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Expert Review

Design for Optimized Topical Delivery: Prodrugs and a Paradigm Change

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Abstract. In theory, topical delivery has substantial potential to treat local and some systemic disease states more effectively than systemic delivery. Unfortunately many, if not most, drug candidates for topical delivery lack the requisite physicochemical properties that would allow them to permeate the skin to a clinically useful extent. One way to overcome this obstacle to effective topical delivery is to make a transient derivative of the drug, a prodrug, with the correct physicochemical properties. But what are those correct properties and can the directives for the design of prodrugs be applied to the design of new drugs, their analogs or homologs? For some time increasing the lipid solubility (S_{LIPID}) or its surrogate, the partition coefficient between a lipid (LIPID) and water (AQ) ($K_{LIPID:AQ}$), has been the standard working paradigm for increasing permeation of the skin, and the permeability coefficient (P = distance/time) has been the quantitative measure of the result. However, even the earliest reports on non-prodrugs such as alcohols showed that working paradigm was incorrect and that P should not be the relevant measure of permeation. The shorter chain and more water soluble alcohols exhibiting lower $K_{LIPID:AQ}$ values gave the greater flux values (J = amount/area × time; the more clinically relevant measure of permeation), regardless of whether they were applied neat or in an aqueous vehicle, while P showed opposite trends for the two applications. Subsequently a large volume of work has shown that, for prodrugs and non-prodrug homologs or analogs alike, S_{AQ} (not solubility in the vehicle, S_{VEH}) as well as S_{LIPID} should be optimized to give maximum flux from any vehicle, J_{MVEH}: a new working paradigm. The dependence of J_{MVEH} on S_{AQ} is independent of the vehicle so that S_{AQ} as well as S_{LIPID} are descriptors of the solubilizing capacity of the skin or S_{M1} in Fick's law. The inverse dependence of J (or P) on molecular weight (MW) or volume (MV) remains. Here we review the literature that leads to the conclusion that a new working paradigm is necessary to explain the experimental data, and argue for its use in the design of new prodrugs or in the selection of candidate analogs or homologs for commercialization.

KEY WORDS: lipid solubility; partition coefficient; Potts–Guy equation; prodrugs; Roberts–Sloan equation; water solubility.

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ABBREVIATIONS: $\Delta \log J$, absolute difference between experimental and calculated fluxes; AQ, water; $C_{7.4}$, concentration in pH 7.4 buffer; C_{AQ}, concentration in water; C_{LIPID}, concentration in a lipid; C_{M1}, concentration in the first few layers of membrane; C_{Mn}, concentration in last layer of membrane; C_{OCT}, concentration in octanol; C_{VEH}, concentration in a nonspecified vehicle; D, diffusion coefficient; D_0, diffusion coefficient of a molecule with zero volume; IPM, isopropyl myristate; J, flux; J_M, maximum flux; $J_{M4.0}$, maximum flux from pH 4.0 buffer; $J_{M5.0}$, maximum flux from pH 5.0 buffer; $J_{M5.5}$, maximum flux from pH 5.5 buffer; $J_{M6.4}$, maximum flux from pH 6.4 buffer; $J_{M7.4}$, maximum flux from pH 7.4 buffer; J_{MAQ}, maximum flux from water; J_{MIPM}, maximum flux from isopropyl myristate; J_{MLIPID}, maximum flux from a lipid; J_{MMO}, maximum flux from mineral oil; J_{MOCT}, maximum flux from octanol; J_{MVEH}, maximum flux from a nonspecified vehicle; J_{VEH}, flux from a nonspecified vehicle; $K_{AQ:MO}$, partition coefficient between water and mineral oil; $K_{IPM:AQ}$, partition coefficient between IPM and water; $K_{LIPID:AQ}$, partition coefficient between a lipid and water; $K_{LIPID:VEH}$, partition coefficient between a lipid and a nonspecified vehicle; $K_{MEM:AQ}$, partition coefficient between a membrane and water; $K_{MEM:LIPID}$, partition coefficient between a membrane and lipid; $K_{MEM:VEH}$, partition coefficient between a membrane and a nonspecified vehicle; $K_{OCT:4.0}$, partition coefficient between octanol and pH 4.0 buffer; $K_{OCT:5.0}$, partition coefficient between octanol and pH 5.0 buffer; $K_{OCT:7.0}$, partition coefficient between octanol and pH 7.0 buffer; $K_{OCT:7.4}$, partition coefficient between octanol and pH 7.4 buffer; $K_{OCT:AQ}$, partition coefficient between octanol and water; $K_{SO:AQ}$, partition coefficient between silicone oil and water; L, effective thickness of membrane; MEM, membrane; MO, mineral oil; MV, molecular volume; MW, molecular weight; OCT, octanol; $P_{4.0}$, permeability coefficient for delivery from pH 4.0 buffer; $P_{5.0}$, permeability coefficient for delivery from pH 5.0 buffer; $P_{5.5}$, permeability coefficient for delivery from pH 5.5 buffer; $P_{7.0}$, permeability coefficient for delivery from pH 7.0 buffer; $P_{7.4}$, permeability coefficient for delivery from pH 7.4 buffer; P_{AQ}, permeability coefficient for delivery from water; PG, Potts–Guy model; P_{IPM}, permeability coefficient for delivery from IPM; P_{LIPID}, permeability coefficient for delivery from a lipid; P_{MO}, permeability coefficient for delivery from mineral oil; P_{OCT}, permeability coefficient for delivery from octanol; P_{VEH}, permeability coefficient for delivery from a nonspecified vehicle; RS, Roberts–Sloan model; $S_{4.0}$, solubility in pH 4.0 buffer; $S_{5.0}$, solubility in pH 5.0 buffer; $S_{6.4}$, solubility in pH 6.4 buffer; $S_{7.0}$, solubility in pH 7.0 buffer; $S_{7.4}$, solubility in pH 7.4 buffer; S_{AQ}, solubility in water; SC, stratum corneum; S_{IPM}, solubility in isopropyl myristate; S_{LIPID}, solubility in a lipid; S_{M1}, solubility in the first few layers of membrane; S_{MO}, solubility in mineral oil; S_{OCT}, solubility in octanol; S_{SO}, solubility in silicone oil; S_{VEH}, solubility in a nonspecified vehicle; VEH, vehicle.

INTRODUCTION

There are numerous disease states that could benefit if treated topically to avoid the high systemic burdens of drugs that are often responsible for their adverse effects. Thus, there exists considerable promise for topical delivery which includes both dermal and transdermal delivery. However many, if not most, drug candidates for topical delivery lack the requisite physicochemical properties that would allow them to permeate the skin to a clinically useful extent under conditions acceptable to patients. Some of these drug candidates are quite large such as steroids; and, since diffusion is inversely proportional to size (see below), the topical delivery of drugs larger than 500 Da is somewhat limited (1,2). Some are not very soluble in lipids and exhibit high melting points such as 5-fluorouracil (5-FU); and, since the intercellular multilamellar lipid bilayers in the stratum corneum (the outermost layer of the skin) are considered to serve as the primary barrier to permeation, the delivery of drugs that are poorly soluble in lipids is also limited (2,3). On the other hand, some drugs such as levonorgestrel are apparently too soluble in lipids (in addition to being in this example a large steroid), and their topical delivery from water has been assumed to be limited by diffusion layer control in the aqueous vehicle or solubility in the viable epidermis (3,4).

There are three approaches to solving this problem of poor physicochemical properties which are not necessarily mutually exclusive. The first approach is through the use of various devices (2). Here we do not include patches since ultimately patches depend on the solubility properties of the permeant (or the skin itself) and those solubility properties are considered under the later two approaches. Instead we refer to devices that depend on five different mechanical or electromechanical mechanisms for enhancing permeation. First is iontophresis which uses an electrical field to facilitate the movement of charged and uncharged species across the skin. Second is electroporation which uses short, relatively high-voltage pulses to increase the permeability of the skin. One advantage of electroporation is the rapid reversibility of its effect. Third is various acoustical methods such as ultrasound and sonophoresis. The later method apparently depends primarily on cavitation effects in the skin to increase permeabilities. Fourth is microneedles which pierce the skin surface to create holes large enough to allow solvated drug molecules to enter. Fifth is jet injectors which rely on high velocity application of the drug to affect permeation. We will not consider devices further here.

The second approach is through the use of penetration enhancers (5). Penetration enhancers are chemical components of the formulation in which the drug is applied to the surface of the skin. Penetration enhancers increase delivery into and through the skin by either "pushing" the drug into the skin by increasing the thermodynamic activity of the drug in the formulation (vehicle) or by "pulling" the drug into the skin by permeating the skin itself and increasing the solubility of the drug in the skin (6). The enhancer components in the formulation are usually in a large molar excess of the drug; and their effects should be non-irritating, non-immunogenic and rapidly reversible. This is especially true if the penetration enhancer permeates the skin to change the solubilizing capacity of the skin for the drug. Although there does not appear to be any ideal penetration enhancer available for use today, the search for improved penetration enhancers continues (7). The formulation based enhancer approach also, for the most part, ignores the physicochemical properties of the drug (one penetration enhancer fits all drugs), although there are several reports that suggest that an enhancer that is effective for a polar drug may not be effective for a lipophilic drug and vice versa (8). We will also not consider penetration enhancers further here.

The third approach is through the use of prodrugs (9–11). Prodrugs are transient chemical derivatives of drugs in which the chemical groups that comprise the added promoiety modify the physicochemical properties of the drug such that the solubility of the drug in the skin is increased [see below in Theory, Eq. (1)]. This is compared to penetration enhancers which may increase the ability of the skin to solubilize the drug. However, just like "pulling" penetration enhancers, the components of the promoiety that are released upon reversion of the prodrug to its parent drug should be reasonably non-irritating and non-immunogenic. The advantage that prodrugs have is that the components of the promoiety are not in large molar excess. The components that are responsible for the improved solubility of the drug in the skin are in a 1:1 ratio with the drug so that the local and systemic burden of those components are much less than that of the components of the formulation based enhancer approach (10). Compared to devices and formulation penetration enhancers, prodrugs are designed specifically for each drug and their effectiveness relative to the parent drug and to other prodrugs should be independent of the vehicle (since increased solubility of the prodrugs in the skin compared to the parent drug is the desired end result, see below) as long as the vehicle itself does not interact with the skin.

But what are the design parameters for these prodrugs? What are the physicochemical properties that should be optimized in a prodrug approach that should result not only in increased solubility of the prodrug (compared to the parent drug) in the skin, and hence in increased dermal and transdermal delivery, but also in optimization of those properties for a given type of prodrug for a drug, a stable homolog or analog of that drug or even a completely new drug? Here we will try to answer those questions, and questions about: (a) which measure of permeation should be the basis for analyses, flux (and maximum flux) or permeability coefficient; (b) what is the effect of the extent of hydrolysis of the prodrug to the parent drug on permeation since they each exhibit much different physicochemical properties; (c) what effect does the actual mechanism of permeation have on the choice of physicochemical properties used to direct the design of a better topical therapeutic agent?

