_{M1:VEH}$ tends to decrease and as S_{VEH} decreases $K_{M1:VEH}$ tends to increase. S_{M1} can only be increased by using an interactive component in the vehicle that changes the solubilizing capacity of the skin, the “pull,” or by increasing the thermodynamic activity of the drug in the vehicle, α_{VEH} , so that it is greater than one, the “push,” and hence the activity of the drug in the skin, α_{M1} , is also greater than one.

$$J_M = (D/L)(S_{M1} - C_{Mn}) \quad (10.1)$$

10.2 Basis for Prodrugs as Penetration Enhancers

Although increasing the “push” can be easily accomplished by manipulating the components of the vehicle in which the drug is applied (its

formulation), increasing the “pull” can be more easily accomplished using a prodrug approach that changes the solubility properties of the drug. A prodrug is a chemically or enzymatically reversible derivative of a parent drug that improves the physicochemical or biological properties of the parent drug molecule to overcome some intrinsic problem associated with its therapeutic use: in this case, poor solubility in the skin and hence low topical delivery (Sloan 1992). The particular combination of functional groups that is added to the parent drug is called the promoiety, and the reversible connection between the promoiety and the parent drug is called the enabling functional group. A prodrug approach, then, can be envisaged as a 1:1 molecular combination of the drug and a promoiety that contains functional groups that will increase its solubility in the skin (Sloan and Wasdo 2003). This prodrug approach stands in sharp contrast to most formulation approaches where large molar excesses of penetration enhancers as vehicle components are routinely needed to increase S_{M1} for the drug.

What are the properties of the functional groups in the promoiety which, when added to the parent drug, could be reasonably expected to cause an increase in S_{M1} of the resulting prodrug compared to the parent drug and hence to cause an increase in its maximum flux, J_M ? Since it is difficult to measure S_{M1} of the prodrug, it is more convenient to measure its J_M in diffusion cell experiments and assume, based on Fick’s law Eq. 10.1, that there is a direct relationship between increased J_M and increased S_{M1} . Using increases in J_M as the criterion for increased S_{M1} , it has been observed for quite some time that for homologous series of more lipophilic prodrugs that the more water soluble members of the series gave the greatest increase in J_M and not the more lipid soluble members (Sloan 1989, 1992; Sloan et al. 1984). In order to account for these qualitative observations, S_{M1} in Fick’s law Eq. 10.1 was expanded mathematically to include dependence on solubility in a lipid, S_{LIPID} , and in water, S_{AQ} . This form of Fick’s law is the Roberts-Sloan (RS) Eq. 10.2 (Roberts and Sloan 1999): a transformation of the popular, but very specific, Potts-Guy (PG) Eq. 10.3 (Potts and Guy 1992) into more general, useful terms.

$$\text{Log } J_M = x + y \log S_{\text{LIPID}} + (1 - y) \log S_{\text{AQ}} - z \text{MW} \quad (10.2)$$

$$\text{Log } P = x + y \log K_{\text{OCT:AQ}} - z \text{MW} \quad (10.3)$$

When a database of those homologous series of more lipid soluble prodrugs ($n=42$) comprised of their molecular weights, MW, their solubilities in isopropyl myristate (IPM), S_{IPM} ($S_{\text{IPM}}=S_{\text{LIPID}}$ in Eq. 10.2), and in water, S_{AQ} , and their maximum fluxes from IPM through hairless mouse skin, J_{MMIPM} , were collected and fitted to Eq. 10.2, the values for the coefficients were $x=-0.211$, $y=0.534$, $z=0.00364$, and $r^2=0.937$ (Roberts and Sloan 1999). The size of the J_{MMIPM} database has since been increased to $n=94$, and the values for the coefficients are now $x=-0.377$, $y=0.527$, $z=0.00346$, and $r^2=0.900$ (Majumdar et al. 2012). The maximum fluxes of prodrugs and non-prodrug through human skin in vitro and in vivo, respectively, from mineral oil (MO), J_{MHMO} , their solubilities in mineral oil, S_{MO} ($S_{\text{MO}}=S_{\text{LIPID}}$ in Eq. 10.2), and in water, S_{AQ} , and their MW also gave good fit to Eq. 10.2: $x=-1.83$, $y=0.462$, $z=0.00153$, and $r^2=0.80$ for $n=30$ prodrugs (Sloan et al. 2011); $x=-1.459$, $y=0.72$, $z=0.00013$, and $r^2=0.934$ for $n=10$ nonsteroidal anti-inflammatory drugs (Wenkers and Lippold 1999; Roberts and Sloan 2001). Thus, good fits to Eq. 10.2 are obtained if the vehicle is a lipid (IPM or MO) and the lipid solubility of the permeant, S_{LIPID} , and S_{AQ} are independent variables.

A similar strong dependence of maximum flux through hairless mouse from water, J_{MMAQ} , on S_{IPM} ($S_{\text{IPM}}=S_{\text{LIPID}}$ in Eq. 10.2) and S_{AQ} for some of the members of the $n=94$ J_{MMIPM} database was observed where $x=-2.30$, $y=0.575$, $z=0.0016$, and $r^2=0.903$ for $n=32$ (Sloan et al. 2003; Wasdo et al. 2009). Also a strong dependence of maximum flux through human skin in vitro from water, J_{MHAQ} , on the solubilities of the permeants in octanol, S_{OCT} ($S_{\text{OCT}}=S_{\text{LIPID}}$ in Eq. 10.2) and S_{AQ} , was observed where $x=-2.506$, $y=0.538$, $z=0.00402$, and $r^2=0.839$ for $n=185$ (Juntunen et al. 2008). Even maximum flux through silicone membranes from water, J_{MPAQ} , for some of the members of the $n=94$ J_{MMIPM} database was found to be dependent on S_{IPM} ($S_{\text{IPM}}=S_{\text{LIPID}}$ in Eq. 10.2)

and S_{AQ} where $x=-1.837$, $y=0.742$, $z=0.00435$, and $r^2=0.86$ for $n=38$ (Synovec et al. 2013). Thus, good fits to Eq. 10.2 are obtained regardless of whether the membrane is mouse, human, or silicone and regardless of whether the vehicle is a lipid or aqueous. Since the solubilities of the permeant in a lipid and in water are both necessary to define maximum flux, functional groups should be incorporated into the promoieties of prodrugs that can ideally increase both lipid and aqueous solubilities to increase maximum flux and by inference S_{M1} .