The present (old) paradigm is based on the supposition that skin, and especially the stratum corneum (SC), presents as an essentially lipid barrier. The result is that it has been assumed that topical delivery of a drug could be improved by making increasingly more lipid soluble prodrugs (homologs or analogs) of the drugs, measured by increased log $K_{\mathrm{LIPID:AQ}}$ values, until they became so lipid soluble that delivery from an aqueous vehicle became diffusion layer controlled (or controlled by limited solubility in the viable

epidermis) and decreased permeation resulted with even more lipid soluble derivatives (12,13). This assumption would also be valid for the design of new drugs, their analogs or their homologs as well. The new paradigm is that, although the SC presents as a predominantly lipid barrier, the intercellular multilamellar bilayers (see above) that comprise that lipid barrier are composed of alternating lipid and aqueous phases across which the permeant must traverse (14–16). The net result is that the new paradigm suggests that increases in both water (S_{AQ}) and lipid (S_{LIPID}) solubilities, or a balance of the two, are important to optimize permeation of a prodrug or of a new drug entity. Thus, although the focus here will be on prodrugs, the same paradigms apply to the design of new analogs or homologs of known drugs or new drugs. Hence, examples of series of homologs that are not prodrugs and unrelated permeants will also be considered, and the effect of the physicochemical properties (partition coefficients and solubilities in vehicles—old paradigm, *versus* solubilities in lipid and water—new paradigm) of homologs as well as of prodrugs on flux will be evaluated as supporting one or the other paradigm.

THEORY

In order to resolve the differences between the two paradigms, we first consider the empirical law governing the permeation process, Fick's law, and the implications of its extension to consideration of the experimental parameters that are measured and that lead to the two paradigms. Here we consider only permeation in the multilamellar bilayer matrix around the cells of the SC and not through them via a shunt pathway. Fick's first law in its simplest form is:

$$J = D/L(C_{M1} - C_{Mn}) \tag{1}$$

where J is flux (here we will use units of μmol cm^{-2} h^{-1}), D is the diffusion coefficient (cm^2 h^{-1}), L is the thickness of the stratum corneum (SC) (cm), C_{M1} is the concentration of the permeant in the first few layers of the SC (mM or μmol cm^{-3}) and C_{Mn} is the concentration of the permeant in the last layer of the barrier to permeation in the SC. It is generally assumed that C_{Mn} approaches zero concentration, that the permeant is effectively removed from the viable tissue on the underside of the SC (sink conditions obtain), and that, since it is difficult to measure C_{M1} experimentally, C_{M1} can be estimated from the product of the concentration of the permeant in the vehicle, C_{VEH}, and the partition coefficient between the SC membrane, MEM, and the vehicle, VEH, which is $K_{MEM:VEH}$ (or C_{MEM}/C_{VEH}) (17–19). This gives:

$$J_{VEH} = (D/L)(C_{VEH})(K_{MEM:VEH}) \tag{2}$$

Normalization of J_{VEH} for the use of different concentrations of permeant in the vehicle gives the permeability coefficient, P_{VEH} (cm h^{-1}), which does not contain units of amount permeated as does J_{VEH}:

$$P_{VEH} = J_{VEH}/C_{VEH} = (D/L)(K_{MEM:VEH}) \tag{3}$$

Although P_{VEH} is often used to measure permeation in the old paradigm, topical delivery in the context of pharmaceutical and medicinal chemistry implies delivery of a therapeutic agent. The therapeutic effects are usually measured experimentally *in vitro* by the fit of the therapeutic agent to a receptor or its action with a specific enzyme. Typically, a log dose-response curve is generated where the dose at which the drug is 50% effective is determined and compared with other therapeutic agents on a molar basis. Since P_{VEH} values have no molar basis, but J_{VEH} values are in units of amount (dose) delivered per unit time and area, J_{VEH} is the correct descriptor to measure the effectiveness of delivering a therapeutic agent topically since it describes permeation in terms of dose delivered. The use of J_{VEH} in the development of models for permeation is not a new concept (1–3). Thus, we will focus on flux and transformations of P_{VEH} in terms of J_{VEH} for the remaining discussions.

The use of saturated solutions as the donor phases in diffusion cell experiments results in the maximum flux, J_M, from that vehicle, J_{MVEH}, where C_{VEH} is replaced by the solubility of the permeant in that vehicle, S_{VEH} (17–19). Thus C_{M1} in Eq. (1) becomes S_{M1} which is given by S_{VEH} ($K_{MEM:VEH}$) and Eq. (2) becomes:

$$J_{MVEH} = (D/L)(K_{MEM:VEH})S_{VEH} \tag{4}$$

It should be noted that, since C_{VEH} values less than S_{VEH} are proportional to % saturation in the vehicle, J_{VEH} values [Eq. (2)] can be estimated from the product of predicted J_{MVEH} and (C_{VEH}/S_{VEH}). However, this can only be an estimate of J_{VEH} since thermodynamic activity and (C_{VEH}/S_{VEH}) are not always linearly related. The use of a saturated solution of a permeant in a vehicle, so that maximum flux, J_{MVEH}, is the measurement of permeation, is essential to evaluating the variable physicochemical properties of a permeant that affect its topical delivery by eliminating one of those variables, S_{VEH}. At saturation a permeant is at its maximum thermodynamic activity in that vehicle. Since a saturated solution of a permeant in one vehicle has the same maximum thermodynamic activity as it does in another (regardless of the actual concentration at saturation), the chemical potential of a permeant is the same in each vehicle as long as the vehicle does not interact with the skin. At equilibrium between a saturated solution of a permeant in a vehicle and the skin, a saturated solution of a permeant in the skin obtains, S_{M1}. That concentration, S_{M1}, will be the same regardless of the actual concentration of the permeant in each vehicle S_{VEH}, and ($K_{MEM:VEH}$) S_{VEH} will be a constant: S_{M1}. For different permeants, all at saturation in a vehicle (20), each of their thermodynamic activities, and hence chemical potentials, will be at its maximum in that vehicle and in the initial layer of the skin with which it is in equilibrium. Regardless that the actual value for S_{M1} for each permeant will be different, their chemical potentials will be the same. Hence the maximum fluxes of each permeant, J_{MVEH}, will be measured at the same chemical potential in the skin and S_{M1} will be the only solubility related variable predicting flux (1).

Regardless of whether S_{M1} is the only important solubility related variable predicting flux, and the product of $K_{MEM:VEH}$ and S_{VEH} is a constant (S_{M1}) which is independent of the actual vehicle, how do we estimate S_{M1}? For practical purposes we estimate S_{M1} from ($K_{MEM:VEH}$)

S_{VEH} or its transformations, and it is from those transformation that the fundamental differences in design directives from the two paradigms arise. Unfortunately it is also difficult to measure $K_{MEM:VEH}$ in Eq. (4), so a surrogate for $K_{MEM:VEH}$ is usually measured and substituted for it (17–19). The concentration in a lipid (C_{LIPID}) is substituted for C_{MEM} in $K_{MEM:VEH}$ and the concentration in water (C_{AQ}) or in a buffer (for instance pH 7.4 buffer, $C_{7.4}$) is substituted for C_{VEH} in $K_{MEM:VEH}$ [Eq. (2)]. Water is chosen as a representative vehicle since (a) many diffusion cell experiments are run using water (or buffer) as the vehicle, (b) it is not possible to directly measure K where the vehicle is miscible with lipids in the MEM, and (c) water is usually a major component of commercial topical formulations. In most examples the lipid that functions as the surrogate for C_{MEM} in $K_{MEM:VEH}$ is octanol, OCT; although a number of publications evaluating prodrugs for the topical delivery of their parent drugs use isopropyl myristate, IPM (21), or mineral oil, MO (22), as the vehicle and often the surrogate for C_{MEM}. Thus, $K_{MEM:VEH}$ is usually replaced by $K_{OCT:AQ}$ (or C_{OCT}/C_{AQ}). However, $K_{OCT:AQ}$ does not take into account the facts that C_{OCT} (a) cannot represent the true lipid environment of the SC, and (b) cannot represent the anistropic nature of the SC. So $K_{OCT:AQ}$ is replaced by $(K_{OCT:AQ})^f c$ (constant) and log $K_{MEM:VEH}$ becomes f log $K_{OCT:AQ}$ + log c or f log C_{OCT} − f log C_{AQ} + log c. When a saturated solution of the permeant in water is used as the vehicle:

$$J_{MAQ} = (D/L)(K_{OCT:AQ})^f c S_{AQ} \quad (5)$$

In addition, D can be estimated from $D = D_0\, e(-\beta MV)$ where β is a constant, MV is molecular volume (although molecular weight, MW, can be substituted for MV with little difference in fit) and D_0 is the diffusivity of a hypothetical molecule of zero molecular volume (1). Thus, Eq. (5) becomes:

$$J_{MAQ} = [D_0\, e(-\beta MW)/L](K_{OCT:AQ})^f c S_{AQ} \quad (6)$$

Taking the logs of the parameters and combining log (D_0/L) with the constant from (f log $K_{OCT:AQ}$ + log c) to give another constant, x, gives:

$$\log J_{MAQ} = x - (\beta/2.303)MW + f \log K_{OCT:AQ} + \log S_{AQ} \quad (7)$$

which is the form of the Potts–Guy equation (24) where J_{MAQ} is the dependent variable and a basis for the old paradigm. Substitution of z for (β/2.303), and y for f, gives:

$$\log J_{MAQ} = x - zMW + y \log K_{OCT:AQ} + \log S_{AQ} \quad (8)$$

If it is assumed that at steady state the concentration in the alternating lipid and aqueous phases (C_{OCT} and C_{AQ}) of the barrier to permeation approach the saturated solubilities of the permeant in those phases (S_{OCT} and S_{AQ}), y log $K_{OCT:AQ}$ can be expanded to y log S_{OCT} − y log S_{AQ} instead of y log C_{OCT} − y log C_{AQ}, and after collecting terms Eq. (8) becomes:

$$\log J_{MAQ} = x - zMW + y \log S_{OCT} + (1 - y) \log S_{AQ} \quad (9)$$

which is a form of the Roberts–Sloan equation and the basis for the new paradigm (21). Thus, when water is the vehicle, the Potts–Guy, **PG**, Eq. (7) can be converted directly to the Roberts–Sloan, **RS**, Eq. (9). However, the original Potts–Guy analysis was based on P_{AQ} values and transformation of reported P_{AQ} values to J_{MAQ} from $(P_{AQ})(S_{AQ})$ for use as the dependent variable in regression analysis based on Eqs. (7) or (9), where log S_{AQ} is an independent variable, is statistically not ideal. Measuring J_{MAQ} directly, and then fitting the data to Eqs. (7) or (9) is much preferred.

The difference between the two models, the parameters that affect flux, and their attendant Eqs. (7) (or 8) and (9), is one of emphasis on partition coefficients which can be calculated theoretically (19,25) (and S_{VEH}) in the **PG** model (old paradigm) and on measured or estimated solubilities in a lipid and in water (not S_{VEH}) in the **RS** model (new paradigm) to predict S_{M1}. When AQ is the vehicle $S_{M1} = y$ log $K_{OCT:AQ}$ + log S_{VEH} (or log S_{AQ}) for Eq. (8), which is derived from Eq. (7), and $S_{M1} = y$ log S_{OCT} + $(1-y)$ log S_{AQ} for Eq. (9). If C_{M1} (and hence S_{M1}) is the driving force for J_{VEH} (and hence J_{MVEH}) from Eq. (1), the design directives for the two models are different. It should be noted that, by comparison, Kasting *et al.* (1) assumed that solubility in a lipid (S_{OCT}) alone was a sufficient predictor of S_{M1}.

However it is the application of the Potts–Guy, **PG**, or the Roberts–Sloan, **RS**, models and their corresponding Eqs., (7) and (9), respectively, to model flux from a lipid that the differences in the usefulness of the two models becomes more apparent. Both the **PG** and **RS** equations would start with Eq. (2) and both would have to substitute $K_{MEM:LIPID}$ for $K_{MEM:VEH}$ when the vehicle is a lipid. In the development of the **RS** model for flux from lipids, the following identity was used:

$$K_{MEM:LIPID} = (K_{MEM:AQ})/(K_{LIPID:AQ}) \quad (10)$$

Since it had already been shown that $(K_{LIPID:AQ})^f c$ can substitute for $K_{MEM:VEH}$ in Eq. (4), and that where OCT is the lipid and AQ is the vehicle Eq. (4) becomes Eq. (5), it is reasonable that where IPM (or MO) is the lipid, Eq. (10) becomes:

$$K_{MEM:LIPID} = (K_{IPM:AQ})^f c \Big/ (K_{IPM:AQ})$$
$$\log K_{MEM:LIPID} = f \log S_{IPM} - f \log S_{AQ} - \log S_{IPM} + \log S_{AQ} + \log c \quad (11)$$

Substitution of y for f and Eq. (11) into Eq. (8) for y log $K_{OCT:AQ}$ where the vehicle is now IPM (log S_{VEH} or log S_{AQ} becomes log S_{IPM} and log J_{MAQ} becomes log J_{MIPM}) gives:

$$\log J_{MIPM} = x - z\,MW + y \log S_{IPM} - y \log S_{AQ} - \log S_{IPM} + \log S_{AQ} + \log S_{IPM}$$

Collecting terms gives:

$$\log J_{MIPM} = x - z\,MW + y \log S_{IPM} + (1 - y) \log S_{AQ} \quad (12)$$

which is exactly the same form as Eq. (9) except that the lipid is now IPM instead of OCT.

Both Eqs. (9) and (12) start with Eq. (2) and arrive at the same dependency of S_{M1} on solubility in a lipid and in water (not solubility in the vehicle). This suggests that, regardless of the vehicle, a balanced combination of positive contributions by lipid and aqueous solubilities are universal

descriptors of the solubility of the permeant in the skin, S_{M1}, which is the driving force for maximum flux, J_{MVEH}, from Fick's first law Eq.(1). The term $y \log S_{LIPID} + (1 - y) \log S_{AQ}$ is not only a measure of a macroscopic term S_{M1}, it is also a measure of the capacity of the microscopic alternating lipid and aqueous phases in the intercellular lipid matrix barrier to carry permeating molecules (16). The value for y will vary depending on the species from which the membrane (skin) has been obtained and the method of its preparation. Similarly, the constant x contains a measure of L, reflecting the tortuosity of the path of the permeant through the SC, which is assumed to be a constant, but only for skin from the same species which has been prepared in the same way; and z is a measure of the effect of size on diffusivity, which is also assumed to be a constant, but only for non-interactive vehicles and for skin from the same species which has been prepared in the same way. Thus, the values for x, y and z will change with the vehicle since each vehicle will affect skin differently, they will change for skin for different species, e.g., hairless mouse is different from heat separated human epidermis, and they will change for *in vitro versus in vivo* experiments since skin in *in vitro* experiments will be much more highly hydrated. However, for a given vehicle, species of skin and *in vitro versus in vivo* conditions, x, y and z should remain constant.

The Potts–Guy equation, which relies on easily calculated $K_{OCT:AQ}$ values to predict log P_{AQ} ($\log J_{MAQ} - \log S_{AQ}$) in Eq. (7), cannot be used when the vehicle is a lipid such as IPM because the vehicle is defined as AQ by $K_{OCT:AQ}$ [Eq. (5)]. Of course the same approach as used in the development of the Roberts–Sloan equation could be used in the development of a Potts–Guy equation analogous to Eq. (7) for a lipid vehicle such as IPM:

$$\log J_{MIPM} = x - (\beta/2.303)MW + f \log K_{IPM:AQ} - \log K_{IPM:AQ} + \log S_{IPM} \quad (13)$$

where $(K_{IPM:AQ})^f c$ is used as the substitute for $K_{MEM:AQ}$ and $K_{IPM:AQ}$ is used as the substitute for $K_{LIPID:AQ}$ in Eq. (10). However, one is still left with an equation that relies on partition coefficients instead of solubilities as independent variables, which can lead to misleading conclusions about which properties should be enhanced to increase topical delivery (see below). In other words, what are the design directives from Eq. (13), or for that matter Eq. (8)? The design directives from Eqs. (12) and (9) are clear regardless of the vehicle: increase S_{M1} by increasing both lipid and aqueous solubilities or by introducing a better balance between the two to increase J_{MVEH}.

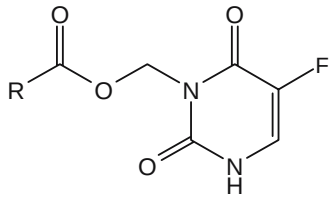
ANALYSIS OF PREVIOUS *IN VITRO* DATA

One can argue about the relative merits of the Potts–Guy equation (24) and permeability coefficients, P_{VEH}, which rely on partition coefficients (and solubility in the vehicle, if it is water, to estimate J_{MVEH}) as independent variables *versus* the Roberts–Sloan equation (21) and maximum fluxes, J_{MVEH}, which rely on positive dependencies on solubilities in lipid and water (not solubility in the vehicle) as independent variables regardless of the vehicle. However, the only important criteria for choosing one model over the other must be how well the independent variables in the model directly predict the changes that can be affected in the physicochemical properties of the molecule in question (whether prodrug, homolog or analog) to improve its clinically relevant dependent variable. In this case the clinically relevant dependent variable must be flux or maximum flux, J_{MVEH}. Thus, we will compare how effective the variables in Eqs. (8) ($f \log K_{OCT:AQ} + \log S_{AQ}$) and (9) ($y \log S_{OCT} + (1-y) \log S_{AQ}$), and other lipid variation thereof, are in predicting changes in J_{MVEH}.

Prodrugs

There are numerous sets of flux data for the delivery of parent drugs by prodrugs from an aqueous or a lipid vehicle which could be analyzed by the two models to determine which one gives the best insight into how to modify the physicochemical properties of the prodrug (homolog or analog) to optimize flux. One set that has been chosen here is a unique set of $n = 16$ prodrugs of 6-mercaptopurine (6-MP) and 5-fluorouracil (5-FU) for which flux values for delivery of total species containing the parent drugs from both water and a lipid, IPM, are available from one source (26).

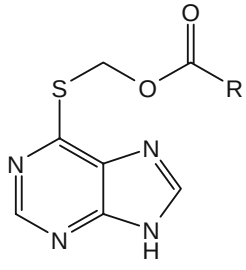
Inspection of the S_{IPM} data (Table I) shows that all of the prodrugs are much more soluble in IPM (>25 times) than the parent drugs. This result is attributable to the fact that a hydrogen bond donor in the parent drug has been masked by the promoiety. Interestingly, in each case, although S_{IPM} values increase dramatically at first, they eventually start to decrease at about 5 to 7 carbons in the alkyl group. This is



3-ACOM-5-FU

1 - 6

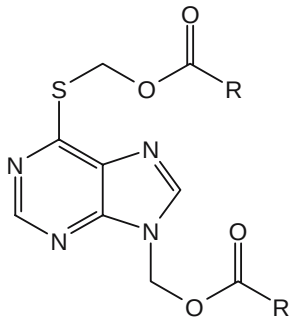
not unusual for homologous series of derivatives (10). On the other hand, the log $K_{LIPID:AQ}$ values (here log $K_{IPM:AQ}$ values) which are often used as a surrogate for lipid solubility or lipophilicity, continue to increase in a regular incremental



6-ACOM-6-MP

7 - 12

manner. The average differences in the log K values for increases of one CH_2 group, the π value, are 0.50 ± 0.01 for **1**



6,9-ACOM-6-MP
13 - 17

to **6**, 0.50 ± 0.06 for **7** to **12** and 0.56 ± 0.04 for **13** to **17**. Most importantly for comparison purposes, there is no decrease in π for the last member of each series. Although S_{IPM} is decreasing for the last member of the series, $K_{IPM:AQ}$ is not: $K_{IPM:AQ}$ is not a good surrogate for absolute lipophilicity. The S_{AQ} values, for the most part, decrease as the lipophilic alkyl chain length increases in each series, as expected, except for **1** and **2** where the S_{AQ} for **1** is less than that for **2** or **3**. However, even in the comparisons of **1** with **2** and **2** with **3**, the π value remained constant. It is also important that although a polar hydrogen bond donor group is masked in each series, several of the prodrugs with shorter alkyl chains are not only more lipid soluble, they are also more soluble in water than the parent drug.

The J_{MIPM} value for delivering total species containing the parent drug (parent drug plus intact prodrug) from IPM increased at first in all three series, then decreased after the second or third member of each series as S_{AQ} decreased. So did the J_{MAQ} values for delivering total species containing the parent drug from AQ. The relative J_{MVEH} values of the members of each series remained the same regardless of the vehicle (S_{M1} is independent of S_{VEH}, as long as VEH is not interactive, see below). The prodrug that gave the highest J_{MVEH} value from an IPM vehicle gave the highest J_{MVEH} value from an AQ vehicle. In each homologous series of more lipid soluble prodrugs the shorter chain, more water soluble members gave the higher flux values and not the longer chain more lipid soluble members exhibiting higher $K_{IPM:AQ}$ values: $K_{IPM:AQ}$ is not a good predictor of J_{MIPM} or J_{MAQ} but S_{AQ} and S_{IPM} are (see fits to Eq. (9) and (12) below). The shorter chain members also exhibited high mp values (values not shown) so there is no correlation between decreased mp and increased flux in series such as these.

Similarly the P_{VEH} values from Table I for delivery of total species from IPM tend to decrease while the P_{VEH} values for delivery from AQ tend to increase (Fig. 1). Obviously P_{VEH} is not a good direct predictor of J_{MVEH} unless one knows or can predict the respective S_{VEH} values since P_{VEH} trends in opposite directions for delivery from lipid and aqueous vehicles while J_{MVEH} trends in the same direction regardless of the vehicle. The previous paradigm

Table I. Fluxes of Prodrugs of 6-Mercaptopurine (6-MP) and 5-Fluorouracil (5-FU) through Hairless Mouse Skin *in vitro* from IPM and AQ (26)

Compound	MW	S_{IPM}[a]	S_{AQ}[a]	log K[b]	J_{MIPM}[c]	P_{IPM}[d]	J_{MAQ}[c]	P_{AQ}[d]
3-ACOM-FU								
1, C1[e]	202	1.22	63.1	−1.62	0.60	0.49	0.017	0.00027
2, C2	216	15.9	178.0	−1.03	2.18	0.14	0.039	0.00022
3, C3	230	26.4	85.1	−0.45	2.87	0.11	0.074	0.00087
4, C4	244	29.8	20.9	0.13	1.32	0.045	0.037	0.0018
5, C5	258	42.8	8.32	0.74	1.01	0.023	0.039	0.0047
6, C7	286	40.2	0.56	1.90	0.17	0.0043	0.014	0.025
6-ACOM-6-MP								
7, C1	224	1.05	7.17	−0.83	0.203	0.19	0.0028	0.00039
8, C2	238	2.30	4.08	−0.25	0.214	0.093	0.0065	0.0016
9, C3	252	3.29	2.04	0.21	0.262	0.079	0.010	0.0049
10, C4	266	4.21	0.79	0.73	0.220	0.052	0.0066	0.0083
11, C5	280	3.68	0.24	1.19	0.055	0.015	0.0043	0.019
12, C7	308	4.14	0.024	2.24	0.013	0.0031	–	–
6,9-bisACOM-6-MP								
13, C1	296	5.27	2.88	0.26	0.227	0.044	0.010	0.0036
14, C2	324	33.6	1.67	1.30	0.232	0.0069	0.013	0.0078
15, C3	352	90.9	0.20	2.66	0.141	0.0015	0.0054	0.028
16, C4	380	174	0.047	3.57	0.102	0.00059	0.0033	0.071
17, C5	408	49.8	0.0011	4.67	0.012	0.00023	0.00085	0.81
Parent								
5-FU	130	0.049	85.4	−3.24	0.240	4.9	0.011	0.00013
6-MP	152	0.022	1.12	−1.71	0.0038	0.17	0.0024	0.0021

[a] Units of mM.
[b] The partition coefficient between IPM and AQ.
[c] Units of μmol $cm^{-2}\,h^{-1}$.
[d] Units of cm h^{-1}.
[e] C1,C2.... refers to the number of carbons in the alkyl side chain.