The reason that increasing both lipid and aqueous solubilities of the drug is important to increasing its solubility in skin, and hence its topical delivery, can be found in the structure of the barrier to topical delivery – the intercellular compartment of the stratum corneum (SC). The intercellular compartment consists of lamellar double bilayers comprised of lipid components such as ceramides, cholesterol, and fatty acids which have polar groups attached to them. These polar head groups have water associated with them so that for a permeant to cross these bilayers perpendicular to the axis of the bilayers, it must alternately cross lipid and aqueous phases (Sloan and Wasdo 2003; Sloan et al. 1984, 2011a, b). Thus, a balance of solubility in both lipid and aqueous phases by the drug (or increased lipid and aqueous solubility by its prodrug) is necessary for its most efficient permeation of the intercellular compartment of the SC. The agreement between the experimentally measurable physico-chemical parameters in the theoretically derived Roberts-Sloan equation and in the biochemically based biphasic solubility model (Sloan et al. 2011a, b) for the barrier to permeation is encouraging.

10.3 Acyl Versus Soft Alkyl Promoieties

The promoieties that have been used to increase lipid and aqueous solubilities can be divided into two types based on whether they are attached directly to the functional group in the parent drug that is to be modified or indirectly through a

methylene or vinylogous methylene (aryl methylene) spacer (Sloan 1989, 1992; Sloan and Wasdo 2003). In each type, the enabling functional group is usually a carbonyl-type functional group because of its sensitivity to cleavage by chemical or enzymatic hydrolysis. Generally these types have been referred as acyl and soft alkyl-type promoieties, respectively. Cleavage of the acyl-type promoiety regenerates the parent drug directly while cleavage of the acyl group in the soft alkyl promoiety generates an intermediate drug–X–CHR–X'H from drug–X–CHR–X'–(C=X'')–X'''R': X, X', X'', and X''' can be O, N, or S and R and R' can be alkyl or aryl. The intermediate is designed to be intrinsically unstable and undergo rapid and complete chemical hydrolysis to the parent drug–X–H. The advantage of the soft alkyl prodrug approach is that the stability of the prodrug (as well as its attendant physicochemical properties) is not limited by the functional group in the parent drug to which it is attached. Generally, changing X will change the biochemical and/or pharmacological activity of the drug, but changing X' to obtain a more or less stable or more or less soluble prodrug will not. Of course X'' and X''' can be changed in the same ways that they could have been if an acyl prodrug approach had been used.

10.4 Mechanisms for Penetration Enhancement

10.4.1 Decrease Crystal Lattice Energy by Masking Hydrogen Bond Donor Functional Groups

Regardless of whether the prodrug is derived from an acyl or soft alkyl-type promoiety, there are two general mechanisms by which both types of promoieties can increase both lipid and aqueous solubilities. The first mechanism has its basis in decreasing the crystal lattice energy of the parent drug by modifying polar groups capable of forming intermolecular hydrogen bonds. In many if not most drug molecules, the X in drug–X–H is a heteroatom which causes X–H to be polarized because

of the difference in electronegativities between X and H. This polarized drug–X–H bond is capable of forming intermolecular hydrogen bonds within the crystal lattice which leads to low solubilities especially in lipids but also frequently in water. The polarization is further attenuated if an electron withdrawing carbonyl-type functional group is attached to X–H to give drug–(O=C)–X–H. Examples of this type of drug molecule, which can be measurably but not highly ionized at physiological pH, include heterocycles such as 5-fluorouracil (5-FU) (drug–(O=C)–NH) and 6-mercaptopurine (6-MP) (drug–(S=C)–NH) which are very high melting and exhibit low solubilities in both water and lipids. In other examples such as parent drugs containing a carboxylic acid functional group (drug–(O=C)–OH), the functional group is so highly polarized that it becomes highly ionized at physiological pH which does not allow it to readily cross the lipid phase of the alternating lipid-aqueous phases of the biological barrier. An important class of drugs that belong to this category is the nonsteroidal anti-inflammatory drugs. Another example of this class are the nucleotide-based drugs where the highly ionized functional group is a phosphate group. Simply masking the hydrogen bond donating abilities of the functional group by replacing the H in the drug–X–H with either an acyl or soft alkyl group decreases the melting point (*mp*) and increases the lipid solubility (S_{LIPID}) as well as frequently increasing the aqueous solubility (S_{AQ}) of the prodrug compared to the parent drug, especially for the shorter alkyl chain members of a homologous series (Sloan 1989).

Examples of the results that can be obtained by masking the polar functional groups in drugs to increase S_{LIPID} (S_{IPM}) and S_{AQ} and to increase topical delivery of the parent drug are several prodrugs of 5-FU.

The *mp*, S_{AQ} , S_{IPM} , log partition coefficients between IPM and pH 4.0 buffer ($\log K_{\text{IPM:AQ}}$), and rates of delivery of total 5-FU containing species through hairless mouse skin from an IPM vehicle in vitro (J_{MMIPM}) for four different series of prodrug of 5-FU are given in Table 10.1: three acyl types and a one soft alkyl type. The first acyl type of prodrug of 5-FU that was evaluated for its ability to increase the delivery of 5-FU was the alkylaminocarbonyl-5-FU (1-AAC-5-FU) prodrugs

Table 10.1 Prodrugs of 5-fluorouracil

Prodrugs, $R=^a$	mp^b	S_{IPM}^c	$S_{AQ}^{c,d}$	$\text{Log } K_{IPM:AQ}^e$	J_{MMIPM}^f
1-AAC-5-FU					
1 , C1NHC=O	212	0.30	3.69	-1.09	0.208
2 , C2NHC=O	180	2.79	7.76	-0.44	0.600
3 , C3NHC=O	139	12.4	8.98	0.14	0.746
4 , C4NHC=O	133	24.6	5.11	0.68	0.515
5 , C6NHC=O	113	44.9	0.36	2.09	–
6 , C8NHC=O	91	46.9	0.030	3.21	0.060
1-AOC-5-FU					
7 , C1OC=O	160	2.13	112	-1.72	2.62
8 , C2OC=O	128	13.1	175	-1.12	5.92
9 , C3OC=O	126	15.2	42.2	-0.44	2.31
10 , C4OC=O	98	33.8	24.1	0.15	2.23
11 , C6OC=O	67	153	4.94	1.49	1.54
12 , C8OC=O	98	36.2	0.13	2.45	0.29
1-AC-5-FU					
13 , C1C=O	130	22.1	120	-0.73	9.3
14 , C2C=O	131	36.4	47.6	-0.12	4.3
15 , C3C=O	146	17.4	6.50	0.43	1.3
16 , C4C=O	121	39.2	3.48	1.05	1.0
17 , C5C=O	102	112.7	2.94	1.58	1.1
18 , C7C=O	84	110.7	0.15	2.88	0.60
1-ACom-5-FU					
19 , C1(C=O)OCH ₂	124	3.29	183	-1.74	2.88
20 , C2(C=O)OCH ₂	102	9.83	167	-1.23	3.82
21 , C3(C=O)OCH ₂	91	14.4	42.4	-0.47	2.57
22 , C4(C=O)OCH ₂	88	14.8	12.3	0.08	1.29
23 , C5(C=O)OCH ₂	91	14.7	2.23	0.82	0.56
24 , C7(C=O)OCH ₂	108	9.99	0.17	1.77	0.12
5-FU, H	284	0.049	85.4 ^g	-3.24 ^h	0.240