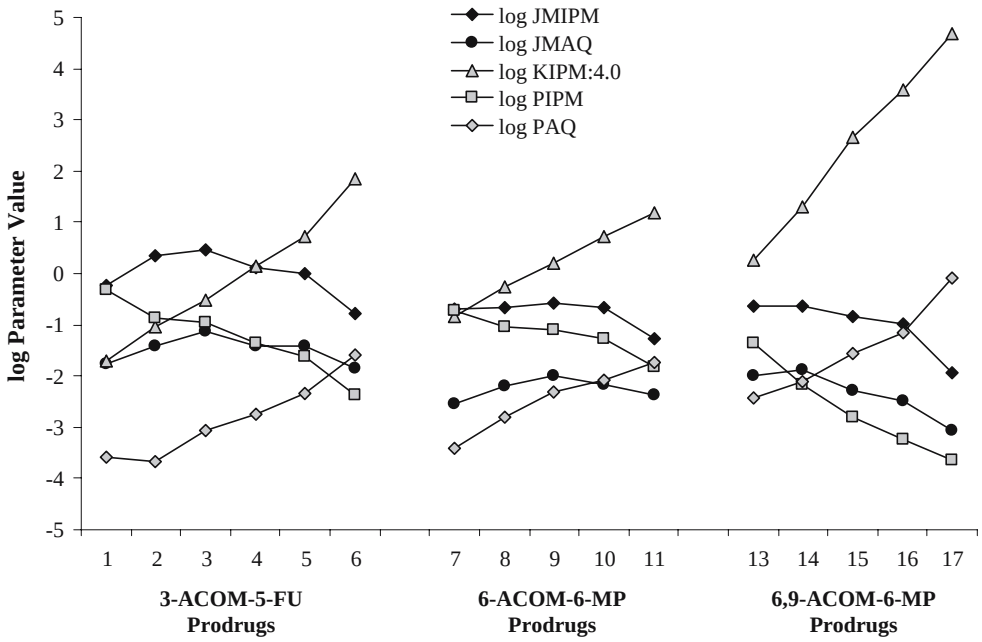


Fig. 1. Plot of log flux from IPM (JMIPM), log flux from water (JMAQ), log IMP-water partition coefficient (KIPM:4.0), log IPM permeability coefficient (PIPM) and log aqueous permeability coefficient (PAQ) for the 3-ACOM-5-FU, 6 ACOM-6-MP and 6,9-ACOM-6-MP prodrugs.

that required the synthesis of increasingly more lipid soluble prodrugs (increased $K_{OCT:AQ}$) for delivery from an aqueous vehicle, based on a correlation between increased K values, and hence increased P_{VEH} values, leads to erroneous design directives for increasing J_{MVEH}.

When the MW, S_{AQ}, S_{IPM} and J_{MIPM} values in Table I are fitted to the Roberts–Sloan Eq. (12) (26), the following coefficients, r^2 and average absolute differences in experimental log J_{MIPM} and calculated log J_{MIPM} (Δ log J_{MIPM}) are obtained:

$$\log J_{MIPM} = -0.557 + 0.536 \log S_{IPM} + 0.464 \log S_{AQ} - 0.0026\,MW$$
$$n = 18, \quad r^2 = 0.941, \quad \Delta \log J_{MIPM} = 0.109 \text{ log units}$$

The Δ log J_{MIPM} value suggests that the error in calculating J_{MIPM} is only about 29% (within the expected error for experimentally determining J_{MIPM}), and the y value of 0.536 suggests that a close balance between S_{IPM} and S_{AQ} is necessary to optimize flux. This agrees well with the qualitative observations. On the other hand, although an equally good fit to the data could be obtained using an expanded version of the Potts–Guy type Eq. (13), it is not clear what design directions should or could be taken to optimize flux based on P_{IPM} and K values.

Similarly, when the MW, S_{AQ}, S_{IPM} and J_{MAQ} values in Table I are fitted to the Roberts–Sloan Eq. (9) (26), the following results are obtained:

$$\log J_{MAQ} = -1.497 + 0.660 \log S_{IPM} + 0.340 \log S_{AQ} - 0.00469\,MW$$
$$n = 18, \quad r^2 = 0.765, \quad \Delta \log J_{MAQ} = 0.193 \text{ log units}$$

The fit is much poorer when J_{MAQ} is the dependent variable; the error in calculating J_{MAQ} was about 56%. Since IPM is such an interactive vehicle with mouse skin (see below), it is not surprising that the values for x, y and z for calculating J_{MAQ} are quite different from those for calculating J_{MIPM}. The key point remains: the lipid and water solubilities of the permeant (as well as its molecular weight) are important parameters not only to calculate J_{MVEH} but also to serve as a basis for the design of new prodrugs (and homologs or analogs) for topical delivery. Again, the Potts–Guy Eq. (8) and the old paradigm would give the same fit to the data, but what are the design directives?

Effect of Hydrolysis

This trend in the dependence of J_{MVEH} on S_{AQ} and S_{IPM} in Table I (and not on $K_{IPM:AQ}$ or S_{VEH}) cannot be due to lack of hydrolysis of the longer chain more lipid soluble prodrugs whose permeation would then become limited by the more water rich layers of the viable epidermis. All of the 6-MP prodrugs of the **7** to **12** and **13** to **17** series delivered only 6-MP into the receptor phases from IPM except for the first two members of the **13** to **17** series (**13** delivered <12% intact prodrug while **14** delivered <2% intact prodrug), under conditions where the prodrugs were stable in the receptor phases. Even less intact prodrug was delivered from AQ for those series. The delivery of intact prodrug by the **1** to **6** series of 5-FU from IPM was greater than by the other two series, but again the longer chain, more lipid soluble and less effective prodrugs delivered less intact prodrug (5–6%) than the shorter chain, more water soluble and effective prodrugs (20–31%). The longer chain members were more completely converted to the parent drug which was more soluble in water than any prodrug in the **1** to **6** series except for **2**. The poor water solubility of the more lipid soluble prodrugs, and hence their assumed lack of ability to permeate

Table II. Fluxes of *O*-Acyl Prodrugs of Propranolol through Human Skin *in vitro* from pH 4.0 Buffer (28)

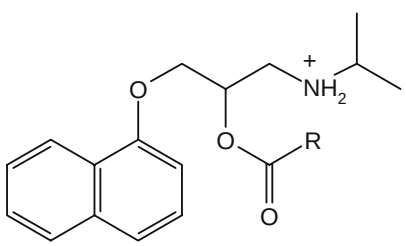
Compound	$S_{4.0}$[a]	$K_{OCT:4.0}$[b]	S_{OCT}[a,c]	$J_{M4.0}$[d]	%[e]	$P_{4.0}$[f]
18, PL *R*	392	2.40	941	30.6		0.0092
S				30.2		
19, C1[g] *R*	33.7	4.15	140	24.2	6.8	0.72
S				24.5	2.4	0.72
20, C2 *R*	31.2	11.4	356	19.5	37.1	0.63
S				22.4	2.4	0.72
21, C3 *R*	162.7	34.6	5,629	57.0	64.8	0.35
S				52.2	13.1	0.32
22, C4 *R*	17.2	97.4	1,675	31.5	89.6	1.83
S				26.0	32.7	1.51
23, C5 *R*	6.40	197.0	1,261	26.1	96.8	4.08
S				18.9	69.9	2.95

[a] Units of mM. The values for the solubilities of racemic mixtures are twice the listed value. *R* and *S* isomers have identical values.
[b] Partition coefficients between octanol and pH 4.0 buffer.
[c] Calculated from $(K_{OCT:4.0})$ $(S_{4.0})$.
[d] Units of μmol cm^{-2} h^{-1}.
[e] Percent of prodrug hydrolyzed during permeation.
[f] Units of cm h^{-1}.
[g] C1,C2..... refers to the number of carbons in the alkyl chain.

the more aqueous viable epidermis, could not have inhibited their permeation of the skin since they were more completely hydrolyzed to the much more water soluble parent drug. On the other hand, their initial poor water solubility did decrease their solubility in the SC, and especially S_{M1} (y log S_{LIPID} + $(1-y)$ log S_{AQ}), and hence their flux.

This conclusion is even more strongly supported by data from the delivery of 5-FU by 1-alkylcarbonyl 5-FU prodrugs from IPM through hairless mouse skin (27). Here the prodrugs hydrolyze chemically with a $t_{1/2}$ of 3–5 min under the experimental conditions. Again the shorter chain, more water soluble prodrugs gave the higher flux values regardless of the fact that only 5-FU was found in the receptor phases. Hydrolysis cannot be a limiting factor but solubility (S_{M1}) can be. However, the rapid hydrolysis of the more lipid soluble and, in the acetyl case, more water soluble prodrugs to 5-FU, whose S_{M1} value should be less than those of the prodrugs, does raise the question of how the prodrugs can give higher J_{MIPM} values than that from 5-FU. One possible suggestion is that the rapid hydrolysis of the prodrugs, exhibiting apparently higher S_{M1} values than 5-FU, leads to supersaturated solutions of 5-FU in the skin, i.e., thermodynamic activity greater than 1.

An example from another lab of this lack of any substantial effect of rate of bioconversion of prodrugs on their fluxes can be seen for the *O*-acyl prodrugs of *R* and *S* propanolol in Table II (28). In this case the butyryl prodrugs were the most soluble in water and in lipid ($\log K_{OCT:AQ} + \log S_{AQ} = \log S_{OCT}$) of the *R* and *S* series and they gave the highest J_{MAQ} as would have been predicted qualitatively. The butyryl *R* isomer delivered over five times more parent drug on its permeation of mouse skin *in vitro* than the butyryl *S* isomer prodrug (65 versus 13%) and yet the *R* isomer gave only a 9% increase in delivery of total species (parent plus intact prodrug, 57 ± 5.4 versus 52.2 ± 5.4 μmol cm^{-2} h^{-1}). The butyryl *S* isomer also gave a higher flux value than any of the other R isomers of the more lipid soluble prodrugs which delivered substantially more of the more water soluble parent drug (90 and 97%, respectively, for the valery and caproyl members) and which exhibited higher log $K_{OCT:AQ}$ values. Thus, the rank order of delivery of total species within the members of a series of ester prodrugs, and hence the optimum member of the series, will depend more on S_{M1} (y log S_{OCT} + $(1-y)$ log S_{AQ}) than on their relative rates of bioconversion or on their increased $K_{OCT:AQ}$ values.



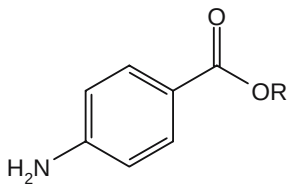
18 - 23

As a result of the abilities of more lipophilic prodrugs to hydrolyze to their more water soluble parent drugs, prodrugs provide a particularly useful mechanism to compare how well the old and the new paradigm explain experimental results. If a more lipophilic, stable homolog did not exhibit increased J_{MVEH} compared to a less lipophilic homolog, the viable epidermis could be blamed for the lack of permeation of the more lipophilic homolog (13,29,30). On the other hand, if the more lipophilic prodrug does hydrolyze completely to the more water soluble parent drug and still gives a lower J_{MVEH} value than the more water soluble members of the series, its lack of permeation cannot be due to lack of permeation of the viable epidermis but has to be due to its poor solubility in the SC and to low S_{M1}. The viable epidermis/dermis layers do present a barrier to permeation by highly lipid soluble, water insoluble drugs, but S_{M1} values are the best predictors of flux and of the best performers in a series. In addition, use of a homologous series of prodrugs to vary $K_{LIPID:AQ}$, S_{LIPID} and S_{AQ}, and then to correlate those changes with

P_{AQ} and J_{MAQ} without changing the functional groups makes it much easier to see trends between the two sets of descriptors (9–11).

Donor Phase Solubility

These trends in the dependency of J_{MVEH} on S_{AQ} and S_{IPM} (and not $K_{IPM:AQ}$ or S_{VEH}) are not due to the donor phase solubility being a limiting factor for the delivery of the more lipid soluble prodrugs from water (diffusion layer control in vehicle). When IPM is the vehicle and the longer



24 - 30

chain members are more soluble in the vehicle than the shorter chain members, the same trends in performance by the prodrugs are obtained as when water was the vehicle. At saturation S_{VEH} does not affect trends in J_{MVEH}. However, it should be noted that the J_{MVEH} values for the delivery of total species containing the parent drug by prodrugs from IPM are on average about 50 times greater than those for delivery from AQ (26). This difference is due to the fact that IPM is an interactive vehicle (at least with mouse skin) that consistently and irreversibly increases the permeability of the skin. Second application studies (19,26) using a known solute and vehicle (theopylline/propylene glycol) confirm the consistency and reproducibility of the effect. Thus, the trends hold even if the vehicle is interactive: $S_{M1} = (y \log S_{LIPID} + (1 - y) \log S_{AQ})$ still obtains but the absolute value for S_{M1} is greater if the vehicle is IPM.

An additional point on diffusion layer control is appropriate here. The initial data that was the basis for the suggestion that diffusion layer control by the vehicle in the permeation of the more lipophilic members of a series through a completely lipoidal membrane, at least from an aqueous vehicle, has been reproduced in Table III (31). The J_{MAQ} and P_{AQ} data are generated from the permeation of a homologous series of *p*-aminobenzoic acid esters from their saturated aqueous solution through a dimethylpolysiloxane, DMPS, membrane. As was observed for J_{MAQ} and P_{AQ} values for permeation of homologous series through hairless mouse skin, J_{MAQ} values decreased after the third member of the series while P_{AQ} and $K_{SO:AQ}$ (SO is silicone oil) values continued to increase with continued increase in alkyl chain length.

The authors assumed that diffusivity did not vary much in the series so in the context of the descriptors used in this paper, that would give:

$$J_{MAQ} = (K_{SO:AQ})(S_{AQ})/L$$

Since the DMPS membrane presented as a completely lipoidal barrier and since the barrier to permeation of skin was assumed to be only lipoidal, it was assumed that DMPS could serve as a surrogate for skin and conclusions arrive at for DMPS experiments could be directly applied to analyses of experiments with skin. A complete discussion of all the ramifications of these assumptions and conclusions is beyond the scope of this article. However, suffice it to say that when the effect of MW on diffusivity is included in the calculation of J_{MAQ}, as it is in the Kasting *et al.* (1), Anderson and Raykar (23), Potts and Guy (24) and Roberts and Sloan (21) models, and the fact that the DMPS membrane is completely lipoidal is included in the model so that $(y \log S_{LIPID} + (1 - y) \log S_{AQ} = S_{M1})$ becomes $(y \log S_{SO} = S_{M1})$, a perfectly good fit of the data in Table III to the corresponding **RS** equation (Fig. 2) is obtained where:

$$\log J_{MAQ} = 0.804 + 2.274 \log S_{SO} - 0.0195 \text{ MW}$$

and $n = 7$, $r^2 = 0.96$ and $\Delta \log J_{MAQ} = 0.093$.

Since the values for the two best performers in Table III are so close, the prediction of which actually gives the higher flux is reversed for the two best, but the rest of the order is

Table III. Fluxes of Esters of *p*-Aminobenzoic Acid through Dimethylpolysiloxane Membranes from AQ (31)

		Exp					Calc
Compounds	MW	log S_{SO}[a]	log J_{MAQ}[b]	log S_{AQ}[a]	log P[c]	log $K_{SO:AQ}$[d]	log J_{MAQ}[b]
24, C1[e]	151	0.720	−0.609	1.403	−2.01	−0.682	−0.503
25, C2	165	0.921	−0.205	1.009	−1.21	−0.088	−0.320
26, C3	179	1.111	−0.107	0.672	−0.78	0.438	−0.161
27, C4	193	1.250	−0.140	0.236	−0.37	1.013	−0.116
28, C5	207	1.250	−0.502	−0.347	−0.16	1.597	−0.389
29, C6	221	1.049	−0.959	−0.971	0.03	2.021	−1.120
30, C7	235	1.000	−1.585	−1.602	0.02	2.602	−1.505

[a] Units of mM.
[b] Units of μmol cm^{-2} h^{-1}.
[c] Units of cm h^{-1}.
[d] Partition coefficient between silicone oil, SO, and water, AQ.
[e] C1, C2.... refers to the number of carbons in the alkyl chain.

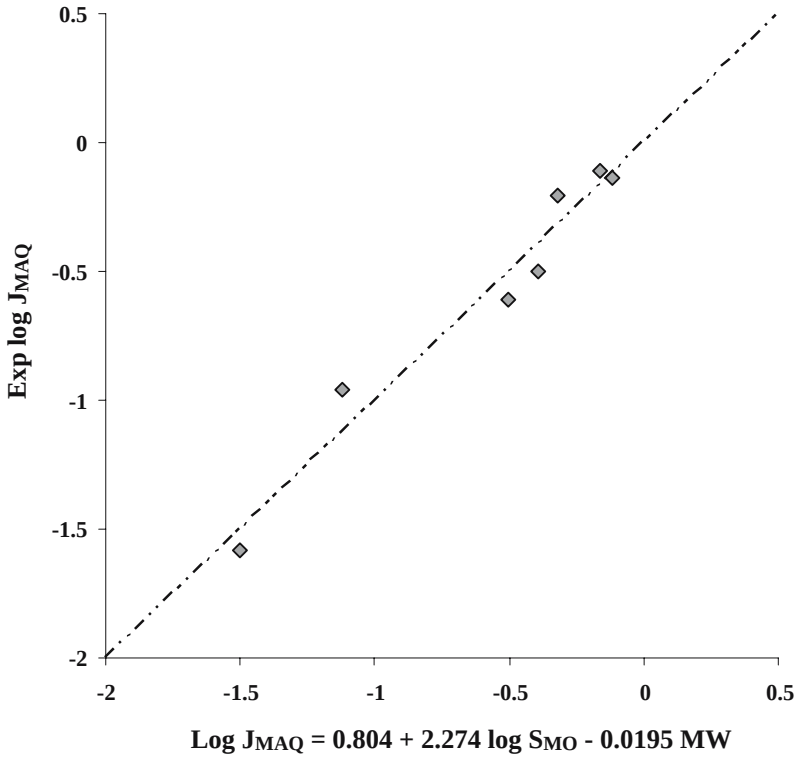


Fig. 2. Plot of calculated *versus* experimental flux for PABA esters through silicone membrane.

predicted and agreement with experimental values is ± 24%. There is no diffusion layer control because J_{MAQ} depends only on the solubility in the membrane, S_{M1}, for its driving force and inversely on diffusivity (and MW or MV), both of which are properties of the membrane and the permeant and not of the vehicle as long as the vehicle is not interactive. From this analysis, diffusion layer control is not a factor in the permeation of this short homologous series through a DMPS membrane and hence diffusion layer control of the flux of other series through skin is also probably questionable. All that was or is needed is inclusion of a dependence on MW or MV in the model and equation.

However, dissolution (in the vehicle) rate control remains as a possible factor in predicting flux. That factor should be evaluated on a case to case basis but even for a molecule as poorly soluble in lipids and in water as 6-MP, no dissolution rate dependence was observed (unpublished data).

Stable Homologs

Stable homologs show the same trends as prodrugs do in their dependencies on solubilities in water and lipids to calculate J_{MVEH}, as predicted from J in Fick's law being

Table IV. Fluxes of Alcohols through Human Skin *in vitro* Neat and from AQ (32,39)

Compound	MW	log S_{AQ}[a]	log $K_{OCT:AQ}$[b]	log S_{LIPID}[a,c]	log J_{MLIPID}[d]	log P_{LIPID}[e]	log J_{MAQ}[d]	log P_{AQ}[e]
31, C1[f]	32	–	−0.77	4.40	2.41	−1.99	–	–
32, C2	46	–	−0.31	4.23	1.09	−3.14	–	–
33, C3	60	–	0.25	4.13	0.33	−3.80	–	–
34, C4	74	2.96	0.91	4.04	−0.19	−4.23	0.36[g]	−2.60
35, C5	88	2.40	1.44	3.96	−0.33	−4.29	0.18[g]	−2.22
36, C6	102	1.79	1.97	3.91	−0.37	−4.28	−0.15	−1.94
37, C7	116	1.19	2.51	3.85	−0.74	−4.59	−0.32	−1.51
38, C8	130	0.58	3.05	3.81	−1.20	−5.01	−0.75	−1.33
39, C9	144	−0.02	3.56	3.76	−1.77	−5.53	−1.10	−1.08
40, C10	158	−0.65	4.10	3.72	−2.38	−6.10	−1.70	−1.05

[a] Units of mM.
[b] Partition coefficient between OCT and AQ calculated from $K_{M:W(AQ)}$ / $K_{M:OCT}$.
[c] Molar concentrations of the pure alcohols.
[d] Units of μmol cm^{-2} h^{-1}.
[e] Units of cm h^{-1}.
[f] C1, C2 .... refers to the number of carbons in the alkyl ch ain.
[g] Calculated from (J_{AQ} / C_{AQ}) S_{AQ}.

Table V. Fluxes of Thalidomide Homologs through Human Skin *in vivo* from OCT and pH 6.4 Buffer (34,35)

Compound	MW	log $S_{6.4}$[a]	log $K_{OCT:AQ}$	log S_{OCT}[a]	log J_{MOCT}[b]	log P_{OCT}[c,d]	log $J_{M6.4}$[b]	log P_{AQ}[c,e]
41, H	258	−0.62	0.49	−0.57	−3.87	−3.30	–	–
42, C1[f]	272	0.134	1.15	0.99	−3.17	−4.16	−2.80	−2.94
43, C3	300	−0.71	2.11	1.32	−3.26	−4.58	−2.95	−2.24
44, C5	328	−1.56	3.01	1.79	−3.42	−5.21	−3.26	−1.70

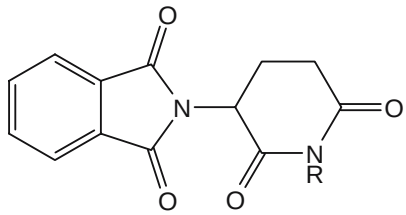
[a] Units of mM.
[b] Units of μmol cm^{-2} h^{-1}.
[c] Units of cm h^{-1}.
[d] Calculated from log J_{MOCT} − log S_{OCT}.
[e] Calculated from log $J_{M6.4}$ − log $S_{6.4}$.
[f] C1, C2 .... refers to number of carbons in alkyl chain.

dependent on C_{M1} (and hence J_{MVEH} on S_{M1}) to provide the driving force for permeation. Here we will use two examples. One example is for a series of homologous permeants from the Flynn database: aliphatic alcohols, Table IV (32). In one part of the dataset we list the fluxes from the application of the pure alcohols, J_{MLIPID}, with the corresponding P_{LIPID} and $K_{OCT:AQ}$ values. In the other part we list the fluxes of the

ROH

31 - 40

hairless mouse experiments also showed that the apparently irreversible interaction of the shorter chain alcohols with skin was less than that of the longer chain alcohols. Thus, the flux



41 - 44

alcohols (that are not miscible with water), from water, J_{MAQ}, with their corresponding P_{AQ} and common $K_{OCT:AQ}$ values. For fluxes from the application of the pure alcohols, J_{MLIPID} and P_{LIPID} become increasingly smaller as the alkyl chain length is extended while $K_{OCT:AQ}$ values increase as S_{AQ} and S_{LIPID} both decrease. Since all of the alcohols in the dataset are miscible with octanol, it is not possible to obtain experimental S_{OCT} values. Instead, we have chosen to use the molar concentrations of the pure alcohols, as did Scheuplein (32), in place of S_{OCT} to calculate P_{LIPID}. For the fluxes of alcohols from water, J_{MAQ} also becomes smaller as the alkyl chain length increases ($K_{OCT:AQ}$ increase and S_{LIPID} and S_{AQ} values decrease), but for this part of the dataset, P_{AQ} values increase. Thus, the observation that J_{MVEH} trends in the same direction regardless of the vehicle while P_{VEH} trends in opposite directions for delivery from a lipid or aqueous vehicle holds for non-prodrug homologs as well as prodrugs. On the other hand, $K_{OCT:AQ}$ trends in the same direction for both types of vehicles but it is in the opposite direction of the J_{MVEH} trends: $K_{OCT:AQ}$ and P_{VEH} are not good predictors of J_{MVEH}.