^aC1, C2, etc., refer to the number of carbons in alkyl chain

^bUnits of °C

^cSolubilities in units of mM

^dEstimated from $S_{IPM}/K_{IPM:AQ}$

^ePartition coefficient between IPM and pH4.0 buffer at 23 ± 1 °C

^fValues for the delivery of total species containing 5-FU through hairless mouse skin from IPM in vitro in units of $\mu\text{mol cm}^{-2} \text{h}^{-1}$

^gSolubility in pH 4.0 buffer

^hLog solubility ratio between pH 4.0 buffer and IPM

(Table 10.1 and Fig. 10.1). Initially only the longer alkyl chain members of the series were evaluated (4–6) (Sasaki et al. 1990), but subsequently the shorter alkyl chain members (1–3) were evaluated, and one of them, 3, was found to give the greatest increase in the delivery of the total 5-FU containing species, J_{MMIPM} (Sloan et al. 1993). All of the 1-AAC-5-FU prodrugs exhibited lower mp than 5-FU and all of them were more soluble in IPM than 5-FU: from 6 times for 1 to almost

1,000 times for 6. However, the most lipid soluble member evaluated, 6, gave only 0.25 times the flux of 5-FU. None of the 1-AAC-5-FU prodrugs was even as soluble in water as 5-FU, and the C3 member (3), not the shortest alkyl chain member of the series (1), gave the highest S_{AQ} value: only 0.11 times S_{AQ} for 5-FU. The C3 member also gave the greatest increase in J_{MMIPM} values for the series, albeit only three times. Thus, as predicted (Sloan 1992, 1989; Sloan and

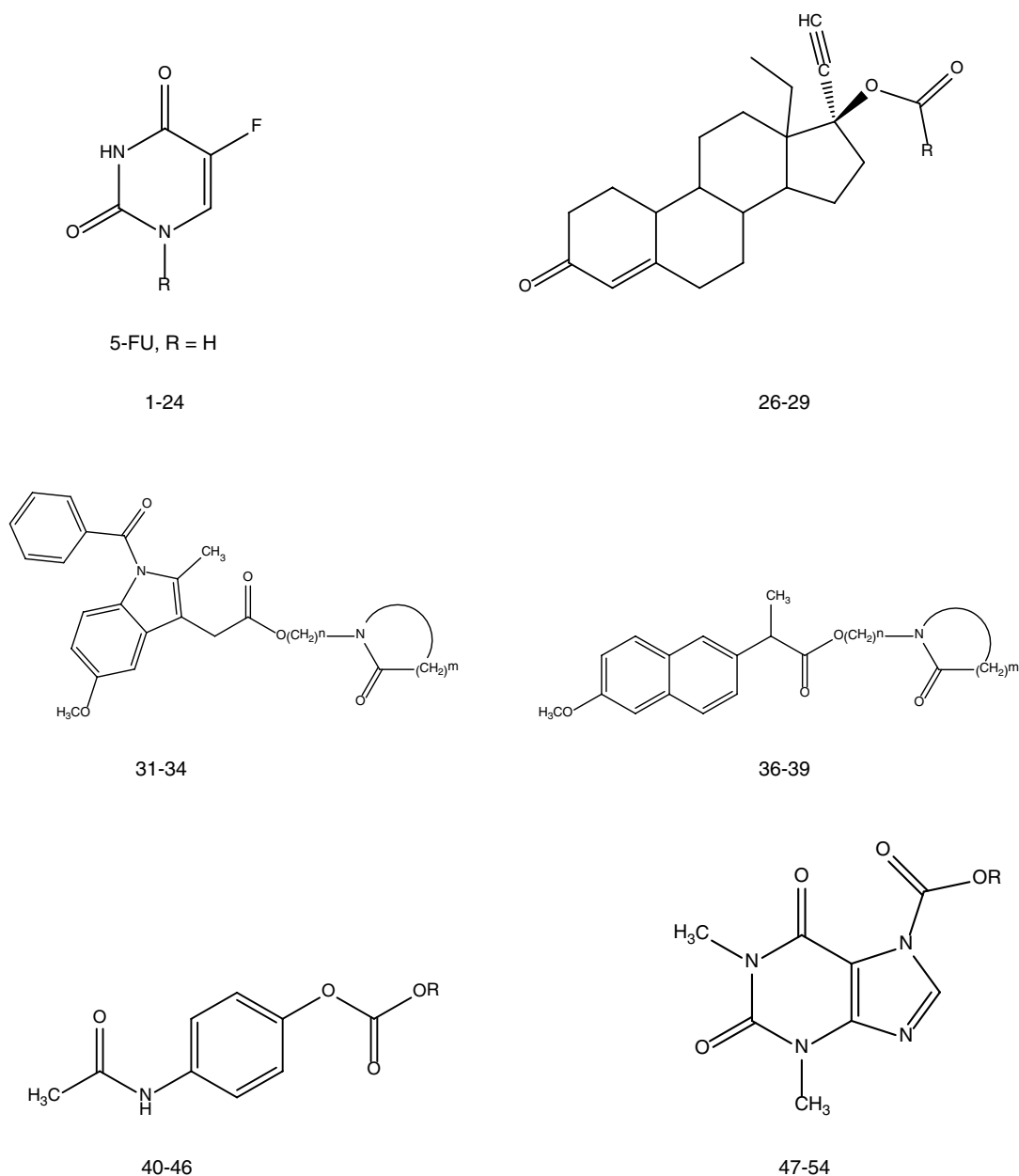


Fig. 10.1 Chemical structures of prodrugs for compounds 1-54

Wasdo 2003; Sloan et al. 1984), for a more lipid soluble homologous series of prodrugs, the more water soluble member gave the highest J_{MMIPM} value. The low increase in J_{MMIPM} can be attributed to the low S_{AQ} values exhibited by the 1-ACC-5-FU prodrugs compared to subsequent

series, and the low S_{AQ} values can be attributed to the fact that one of the hydrogen bond donor functional groups, $(\text{O}=\text{C})-\text{NH}$, in 5-FU was merely replaced with another hydrogen bond donor group, $\text{N}-(\text{O}=\text{C})-\text{NH}$, in the pro-moiety. The potential for forming intermolecular

hydrogen bonds was not decreased significantly and the added alkyl group in the promoiety further depressed S_{AQ} .