With the alcohols it is a possibility that the alcohols are acting as penetration enhancers to give increased flux (5,8). The problem with that rationale is that the fluxes of the longer chain, known penetration enhancers are less than that of the shorter chain alcohols. In addition, the flux of pure alcohols through hairless mouse skin has also been studied (33). Regardless of any arguments about how well one can predict absolute flux values through human skin from hairless mouse skin, the J_{MLIPID} values are in the same rank order through both membranes. Second application studies in the of the standard theophylline from propylene glycol after the applications of the pure alcohols was lowest for the shorter chain alcohols (C1 to C3) but increased dramatically for C4 (46 times) and remained high for the rest of the series (C5 to C8). If the shorter chain alcohols are increasing their own flux, it is not substantially different from controls as measured as an irreversible effect. Hairless mouse skin is apparently quite sensitive to interaction with vehicles which may make the model useful for predicting potential interactions of vehicles with human skin where the result may be more subtle and difficult to identify.

Another example of the effect of vehicle polarity on the flux of homologs can be seen in the extensive studies on the flux of thalidomide homologs through human skin *in vitro* from alcohol and water suspensions (34,35). In Table V we have chosen to give only the example of the flux of the homologs from octanol. However, it should be noted that in each case the solubility of the series of homologs in an alcohol increased with the increased length of the alkyl side chain of the homolog, but the solubility of a homolog in the series of alcohols of increasing chain length decreased with increasing chain length of the alcohol (34). For each combination of homolog and alcohol, flux was dramatically increased by the methyl homolog compared to the parent drug and the methyl homolog gave the highest flux of any homolog/alcohol combination except for the combination of nonanol with the propyl homolog. The J_{MAQ} and J_{MOCT} values decreased with increasing chain length of the homologs as expected by analogy to series of prodrugs and other homologs (35). On the other hand, S_{AQ} decreased while S_{OCT} and $K_{OCT:AQ}$ values increased and P_{AQ} and P_{OCT} trended in

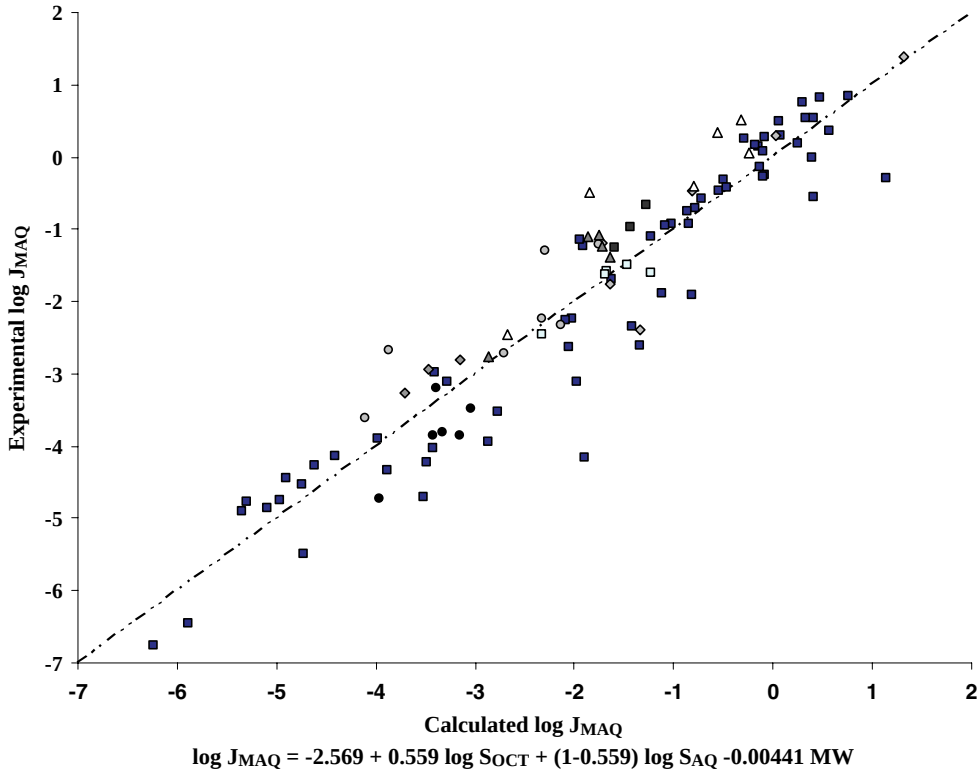


Fig. 3. Calculated *versus* experimental flux for the edited plus extended flynn database using the Roberts-Sloan Equation (n = 103).

opposite directions, also as expected by analogy to series of prodrugs and other homologs. Again P_{VEH} and $K_{LIPID:AQ}$ are simply not good positive predictors of trends in flux. Although only $K_{OCT:AQ}$ values were determined, K values derived using other alcohols, which were not miscible with water, should be expected to behave similarly.

FLYNN DATABASE FIT TO NEW PARADIGM

Although data from each *in vitro* human skin study at least qualitatively supports the new paradigm as can be seen in the trends in J_{MVEH} from lipid or aqueous vehicles as outlined above, the most important criteria for how well a model works is how well it predicts results from experiments not included in the model database. Also, although the Roberts–Sloan equation works well for data from hairless mouse skin *in vitro*, how well does it fit data from human skin *in vitro* and ultimately *in vivo*. A large database that has often been analyzed is the Flynn database comprised of the P_{AQ} and $K_{OCT:AQ}$ values for 97 compounds all delivered through human skin *in vitro* from water. We recently fitted the Roberts–Sloan equation (36) to an edited (we removed compounds which were water miscible or for which no reliable S_{AQ} data could be found and the Scheuplein *et al.* steroids for $n = 62$) (3,32,37–42) and extended database (we

Table VI. Fluxes of Aminocarbonyloxymethyl Esters through Human Skin *in vitro* from pH 5.0 Buffer (51)

Compound	MW	log $S_{5.0}$[a]	log $K_{OCT:5.0}$	log S_{OCT}[a,b]	Exp log $J_{M5.0}$[c]	Calc log J_{MAQ}[c,d]	Exp log $P_{5.0}$[e]
Naproxen	230	−0.337	2.38	2.04	−2.796	−2.625	−2.459
45, 3k	403	−2.699	3.35	0.65	−4.222	−5.173	−1.523
Benzoic acid	122	1.591	1.35	2.94	−1.290	−0.765	−2.881
46, 3b	295	0.114	2.26	2.37	−2.451	−2.495	−2.565
47, 3c	371	−2.523	3.57	1.05	–	–	–
48, 3d	327	−0.780	3.02	2.24	−3.301	−3.085	−2.521
49, 3e	337	−1.468	3.63	2.16	−3.041	−3.495	−1.573

[a] Units of mM.
[b] Calculated from log $K_{OCT:5.0}$ + log $S_{5.0}$.
[c] Units of μmol cm^{-2} h^{-1}.
[d] Calculated using Eq. (14).
[e] Units of cm h^{-1}.

Table VII. Fluxes of Aminoalkyl Esters of Naproxen, NAP, through Human Skin *in vitro* from pH 7.4 Buffer (52)

Compound	MW	log $S_{7.4}$[a]	log $K_{OCT:7.4}$	log S_{OCT}[a,b]	log $J_{M7.4}$[c,d]	log $P_{7.4}$[e,d]	Predict log $J_{M7.4}$[f,d]
NAP	230	2.01	0.3	2.31	−2.18(3)	−4.19(6)	−1.33(2)
50, C2, NH[g]	342	1.48	0.74	2.22	−2.29(4)	−3.77(5)	−2.18(4)
51, C2, NCH_3	356	1.51	2.29	3.80	−1.23(1)	−2.74(3)	−1.35(3)
52, C4, O	371	−0.70	2.60	1.90	−2.82(5)	−2.12(2)	−3.46(5)
53, C4, NCH_3	384	1.71	2.44	4.15	−1.56(2)	−3.27(4)	−1.19(1)
54, C6, NCH_3	412	−2.22	3.92	1.70	−3.40(6)	−1.18(1)	−4.42(6)

[a] Units of mM.
[b] Calculated from log $K_{OCT:7.4}$+log $S_{7.4}$.
[c] Units of μmol cm^{-2} h^{-1}.
[d] Number in parenthesis is rank order in series.
[e] Units of cm h^{-1}.
[f] Calculated using Eq. (14).
[g] The numbers 2,4 and 6 represent the value for n in the structure and the next notation presents X.

added compounds from eight different labs for $n = 41$) (35,43–50) to give $n = 103$ with only three repeats (36). For many datasets from labs other than the ones used, S_{AQ} or S_{OCT} values were not given so that (a) log S_{AQ} could not be calculated from log S_{OCT} − log $K_{OCT:AQ}$ or (b) log S_{OCT} could not be calculated from log $K_{OCT:AQ}$ + log S_{AQ}. And if S_{AQ} was not given or could not be calculated, J_{MAQ} could not be calculated from experimental P_{AQ}. The $n = 103$ database includes the J_{MAQ}, S_{AQ}, S_{OCT} and P_{AQ} values for the alcohols (Table IV) and thalidomide homologs (Table V) already discussed. The following fit (Fig. 3) was obtained:

$$log\ J_{MAQ} = -2.569 + 0.559\ log\ S_{OCT} + 0.441\ log\ S_{AQ} - 0.00441\ MW \quad (14)$$

where $r^2 = 0.90$ and Δ log J_{MAQ} was 0.438 log units.

The thalidomide homologs all perform better experimentally than their calculated J_{MAQ} values would have predicted with an average Δ log J_{MAQ} value of 0.440 log units, which is about average for the entire database. On the other hand, for some of the alcohols the experimental J_{MAQ} are higher than and some lower than their calculated J_{MAQ} with a Δ log J_{MAQ} value of only 0.137 log units, which was one of the closest agreements between experimental and calculated J_{MAQ} in the database.

PREDICTION OF FIT OF NEW *IN VITRO* DATA TO NEW PARADIGM

With the model database and fit in hand, it is of interest to determine how well the coefficients for S_{OCT}, S_{AQ} and MW predict the log J_{MAQ} for series not in the database. Here we have chosen to analyze datasets from three studies evaluating the flux of potential prodrugs from water through human skin *in vitro*. The first dataset is from the evaluation of aminocarbonyloxymethyl esters of carboxylic acids by Mendes *et al.* (Table VI) (51). Flufenamic acid from the original dataset was not included because no reliable log $K_{OCT:AQ}$ from which to calculate S_{OCT} was available.

Table VIII. Fluxes of Glycoside Esters of NSAIDs through Human Skin *in vitro* from pH 7.0 Buffer (55)

Compound	MW	log $S_{7.0}$[a]	log $K_{OCT:7.0}$[b]	log S_{OCT}[a,c]	Exp log $J_{M7.0}$[d]	Calc log $J_{M7.0}$[d,e]	Exp log $P_{7.0}$[f]
55, Flurbiprofen	244	0.842	3.34	4.18	−0.93	−0.93	−1.77
56, Glucoside	406	0.400	1.92	2.32	−2.52	−2.88	−2.92
57, Mannoside	406	0.451	1.56	2.01	−2.92	−2.93	−3.37
58, Ibuprofen	206	1.110	3.39	4.50	−0.84	−0.47	−1.95
59, Glucoside	368	1.088	1.57	2.66	−2.30	−2.22	−3.39
60, Mannoside	368	0.896	1.79	2.69	−2.10	−2.29	−2.99
61, Ketoprofen	254	1.141	2.44	3.58	−1.45	−1.19	−2.59
62, Glucoside	416	1.089	0.98	2.07	−3.08	−2.76	−4.17
63, Mannoside	416	0.920	1.11	2.03	−3.10	−2.85	−4.02
64, Naproxen	230	1.909	2.72	4.63	−1.75	−0.16	−3.66
65, Glucoside	392	0.864	1.32	2.18	−3.46	−2.70	−4.32
66, Mannoside	392	0.813	1.31	2.12	−3.33	−2.75	−4.14

[a] Units of mM.
[b] Partition Coefficient between OCT and pH 7.0 buffer.
[c] Calculated from log $K_{OCT:7.0}$+log $S_{7.0}$.
[d] Units of μmol cm^{-2} h^{-1}.
[e] Calculated using Eq. (14).
[f] Units of cm h^{-1}.

Table IX. Fluxes of NSAIDs from Mineral Oil through Human Skin *in vivo* (60,61)

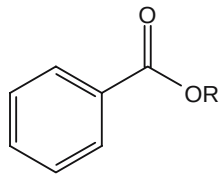
Compound	log S_{MO}[a]	log $K_{OCT:MO}$[b]	log J_{MMO}[c]	log P_{MO}[d]
67, Diclofenac	−1.02	2.91	−2.89	−1.87
68, Flufenamic acid	0.53	1.93	−1.86	−2.39
69, Ibuprofen	2.09	1.15	−0.25	−2.34
70, Ketoprofen	−0.30	3.54	−2.09	−1.79
71, Naproxen	−0.47	2.84	−2.00	−1.53
72, Nabumetone	1.19	0.57	−1.10	−2.29
73, Piroxicam	−0.74	1.49	−2.40	−1.66
74, Tenoxicam	−1.75	1.67	−2.89	−1.14
75, Aspirin	−0.76	3.96	−1.72	−0.96
76, Diflunisal	−1.17	3.36	−2.44	−1.27

[a] Units of mM.
[b] Partition coefficient between OCT and MO calculated from $K_{OCT:AQ}$ / $K_{MO:AQ}$.
[c] Units of μmol cm^{-2} h^{-1}.
[d] Units of cm h^{-1}.

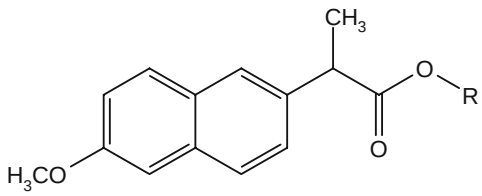
Qualitatively we would predict that the most water soluble member of the dataset which also exhibited good lipid solubility, S_{OCT}, would give the best flux. Indeed that is what has been observed. The problem from a prodrug point of view is that the most water soluble permeant in the dataset is one of the parent compounds, benzoic acid, which also happens to be the most lipid soluble member of the dataset. In spite of the fact that flux was measured using a donor phase of pH 5.0, $J_{M5.0}$, and Eq. (14) was developed from J_{MAQ} or $J_{M7.4}$ data, the fit of the dataset to Eq. (14) was slightly better than the average fit for the edited and extended Flynn database, Δ log J_{MAQ} = 0.393 log units, and correctly identified the rank order of all the compounds except for a switch in the place of the fourth and fifth compounds in the order. So, although the molecules that were evaluated presented with interesting physicochemical properties based on the old paradigm, i.e., increased $K_{OCT:5.0}$, none of them presented with interesting properties based on the new paradigm, i.e., increased $S_{5.0}$ and S_{OCT}, so none of the derivatives gave higher flux values. The old paradigm was not useful in designing derivatives with enhanced abilities to permeate human skin.

A much better design approach for a prodrug based on the new paradigm is illustrated by the series of aminoalkyl ester prodrugs of naproxen (NAP), Table VII (52). Aminoalkyl esters have been used successfully as prodrugs to increase topical delivery in the past by increasing S_{AQ} (53,54), but complete physicochemical properties were not given and only one prodrug was made in each study so no structure *versus* effectiveness of delivery was available. In the series in Table VII, although none of the prodrugs were more water soluble than NAP, three of them (**50, 51**, and **53**) were relatively more water soluble than most other esters of non-steroidal anti-inflammatory drugs, NSAIDs. Two of them, **51** and **53**, were also more soluble in OCT as well, so based on the new paradigm, they gave the highest fluxes and the greatest enhancements of flux compared to NAP; 9 and 4.3 times, respectively. The fit of the dataset to Eq. (14) was slightly worse than the average fit for the entire edited and extended Flynn database, Δ log J_{MAQ} = 0.52 log units, but clearly identified that the prodrugs with the best balances of S_{AQ} and S_{LIPID} gave the best fluxes. Note that both log $P_{7.4}$ and log $K_{OCT:7.4}$, a predictor of flux in the old paradigm, trend in the opposite direction of the trend in $J_{M7.4}$.

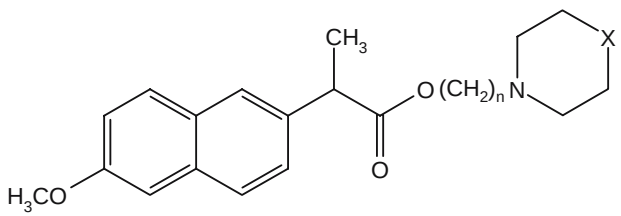
The third example is from the evaluation of glycoside esters of four NSAID agents by Swart *et al*., Table VIII (55). Although it is surprising that none of the glycoside esters,



benzoic acid, R = H
46, 3b, R = CH_2-O_2C-NHCH(CH_3)CO_2Et
47, 3c, R = CH_2-O_2C-NHCH($CH_2C_6H_5$)CO_2Et
48, 3d, R = CH_2-O_2C-NHCH($CHMe_2$)CO_2Et
49, 3e, R = CH_2-O_2C-NHCH(CH_2CHMe_2)CO_2Et



naproxen, R = H
45, 3k, R = CH_2-O_2C-N(CH_3)CH_2CO_2Et



50 - 54

Table X. Fluxes of Nicotinic Acid Esters from pH 5.5 Buffer through Human Skin *in vivo* (62)

Compound	MW	log S_{AQ}[a]	log $K_{OCT:AQ}$[b]	log S_{OCT}[a]	Exp log $J_{M5.5}$[c]	Calc log $J_{M5.5}$[c]	Exp log $P_{5.5}$[d]
77, C1	137	3.907	0.845	4.752	1.85	1.86	−2.06
78, C4	179	1.136	2.47	3.601	−0.34	−0.32	−1.48
79, C6	207	−0.086	3.510	3.424	−1.18	−1.06	−1.09
80, C8	235	−1.371	4.709	3.338	−2.20	−1.96	−0.83

[a] Units of mM.
[b] Partition coefficient between OCT and AQ.
[c] Units of μmol $cm^{-2} h^{-1}$.
[d] Units of cm h^{-1}.
[e] C1, C2 ... refer to the number carbons in the alkyl chain.

which contain three more polar hydroxyl groups than the parent NSAID, are more soluble in water than their parent drugs at the pH at which the diffusion cell experiments were run, that was the experimentally determined result. Since the log $K_{OCT:7.0}$ values for the derivatives are less than those of the parent drug because of all those additional OH groups, the log S_{OCT} values calculated from log $K_{OCT:7.0}$ + log $S_{7.0}$ were also less than those of the parent NSAID as well. Thus, since the log $S_{7.0}$ and log S_{OCT} values were both lower than those of the parent NSAID, the flux values, $J_{M7.0}$, of the derivatives were also predictably lower than those of the parents. However, the fit of this dataset to Eq. (14) was better than the average for the rest of the edited and extended Flynn database, Δ log $J_{M7.0}$ = 0.289 log units (excluding naproxen whose Δ $J_{M7.0}$ was 19 times greater than the average absolute difference) and correctly predicted the best performing compounds (the parent NSAID) in each series.

There are also at least four recent reports of which we are aware, and which contain sufficient data to estimate or calculate all the descriptors used in the new paradigm, where the fit of the reported data to the **RS** Eq. (14) is either poor (Δ log J_{MAQ} = 1.04 to 1.11 log units) (56–58) or does not predict the best member of the series (although Δ log J_{MAQ} = 0.21 log units) (59). However, even in those examples the best performers for each series of prodrugs or homologs are the ones that are the more water soluble members of the series. Thus, although the quantitative fit may be lacking, the qualitative prediction of the importance of a balance of water and lipid solubilities for optimizing flux within a series of prodrugs, homologs or analogs is still true. The design directive from the new paradigm still holds.

PREDICTION OF FIT OF *IN VIVO* DATA TO THE NEW PARADIGM

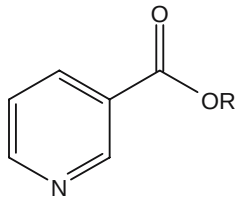
Finally, how well does the new paradigm fit *in vivo* flux through human skin? Here we choose to discuss datasets from two studies conducted by the same lab. The first dataset is from the evaluation of the fluxes of NSAIDs from mineral oil, MO (60). The fit of this dataset to the Roberts–Sloan equation has recently been published (61):

$$\log J_{MMO} = -1.459 + 0.722 \log S_{MO} + 0.278 \log S_{AQ} - 0.00013\ MW$$

where r^2 = 0.934 and Δ log J_{MMO} = 0.179 log units. The x and y coefficients are statistically different from zero while z is not. As expected, the coefficients for the parameters are quite different from those obtained from the edited and extended Flynn database since a different vehicle was used and because of the differences between *in vivo* and *in vitro* experiments: the latter skin is abnormally hydrated. Although it is difficult to pick out trends in log J_{MMO} *versus* log P_{MO} and log $K_{OCT:MO}$ values in Table IX that run through the entire dataset because they are not homologs or prodrugs, a plot of log J_{MMO} *versus* log P_{MO} (but excluding aspirin) gives a negative slope, −1.35, with r^2 = 0.72. If aspirin is included in the plot, the slope is still negative, −0.88, but with r^2 = 0.56. Thus, there is a negative correlation between log J_{MMO} and log P_{MO} which means that P_{VEH} is not a good positive predictor of J_{MVEH}. However, this result is different from that usually seen for the delivery of prodrugs or homologs from lipids or water where P_{VEH} trends in the same direction as J_{MVEH} for delivery from the lipid but in the opposite direction from water.