The second acyl type of prodrug of 5-FU that was evaluated was the alkyloxycarbonyl-5-FU (1-AOC-5-FU) prodrugs (Table 10.1, Fig. 10.1) (Beall et al. 1994). In this series the hydrogen bond donating group in the parent drug has not been replaced with another hydrogen bond donating group in the promoiety so the mp are somewhat lower than the corresponding members in the 1-AAC-5-FU series except for the C8 member of the series. Consequently, the members of the 1-AOC-5-FU series were also somewhat more soluble in IPM than the members of the 1-AAC-5-FU series except for the C8 member, **12**; and the worst member of the series in terms of increased S_{IPM} was 43 times instead of 6 times more soluble in IPM than 5-FU. However, the big difference between the two series was in the S_{AQ} values. Not only were two members of the series more water soluble than 5-FU, **7** and **8** (1.3 and 2 times, respectively), but they were all more water soluble than the corresponding members of the 1-AAC5-FU series (from 30 to 4.3 times). Thus, since the 1-AOC-5-FU series was more soluble in lipids and in water, as predicted (Sloan 1989, 1992; Sloan et al. 1984), they delivered more total 5-FU species through hairless mouse skin than the 1-AAC-5-FU series (from 3 to 12.5 times). Also, as predicted (Sloan 1989, 1992; Sloan et al. 1984) the C2 member, **8**, which was the most water soluble member of the series gave the greatest increase in J_{MMIPM} compared to 5-FU (24.7 times), and not the most lipid soluble member of the series, **11**. The next most water soluble member, **7**, gave the next greatest increase in J_{MMIPM} compared to 5-FU (11 times).

Based on previous literature, the 1-AOC series was expected to be more stable than the 1-AAC series of prodrugs of 5-FU. Whereas the amount of intact prodrug delivered by the 1-AAC series was in the 6–10 % range, the amount delivered by the 1-AOC series was in the 40–70 % range and was up to 90 % for the best performing member of the series, **8**. If delivery through the skin and subsequent slower release

of 5-FU systemically was the target of topical delivery, then the members of the 1-AOC-5-FU series performed well. On the other hand, if delivery into the skin was the target, then a more rapidly hydrolyzing type of prodrug of 5-FU would be required.

The third acyl type of prodrug 5-FU that was evaluated was the alkylcarbonyl-5-FU (1-AC-5-FU) prodrugs (Table 10.1, Fig. 10.1) (Beall et al. 1996). The members of this series were known to hydrolyze quite rapidly ($t_{1/2}=3-5$ min), so it was expected that only 5-FU would be delivered through the skin. This expectation was realized, and only 5-FU and no intact prodrug was observed in the receptor phase after application of 1-AC-5-FU prodrugs in IPM in diffusion cell experiments. All of the members of the 1-AC series were much more soluble in IPM than 5-FU (355–2,300 times), and one member, C1 (**13**), was more soluble in water than 5-FU (1.4 times). However, direct comparisons between the 1-AC series and either the 1-AOC or the 1-AAC series based only on the alkyl chain length in the promoiety would be misleading without taking into account the added heteroatom in the latter two series. For example, we will compare the OC1 member (**7**) of the 1-AOC series with the C2 member of the 1-AC series (**14**), the OC2 with the C3, the OC3 with the C4, the OC4 with the C5, and the OC6 with the C7. Using these interseries comparisons, the members of the 1-AC series were more soluble in IPM (1.3–17 times) than those of the 1-AOC series, except for **18** compared to **11**. On the other hand, the members of the 1-AOC series were more soluble in water (2.4–33 times) than those of the 1-AC series, and as predicted (Sloan 1989, 1992; Sloan et al. 1984) they all gave higher J_{MMIPM} values than the corresponding members of the 1-AC series, except for OC1, **7**, versus C2, **14**. Prodrug **7** was only 2.4 times more soluble in water than **14**, while **14** was 17 times more soluble in IPM than **7**. Prodrug **14** exhibited a somewhat better balance of S_{AQ} and S_{IPM} than **7** and gave a higher J_{MMIPM} value (1.6 times). However, within the 1-AC series the C1 member, **13**, which was the more water soluble member of the series and not one of the more lipid soluble members, gave the

greatest enhancement in J_{MMIPM} (39 times that of 5-FU).

In the 1-AC series the effect of the *mp* on solubilities and ultimately on flux can be readily illustrated. The C3 member of the series, **15**, exhibited a higher *mp* than either the shorter, **14**, or longer alkyl chain member, **16**, and hence exhibited a lower S_{IPM} value than those members. The S_{AQ} value for **15** also dropped off more rapidly than expected as did its J_{MMIPM} value. On the other hand, the log *K* values appeared normally spaced and the methylene π values derived from the log *K* values only varied by 10 %: $\pi=0.59\pm 0.05$. Thus, log *K* values are no substitute for experimental solubilities for purposes of predicting trends in J_{M} .

The example of the use of a soft alkyl prodrug in the designs of prodrugs to increase S_{IPM} and S_{AQ} and to increase the topical delivery of the parent drug is also a 5-FU prodrug: the 1-alkylcarbonyloxymethyl-5-FU (1-ACOM-5-FU) prodrugs (Table 10.1, Fig. 10.1) (Taylor and Sloan 1998). As expected each of the 1-ACOM-5-FU prodrugs exhibited a lower *mp* than 5-FU since a hydrogen bond donor group had been masked in the prodrug. Also as expected each was much more soluble in IPM than 5-FU (67–302 times), and there were members, **19** and **20**, that were more soluble in water than 5-FU (2.1 and 1.9 times, respectively). As predicted (Sloan 1989, 1992; Sloan et al. 1984) **19** and **20** were the members that gave the greatest enhancement in J_{MMIPM} (12 and 16 times, respectively) and not the more lipid soluble, longer alkyl chain members of the series. However, to compare members of the 1-ACOM series with members of any one of the 1-acyl series, the added heteroatom and methylene spacer in the 1-ACOM series needs to be taken into account. Thus, comparison should be made between the C1 member of the 1-ACOM series, **19**, and the C3 member of the 1-AC, **15**; or the C2 member of the 1-AOC series, **8**, the C2 member of the 1-ACOM series, **20**, and the C4 member of the 1-AC series, **16**; or the C3 member of the 1-AOC series, **9**, etc. Using these interseries comparisons, the members of the 1-ACOM series were less soluble in IPM but much more soluble in water (15.0–48.0 times) than the members of the

1-AC series, and their J_{MMIPM} values were greater except for the comparison between **23** and **18** where the J_{MMIPM} values were equivalent. On the other hand, although the members of the 1-ACOM series were less soluble in IPM than the members of the 1-AOC series, in this comparison only two members of the 1-ACOM series, **20** and **21**, were substantially more soluble in water (4.0 and 1.8 times, respectively) and hence gave greater J_{MMIPM} values than the corresponding members of the 1-AOC series. In the comparison of **19** and **8**, the S_{AQ} values were very close and **8** was four times more lipid soluble, so **8** gave a two times greater increase in J_{MMIPM} . Similarly, **11** was 2.2 times more water soluble and ten times more IPM soluble than **23**, so **11** gave a three times greater increase in J_{MMIPM} .