A plot of log J_{MMO} *versus* log $K_{OCT:MO}$ also gave a negative slope, −0.47, with r^2 = 0.74, showing that $K_{LIPID:VEH}$ is not a good positive predictor of J_{MMO}. On the other hand, a plot of log J_{MMO} *versus* log S_{MO} gave a positive slope, +0.67, with r^2 = 0.97, showing that S_{LIPID} is important as one leg of the new paradigm. Finally, the contribution of log S_{AQ} was shown to be a statistically significant, albeit minor, contributor to log J_{MMO}, so it is not surprising that a direct plot of log J_{MMO} *versus* log S_{AQ} also showed only a very small positive slope, +0.20.

It should be noted that Wenkers and Lippold came to equations similar to the Roberts–Sloan equations in their Model 2 where the viable epidermis is assumed to be the decisive barrier to permeation. Thus conversion of their Eq. (17), which is a Potts–Guy type equation missing the



77 - 80

dependence on MW or MV, to a Roberts–Sloan equation by adding log S_{MO} to both sides gives:

$$\log P_{MO} + \log S_{MO} = \log J_{MMO} = 0.19 \log K_{AQ:MO} - 2.05 + \log S_{MO} = 0.19 \log S_{AQ} + (1 - 0.19)\log S_{MO} - 2.05$$

Transformation of their Eq. (22) gives:

$$\log J_{MMO} = 0.11 \log K_{AQ:MO} + 0.78 \log S_{MO} - 1.44 = 0.11 \log S_{AQ} + (0.78 - 0.11) \log S_{MO} - 1.44$$

Thus, although the relative dependence on S_{AQ} is not as great, the Wenkers and Lippold analysis is forced to the same conclusions: J_{MVEH} depends on a balance of S_{LIPID} and S_{AQ}.

The results from the second *in vivo* dataset are more closely correlated with the previous results from *in vitro* experiments. For the nicotinic acid esters in Table X (62), as the alkyl chain length in the ester increases and both S_{AQ} and S_{OCT} values decrease, J_M values for their delivery from water, J_{MAQ}, also decrease. On the other hand, as the J_{MAQ} values decrease with increasing alkyl chain length, P_{AQ} and $K_{OCT:AQ}$ both increase. Again, P_{AQ} and $K_{OCT:AQ}$ trend in the opposite direction as J_{MAQ}.

It should be noted that Le and Lippold came to equations similar to the Potts–Guy and Roberts–Sloan equations, but missing the dependence on MW or MV. For Potts–Guy:

$$\log P_{AQ} = x + y \log K_{OCT:AQ}$$

where y is 0.32, we have calculated x to be −2.30. Thus, for Roberts–Sloan:

$$\log J_{MAQ} = -2.30 + 0.32 \log S_{OCT} + (1 - 0.32) \log S_{AQ}$$

where $\Delta \log J_{MAQ}$ is 0.075 log units. Although the coefficients are quite different because MW is not included as a variable in the Le-Lippold treatment, the conclusion is the same: J_{MVEH} depends on a balance of S_{LIPID} and S_{AQ}.

The same nicotinic acid esters with three additional permeants are also included in the edited and extended Flynn database for the delivery of permeants from water through human skin *in vitro* (36). Using the coefficients from Eq. (14), the $\Delta \log J_{MAQ}$ value was 0.26 ± 0.15 log units (without nicotinic acid) for the fit of the data to the Roberts–Sloan equation. If nicotinic acid was included, $\Delta \log J_{MAQ}$ was 0.39 ± 0.35 log units and the fit of nicotinic acid was six times worse than the ΔJ_{MAQ} for the series without it. The trends in P_{AQ} and $K_{OCT:AQ}$ *versus* the trends in J_{MAQ} and S_{OCT} and S_{AQ} are the same *in vitro* as *in vivo*: J_{MAQ} trend to smaller values as the alkyl chain length increases while the P_{AQ} and $K_{OCT:AQ}$ trended to larger values. The J_{MAQ} values for the CH_3, C_4H_9 and C_6H_{13} members that were common to both studies were higher for the *in vivo* than the *in vitro* studies with the average difference being +0.38 log units.

The flux and metabolism of three nicotinic acid esters through hairless mouse skin from saturated AQ has also been reported (63). The more water soluble methyl ester gave the highest flux of combined intact prodrug and parent drug with the ethyl ester giving the next highest flux followed by the butyl ester. On the other hand, the percent conversion of the esters to nicotinic acid was highest for the butyl (77%) and lowest for the methyl ester (8%). Thus, whether the prodrugs were delivered through human skin *in vitro* or *in vivo* and whether through human skin or hairless mouse skin, the qualitative conclusions are the same: (a) the more water soluble member of a series of more lipid soluble series gives the highest flux value, and (b) the more complete hydrolysis of the more highly lipid soluble members to the more water soluble parent does not lead to their increased delivery compared to the more water soluble members. The performances of the more lipid soluble members are compromised by their lower S_{M1} values which are a function of their lower S_{AQ} values. Regardless that they exhibit higher J_{MAQ} values than their parent, the more lipid soluble members do not represent the optimum members of the series. Again, S_{M1} is the driving force for topical delivery and S_{LIPID} and S_{AQ} are its predictors.

SUMMARY

J or J_{MVEH} are the appropriate measures of the effectiveness of a therapeutic agent. Thus, it is essential to use the basic form of Fick's law for analyses of the effects of the various physicochemical parameters, that are measured, on J:

$$J = D/L(C_{M1} - C_{Mn}) \quad (1)$$

Since the concentration of the therapeutic agent, C_{M1}, or its solubility in skin, S_{M1}, is the driving force for flux, increasing C_{M1} or S_{M1} will increase J or J_{MVEH}. Conversely, a measured increase in J or J_{MVEH} means there was an increase in C_{M1} or S_{M1}. Furthermore, if saturated solutions or suspensions of the therapeutic agents are used, S_{M1} of that permeant will not depend on its solubility in the vehicle, S_{VEH}. This conclusion is based on the Higuchi (20) proposal that the maximum flux, J_{MVEH}, of a permeant will be independent of S_{VEH} as long as the vehicle is not interactive, i.e., it does not change the solubilizing properties of the skin as some penetration enhancers do. Only those physicochemical properties of the permeant that affect S_{M1} will successfully direct the design of new prodrugs and metabolically stable homologs or analogs of known drugs. Obviously, the selection of new drugs for topical delivery will be directed by the same considerations.

Based on the dependence of J_{MVEH} on S_{M1}, there are essentially two paradigms that have been used to explain the observed trends in the physicochemical properties and the effect of those trends on J_{MVEH}. On the one hand, J_{MVEH} values for permeants depend on a balance of their absolute solubilities in a lipid and in water (y log S_{LIPID} + $(1-y)$ log S_{AQ}): the new paradigm. On the other hand, J_{MVEH} values for permeants depend on their partition coefficients between a lipid and the vehicle and their solubilities in the vehicle (y log $K_{LIPID:VEH}$ + log S_{VEH}): the old paradigm. An inverse dependence on MW or MV is common to both paradigms,

and the form of the old paradigm is a restatement of $P_{VEH}(\log P_{VEH} = x + y \log K_{LIPID:VEH} - z\,MW)$ in terms of J_{MVEH} where $\log J_{MVEH} = \log P_{VEH} + \log S_{VEH}$. The log S_{VEH} is only necessary to convert log P_{VEH} to log J_{MVEH}. When the vehicle is water, the old paradigm converts directly to the new paradigm and the equations that result give the same fit to the data. However, which set of descriptors can best direct the design of new drugs, prodrugs, homologs or analogs?

The solubility of the permeant in the vehicle, S_{VEH}, has been eliminated as a descriptor based on the proposal by Higuchi (20) that J_{MVEH} (and hence S_{M1}) for a permeant at saturation will not change with the vehicle because at saturation the permeant is at its maximum thermodynamic activity in each vehicle and hence in the skin. It has also been shown here that log $K_{LIPID:AQ}$ trends in the opposite direction of J_{MVEH}. Thus, both descriptors from the old paradigm are not useful directives of the design of better topical therapeutic agents. On the other hand it has been shown here and elsewhere (16,26,36,61) that J_{MVEH} can be predicted based on the solubility in a lipid, S_{LIPID}, and in water, S_{AQ}, of a permeant regardless of the vehicle; even if the vehicle is an interactive one such as IPM. The x, y and z coefficients to the parameters from Eqs. (9) and (12) do change but that is to be expected since the ability of the skin to solubilize the permeant has changed. However, with a given vehicle, species of skin and *in vitro versus in vivo* conditions, x, y and z should remain constant.

Finally, there are four other important observations that can be made based on these discussions of the application of the new paradigm. First, if J_{MVEH} depends on S_{M1}, rates of hydrolysis of the prodrugs can have little effect on the amount of total species (intact prodrug plus parent drug) in the skin and hence on flux. The rates at which various species permeate the skin will of course differ but that should have little effect on which member of a series gives the best J_{MVEH}. J_{MVEH} primarily depends on S_{M1}, and S_{M1} will depend on the S_{LIPID} and S_{AQ} values of the prodrug. Second, since J_{MVEH} is dependent on S_{LIPID} and S_{AQ} to give a macroscopic measure of S_{M1}, the new paradigm is independent of the exact mechanism whereby the permeant traverses the skin. It does not matter whether the permeant crosses alternating lipid and aqueous phases in the intercellular matrix or it alternately crosses polar corneocytes and lipid intercellular material (64). The design directives will be the same. Third, there is no highly correlated dependence of increased J_{MVEH} on decreased mp. This can be easily seen in prodrug series where the medium alkyl chain length members which exhibit the lowest mp give lower J_{MVEH} than the shorter chain length members with higher mp. Lower mp values correlate well with increased S_{LIPID}, but S_{LIPID} is only one leg of the new paradigm. Fourth, although we have reported that J_{MAQ} depends on S_{OCT}, S_{AQ} and inversely on MW for an edited and extended Flynn database (n = 103, r^2 = 0.900) (36), Magnusson *et al.* (65) have reported that, based on regression analysis of a different edited and extended Flynn database (n = 87 for training set), the dominant determinant of maximum flux, J_{MAQ}, is MW (r^2 = 0.847) with only minor contributions by melting point and hydrogen bonding acceptor capabilities. They also reported a low dependency on S_{OCT} (r^2 = 0.36). On the other hand, we found a much higher dependency on S_{OCT} alone (r^2 = 0.717) which was marginally better than the inverse dependency on MW alone (r^2=0.663) or the positive dependency on S_{AQ} alone (r^2 = 0.657), which is consistent with $p < 0.001$ for all three coefficients from the fit of the Roberts–Sloan equation to n = 103 (36). At this point, it is not clear why such different results are obtained other than that the two databases are quite different.

CONCLUSIONS

How does this new paradigm affect the design of new prodrugs, homologs and analogs? Qualitatively it means that for a series of more lipophilic prodrugs, homologs or analogs, those members that exhibit the highest water solubility will give the greatest flux. It also means that if one starts with a very polar permeant, increased S_{LIPID} will be the more important goal; while if one starts with a very lipoidal permeant, increased S_{AQ} will be the more important goal. A balance of S_{LIPID} and S_{AQ} in the final product (not $K_{LIPID:VEH}$ and S_{VEH}) is essential to optimize flux—the clinically useful measure of permeation.

Finally, the new paradigm gives useful directives for the design of prodrugs or new drugs for optimized topical delivery, but what about delivery through other biological membranes? Although there is no data to support an extension of these design directives to delivery by other routes, it seems likely that under conditions where only passive absorption occurs, these same design directives will be found to be useful for optimizing delivery by other routes.

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