Thus, the general mechanism for increasing lipid and aqueous solubilities of a drug by decreasing its ability to form intermolecular hydrogen bonds in the crystal lattice can be very effective (11–40 times enhancement of flux). But it is essential to evaluate the shorter alkyl chain members of any series to be considered because those are the members that are most likely to be more water soluble as well as more lipid soluble. In the examples based on 5-FU, the increases in flux realized with these acyl and soft alkyl prodrug approaches are more than sufficient to enlarge the indicated use of topical 5-FU from treating only actinic keratoses of the scalp (Dillaha et al. 1965) to treating recalcitrant psoriasis on less permeable areas of the body (Tsuji and Sugai 1972).

10.4.2 Incorporation of Water Solubility Enhancing Functional Groups into Promoiety

The second general mechanism by which acyl and soft alkyl promoiety can be used to increase the lipid and aqueous solubilities of prodrugs compared to their parent drugs is to incorporate polar, water solubilizing groups into their promoiety. In the examples illustrating the previous mechanism, the primary effect of the prodrug

modification was to increase lipid solubility because the promoiety contained only an enabling functional group and a simple alkyl group. Although large increases in S_{IPM} were realized for all members of homologous series, increases in S_{AQ} were usually modest (less than two times) and only for the shorter alkyl chain members. In the examples illustrating the second general mechanism, the promoiety contains an additional amine, amide, ether, or diol functional group which in retrospect could have been designed specifically to increase S_{AQ} . However, in most examples S_{AQ} values were not available from the original references.

The first example is the use of a diol functional group in the promoiety to increase the S_{AQ} of the prodrug and hence J_M for the delivery of the parent drug.

Although the stated rationale was that more hydrophilic prodrugs could overcome the perceived rate limiting contribution of the aqueous viable epidermis part of the barrier to permeation of the skin by highly lipophilic drugs (Friend et al. 1988), the success of such prodrugs would also support a model for permeation where alternating lipid-aqueous barriers must be crossed in the intercellular compartment of the SC (Sloan et al. 1984, Sloan et al. 2011a, b. In Table 10.2 the mp ($^{\circ}C$), solubilities in mixtures of ethanol and water (S_{VEH}), $\log K$ between octanol, and pH 7.4 buffer ($\log K_{OCT:AQ}$) and fluxes of total species delivered from suspensions in ethanol and water (VEH) through rat skin in vitro (J_{MHVEH}) are given for the evaluation of four acyl prodrugs of levonorgestrel.

Two of the prodrugs in Table 10.2 (Fig. 10.1) were simple alkylcarbonyl prodrugs: **26** and **27**. Neither was representative of the shorter alkyl chain members of the series which would have had the greatest potential for increased aqueous as well as lipid solubility. Since **26** and **27** were both more soluble in 95 % ethanol than levonorgestrel, **25**, was soluble in 100 % ethanol, it is reasonable to assume they would also be more soluble in octanol and hence be defined as more lipophilic than **25**. Since partition coefficients for **26** and **27** could not be obtained because no **26** or **27** could be measured in the aqueous phase (while **25** could), it is reasonable to assume that

Table 10.2 Prodrugs of levonorgestrel

Prodrugs, $R =$	mp^a	S_{VEH}^b	Log $K_{OCT:AQ}^c$	J_{MHVEH}^d
25 , levonorgestrel	240	19.2 (100)	3.70	0.00019
26 , C_5H_{11}	86	604 (95)		
		12.9 (62)		0.00058
27 , C_4H_9	170	28.3 (95)		0.00026
28 , $OCH_2CH(OH)CH_2OH$	148	30.2 (40)	3.22	0.0063
29 , $O(CH_2)_4CH(OH)CH_2OH$	53	396 (40)	3.75	0.0030

^aUnits of $^{\circ}C$

^bSolubilities in mixtures of ethanol:water in units of mM where the value in parenthesis is percentage of ethanol in the mixture

^cPartition coefficient between octanol and water at 24 $^{\circ}C$

^dValues for delivery of total species containing levonorgestrel from suspensions in mixtures of ethanol:water (given in the S_{VEH} column) through rat skin in vitro in units of $\mu mol\ cm^{-2}\ h^{-1}$

26 and **27** were less hydrophilic than **25**. Finally, since the flux of **25** from various ethanol and water (40–100 %) mixtures did not vary significantly (applications of ethanol and water mixtures did not change S_{MI}), it can be assumed that delivery of total species containing **25** by the prodrugs from widely different ethanol and water mixtures can be compared to the average flux generated by the application of **25** ($0.00020\ \mu mol\ cm^{-2}\ h^{-1}$) in ethanol and water mixtures. Thus, **26** and **27**, which were more soluble in lipids but estimated to be less soluble in water, gave 3 and 1.3 times greater J_{MHVEH} values, respectively, than **25**. Only **25** was observed in the receptor phases.

By comparison, since the two prodrugs containing a diol functional group in the promoiety, **28** and **29**, were both more soluble in an ethanol and water mixture that was primarily aqueous in composition (40 % ethanol) than **25** was in 100 % ethanol, it can be reasonably assumed that **28** and **29** were more soluble in water than **25**. In addition, since **28** and **29** exhibit $\log K_{OCT:AQ}$ that were comparable to that of **25** and were more soluble in water than **25**, it can be reasonably assumed that **28** and **29** were more soluble in octanol than **25**, that is, more lipophilic. Thus, since **28** and **29** were

more soluble in a lipid and in water than their parent drug, as predicted (Sloan 1989, 1992; Sloan et al. 1984), they gave much larger increases in J_{MHVEH} than the simple alkylcarbonyl prodrugs that were only more soluble in a lipid (31 and 15 times, respectively). However, because of their greater stabilities as carbonate esters, they delivered mostly intact prodrug through the skin (80 and 96 %, respectively).

The second example is the use of an amide functional group in the promoiety to increase S_{AQ} of the prodrug and hence J_{M} for the delivery of the parent drug. The first report of the synthesis of a promoiety containing an amide functional group as part of an effort to increase topical delivery was for theophylline: 7-(*N*, *N*-diethylsuccinamoyloxymethyl) theophylline (Sloan and Bodor 1982). However, the prodrug was never completely evaluated. More recently 1-alkylazacycloalkan-2-one esters of indomethacin, **30** (Bonina et al. 1991), and naproxen, **35** (Bonina et al. 1993), have been synthesized and evaluated.

In Table 10.3 (Fig. 10.1) the values of S_{IPM} , S_{AQ} , and rates of delivery of total species containing **30** or **35** from water through human skin in vitro (J_{M}) are given. For the indomethacin series, the second member of the series, **32**, was the only member of the series that exhibited a greater S_{AQ} than indomethacin, and although it was barely as soluble in IPM as indomethacin, it caused the greatest enhancement of J_{MHVEH}

(4 times). The more lipid soluble but less water soluble members gave lower enhancement of J_{MHAQ} . For the naproxen series, the first member of the series, **36**, was more soluble in water (8 times) than naproxen and was more soluble in water than the other members of the series. Prodrug **36** was also more soluble in IPM than the other members of the series but none were as soluble as naproxen. Thus, **36**, which was more soluble in lipids and water than the other members of the series, gave the greatest enhancement in J_{MHAQ} (2.7 times) as would be predicted (Sloan 1989, 1992; Sloan et al. 1984).

There are two additional observations that can be made about these two series of prodrugs which have an amide functional incorporated into the promoiety. First, although the S_{IPM} values for the two series are comparable, the S_{AQ} values for the naproxen series (**36–39**) are almost uniformly ten times greater than those for the indomethacin series (**31–34**), and consequently the J_{MHAQ} values for the naproxen series are almost uniformly ten times greater. Second, although more labile soft alkyl-type prodrugs ($n=1$) had been synthesized, they were never evaluated because they were considered to be too labile. On the other hand, the $n=2$ prodrugs were too stable, and only 10–12 % of either parent drug was observed in the receptor phases of the diffusion cell experiments in which they were evaluated. It would have been interesting to have evaluated the $n=1$ series of prodrugs using an IPM vehicle, in which they would have been stable, to determine how effective they might have been at delivering the parent drug.

The third example is the use of an amine functional group in the promoiety to increase the S_{AQ} of the prodrug and hence J_{M} . Again the first report of the synthesis of a promoiety containing an amine functional group as part of an effort to increase the topical delivery of a parent drug was for theophylline: 7-(*N*, *N*-dimethylaminoacetyloxymethyl) theophylline (Sloan and Bodor 1982). However, again the prodrug was never completely evaluated. More recently the 17-(4'-dimethylaminobutyrate) ester prodrug of testosterone was evaluated using a 10 % solution of the prodrug in pH 7.4 buffer (Milosovich et al. 1993). Compared to the

Table 10.3 Prodrugs of indomethacin and naproxen

Prodrugs	$S_{\text{IPM}}^{\text{a}}$	S_{AQ}^{a}	$J_{\text{MHAQ}}^{\text{b}}$
30 , indomethacin	7.82	0.011	0.23
31 , $n=2, m=3$	6.00	0.0096	0.80
32 , $n=2, m=4$	7.34	0.016	0.96
33 , $n=2, m=5$	19.0	0.012	0.77
34 , $n=2, m=6$	27.5	0.0074	0.19
35 , naproxen	23.5	0.045	5.1
36 , $n=2, m=3$	21.1	0.355	13.8
37 , $n=2, m=4$	18.8	0.249	8.9
38 , $n=2, m=5$	16.7	0.032	4.0
39 , $n=2, m=6$	7.64	0.011	2.8

^aSolubilities in units of mM

^bValues for delivery of total species containing parent drug from water through human skin in vitro in nmol $\text{cm}^{-2} \text{h}^{-1}$

delivery from a suspension of testosterone in pH 7.4 buffer, the prodrug was 60 times more effective at delivering testosterone. Although no solubility data were reported, a 10 % solution of the prodrug was evaluated which suggests that it is substantially more soluble in water than testosterone which was soluble only to the extent of 0.004 %. The 2-diethylaminoethyl ester prodrug of indomethacin was also evaluated by the same group (Jona et al. 1995). It was reported that the prodrug drug was 3.7 times more soluble in pH 7.4 buffer and its partition coefficient between octanol and pH 7.4 buffer was 6.2 times greater than that of indomethacin so the prodrug was also much more soluble in octanol (23 times). Thus, it was entirely predictable (Sloan 1989, 1992; Sloan et al. 1984) that the prodrug gave a 4.3 times enhancement in the delivery of total indomethacin containing species through human skin in vitro.

The fourth example is the use of an ether functional group in the promoity to increase the S_{AQ} of the prodrug and hence J_M . There are numerous reports in the literature where polyoxyethylene (POE) esters have been used as prodrugs to enhance oral delivery (Greenwald 2001) but only a few where POE esters have been used to enhance topical delivery. One of the limiting factors associated with using data from previous reports on the use of prodrugs containing oxyethylene groups in their promoities to enhance the topical delivery of their parent drugs to design new prodrugs is the lack of experimental values

for S_{LIPID} (S_{OCT} , S_{MO} , S_{IPM}), S_{AQ} , and $K_{LIPID:AQ}$ in the literature (Bonina et al. 2001). This lack of experimental solubility and K data makes it impossible to predict changes in the solubility of the prodrug, attributable to the properties of the promoity, compared to its parent in the membrane, S_{M1} , and hence J_M in Eq. 10.2.

However, there are several examples where those experimental S_{LIPID} and S_{AQ} values for prodrugs containing oxyethylene groups in their promoities have been reported together with their corresponding maximum flux values, J_M . In the first example, the effect of incorporating one oxyethylene group into carbonate derivatives of acetaminophen, APAP (Fig. 10.1), on their S_{LIPID} and S_{AQ} was compared with the effect of incorporating an alkyl group into carbonate derivatives of APAP on their S_{LIPID} and S_{AQ} (Table 10.4) (Wasdo and Sloan 2004).

The resulting effect on experimental J_{MMIPM} was predictable based on the fit of the data to Eq. 10.2 (Roberts and Sloan 1999). The best alkyl carbonate in terms of enhancing J_{MMIPM} was the C1 derivative, and the best oxyethylene carbonate was $CH_2CH_2OCH_3$. Although the $CH_2CH_2OCH_3$ carbonate was equally soluble in IPM and somewhat more soluble in water than the C1 carbonate, the C1 carbonate produced the greater J_M . The slightly better S_{AQ} of the $CH_2CH_2OCH_3$ carbonate was offset by its higher molecular weight which was predicted by Eq. 10.2 (Roberts and Sloan 1999) to reduce the value of J_M . Note that the solubility ratio (SR) for

Table 10.4 Acetaminophen, APAP, prodrugs

4-AOC-APAP	MW	mp ^a	Log S_{IPM}^b	Log S_{AQ}^b	Log J_{MMIPM}^c
40, C1 ^d	209	115	1.076	1.314	0.00
41, C2 ^d	223	122	0.968	0.577	-0.76
42, C3 ^d	237	106	1.375	0.427	-0.45
43, C4 ^d	251	120	1.143	-0.377	-1.01
44, C6 ^d	279	110	1.220	-1.328	-1.49
45, $CH_2CH_2OCH_3$	253	81	1.013	1.537	-0.11
46, $CH(CH_3)CH_2OCH_3$	267	123	0.529	0.516	-1.06
APAP	151	170	0.279	2.000	-0.29

^a°C

^bUnits of mM

^cUnits of $\mu\text{mole cm}^{-2} \text{h}^{-1}$

^dC1, C2 indicates the numbers of carbons in alkyl group

the $\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$ carbonate was greater than that for the $\text{CH}_2\text{CH}_2\text{OCH}_3$ carbonate derivative ($\log SR=0.013$ and -0.52 , respectively), but it was less soluble in both IPM and water than the $\text{CH}_2\text{CH}_2\text{OCH}_3$ carbonate derivative so it only produced about one tenth the maximum flux. This illustrates how misleading SR or K can be in predicting flux and indesigning optimized topical products.

Similarly, in the second example the effect of incorporating one or two oxyethylene groups into carbamate derivatives of theophylline, Th-H (Fig. 10.1), on their experimental S_{IPM} and S_{AQ} values was compared with the effect of incorporating alkyl groups into carbamate derivatives of Th-H on their S_{IPM} and S_{AQ} values (Table 10.5) (Majumdar et al. 2012).

Again the resulting effect on experimental J_{MMIPM} was predicted based on the fit of the data to Eq. 10.2 (Roberts and Sloan 1999). The best alkyl carbamate in terms of increasing J_{MMIPM} was the C3 derivative and the best oxyethylene carbamate derivative was the $(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_3$ derivative. The C3 alkyl carbamate was essentially equal in solubility in water to the C2 alkyl carbamate, but it was about 20 times more soluble in IPM. Therefore, the J_{MMIPM} for the C3 alkyl carbamate was about four times that of the C1 regardless of the negative effect of its increased molecular weight predicted by Eq. 10.2 (Roberts and Sloan 1999). Although the $(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_3$

carbamate derivative was only about 0.25 times as soluble in IPM as the C3 alkyl carbamate derivative, it was 11 times more soluble in water. Therefore, the J_{MMIPM} for the $(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_3$ carbamate derivative was about three times that of the C3 alkyl derivative regardless of the negative effect of its increased molecular weight. Among the oxyethylene carbamate derivatives, the $(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_3$ carbamate derivative was three times more soluble in water and 30 % more soluble in IPM than the $\text{CH}_2\text{CH}_2\text{OCH}_3$ carbamate derivative so, as predicted by Eq. 10.2 (Roberts and Sloan 1999), its J_{M} value was about two times that of the $\text{CH}_2\text{CH}_2\text{OCH}_3$ carbamate derivative. Although the $\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$ carbamate derivative was almost two times more soluble in IPM, it was only 0.40 times as soluble in water as the $\text{CH}_2\text{CH}_2\text{OCH}_3$ carbamate derivative so, together with its increased molecular weight, the effect of its solubilities on J_{MMIPM} led to its lower J_{MMIPM} value. Again, the $\log SR$ value for the $\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$ carbamate derivative was much more positive than that of the other oxyethylene carbamate derivatives, but its J_{MMIPM} value was lower, illustrating the misleading effect of SR and K in predicting flux.

In both examples, the incorporation of oxyethylene groups into the promoieties of prodrugs led to enhanced solubility properties of the prodrugs compared to their parent compounds that led to higher J_{M} values.

Table 10.5 Theophylline, Th-H, prodrugs

7-AOC-Th	MW	mp ^a	Log S_{IPM}^b	Log S_{AQ}^b	Log J_{MMIPM}^c
47, C1 ^d	238	175	0.28	1.45	-0.54
48, C2 ^d	252	141	0.65	1.18	-0.68
49, C3 ^d	266	87	1.59	1.43	0.03
50, C4 ^d	280	82	1.70	0.93	-0.19
51, C6 ^d	294	79	1.69	-0.27	-0.82
52, $\text{CH}_2\text{CH}_2\text{OCH}_3$	282	96	0.87	1.99	0.21
53, $(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_3$	326	64	0.97	2.49	0.56
54, $\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$	296	104	1.15	1.61	-0.31
Th-H	180	170	-0.47	1.66	-0.32

^a°C

^bUnits of mM

^cUnits of $\mu\text{mole cm}^{-2} \text{h}^{-1}$

^dC1, C2 indicates the numbers of carbons in alkyl group

Conclusion

Recognizing that one of the mechanisms for topical penetration enhancement involves increasing the solubility of the drug in the skin and that prodrugs increase the delivery of drugs into and through the skin by achieving the same, then it is quite clear that prodrugs constitute one type of penetration enhancer separate from formulation approaches. An even more powerful approach to enhancing topical delivery would be to use combinations of prodrugs with formulation approaches to enhancing topical delivery. So far there have been no reports of the use of such combinations except for simple one-component vehicles which have obviously not been optimized (Waranis and Sloan 1987). However, the possibilities with the use of such a combination approach would seem to be limitless.

References

- Beall H, Prankerd R, Sloan KB (1994) Transdermal delivery of 5-fluorouracil (5-FU) through hairless mouse skin by 1-alkyloxycarbonyl-5-FU prodrugs: physicochemical characterization of prodrugs and correlation with transdermal delivery. *Int J Pharm* 111:223–233
- Beall H, Prankerd R, Sloan KB (1996) Transdermal delivery of 5-fluorouracil (5-FU) by 1-alkylcarbonyl-5-FU prodrugs. *Int J Pharm* 129:203–210
- Bonina FP, Montenegro L, DeCapraris P, Bousquet E, Tirendi S (1991) 1-Alkylazacycloalkan-2-one esters as prodrugs of indomethacin for improved delivery through human skin. *Int J Pharm* 77:21–29
- Bonina FP, Montenegro L, Guerrero F (1993) Naproxen 1-alkylazacycloalkan-2-one esters as dermal prodrugs: in vitro evaluation. *Int J Pharm* 100:99–105
- Bonina FP, Puglia C, Barbuzzi T, DeCapraris P, Palagiano F, Rimoli MG et al (2001) In vitro and in vivo evaluation of polyoxyethylene esters as dermal prodrugs of ketoprofen, naproxen and diclofenac. *Eur J Pharm Sci* 14:123–134
- Coldman MF, Poulson BJ, Higuchi T (1969) Enhancement of percutaneous absorption by use of volatile: nonvolatile systems as vehicles. *J Pharm Sci* 58:1098–1102
- Dillaha CJ, Jansen GT, Honeycutt WM, Holt GA (1965) Further studies with topical 5-fluorouracil. *Arch Dermatol* 92:410–417
- Friend DR, Smedley SI (1993) Solvent drag in ethanol/ethyl acetate enhanced skin permeation of *d*-norgestrel. *Int J Pharm* 97:39–46
- Friend D, Catz P, Heller J, Reid J, Baker R (1988) Transdermal delivery of levonorgestrel II: effect of prodrug structure on skin permeability in vitro. *J Control Release* 7:251–261
- Greenwald RB (2001) PEG drugs: an overview. *J Control Release* 74:159–171
- Jona JA, Dittert LW, Crooks PA, Milosovich SM, Hussain AA (1995) Design of novel prodrugs for the transdermal penetration of indomethacin. *Int J Pharm* 123:127–136
- Juntunen J, Majumdar S, Sloan KB (2008) The effect of water solubility of solutes on their flux through human skin in vitro: a prodrug database integrated into the extended Flynn database. *Int J Pharm* 351:92–103
- Kadir R, Stempler D, Liron Z, Cohen S (1987) Delivery of theophylline into excised human skin from alkanolic acid solutions: a “push-pull” mechanism. *J Pharm Sci* 76:774–779
- Majumdar S, Mueller-Spaeth M, Sloan KB (2012) Prodrugs of theophylline incorporating ethyleneoxy-groups in the promoiety: synthesis, characterization and transdermal delivery. *AAPS PharmSciTech* 13:853–862
- Milosovich S, Hussain A, Dittert L, Aungst B, Hussain M (1993) Testosterone-4-dimethylaminobutyrate HCl: a prodrug with improved skin permeation rate. *J Pharm Sci* 82:227–228
- Potts RO, Guy RH (1992) Predicting skin permeability. *Pharm Res* 9:663–669
- Roberts WJ, Sloan KB (1999) Correlation of aqueous and lipid solubilities with flux of prodrugs of 5-fluorouracil, theophylline and 6-mercaptopurine: a Potts-Guy approach. *J Pharm Sci* 88:515–522
- Roberts WJ, Sloan KB (2001) Application of the transformed Potts-Guy equation to in vivo human skin data. *J Pharm Sci* 90:1318–1323
- Sasaki H, Takahashi T, Mori Y, Nakamura J, Shibasaki J (1990) Transdermal delivery of 5-fluorouracil and alkylcarbonyl derivatives. *Int J Pharm* 60:1–9
- Sloan KB (1989) Prodrugs for dermal delivery. *Adv Drug Deliv Rev* 3:67–101
- Sloan KB (1992) Functional group considerations in the development of prodrug approaches to solving topical delivery problems. In: Sloan KB (ed) *Prodrugs: topical and ocular drug delivery*. Marcel Dekker, New York, pp 17–116
- Sloan KB, Bodor N (1982) Hydroxymethyl and acyloxymethyl prodrugs of theophylline: enhanced delivery of polar drugs through skin. *Int J Pharm* 12:299–213
- Sloan KB, Wasdo S (2003) Designing for topical delivery: prodrugs can make the difference. *Med Res Rev* 23:763–793
- Sloan KB, Koch SAM, Siver KG (1984) Mannich base derivatives of theophylline and 5-fluorouracil: synthesis, properties and topical delivery characteristics. *Int J Pharm* 21:251–264
- Sloan KB, Getz JJ, Beal HD, Prankerd R (1993) Transdermal delivery of 5-fluorouracil (5-FU) through hairless mouse skin by 1-alkylaminocarbonyl-5-FU prodrugs: physicochemical characterization of prodrugs and correlation with transdermal delivery. *Int J Pharm* 93:27–36

- Sloan KB, Wasdo S, Ezike-Mkparu U, Murray TJ, Nichels D, Singh S et al (2003) Topical delivery of 5-fluorouracil (5-FU) and 6-mercaptopurine 6-MP by their alkylcarbonyloxymethyl (ACOM) prodrugs from water: vehicle effects on design of prodrugs. *Pharm Res* 20:639–645
- Sloan KB, Devarajan-Ketha H, Wasdo SC (2011a) Dermal and transdermal delivery: prodrugs. *Ther Deliv* 2:83–105
- Sloan KB, Wasdo SC, Majundar S (2011b) Topical and transdermal delivery using prodrugs. In: Rautio J (ed) *Prodrugs and targeted delivery*. Wiley-VCH Verlag, Weinheim, pp 153–179
- Synovec J, Wasdo SC, Sloan KB (2013) The effect of lipid and aqueous solubilities on flux of nicotinic acid esters from water through silicone membrane. *Drug Dev Ind Pharm* 39(9):1494–1497. doi:[10.3109/03639045.2012.694590](https://doi.org/10.3109/03639045.2012.694590)
- Taylor HE, Sloan KB (1998) 1-Alkylcarbonyloxymethyl prodrugs of 5-fluorouracil (5-FU): syntheses, physico-chemical properties and topical delivery of 5-FU. *J Pharm Sci* 87:15–20
- Tsuji T, Sugai T (1972) Topical administered fluorouracil in psoriasis. *Arch Dermatol* 105:208–212
- Waranis RP, Sloan KB (1987) The effects of vehicles and prodrug properties and their interactions on the delivery of 6-mercaptopurine through skin: bisacyloxymethyl-6-mercaptopurine prodrugs. *J Pharm Sci* 76:587–595
- Wasdo SC, Sloan KB (2004) Topical delivery of a model phenolic drug: alkylcarbonyloxymethyl prodrugs of acetaminophen. *Pharm Res* 21:940–946
- Wasdo SC, Juntunen J, Devarajan H, Sloan KB (2009) A comparison of the fit of flux through hairless mouse skin from water data to three model equations. *Int J Pharm* 366:65–73
- Wenkers BP, Lippold BC (1999) Skin penetration of non-steroidal antiinflammatory drugs out of lipophilic vehicle: influence of the viable epidermis. *J Pharm Sci* 88:1326–1331