Published in final edited form as:

Mol Pharm. 2012 July 2; 9(7): 2111–2120. doi:10.1021/mp300146m.

Estimation of maximum transdermal flux of nonionized xenobiotics from basic physicochemical determinants

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Abstract

An ability to estimate the maximum flux of a xenobiotic across skin is desirable both from the perspective of drug delivery and toxicology. While there is an abundance of mathematical models describing the estimation of drug permeability coefficients, there are relatively few that focus on the maximum flux. This article reports and evaluates a simple and easy-to-use predictive model for the estimation of maximum transdermal flux of xenobiotics based on three common molecular descriptors: logarithm of octanol-water partition coefficient, molecular weight and melting point. The use of all three can be justified on the theoretical basis of their influence on the solute aqueous solubility and the partitioning into the stratum corneum lipid domain. The model explains 81% of the variability in the permeation dataset comprised of 208 entries and can be used to obtain a quick estimate of maximum transdermal flux when experimental data is not readily available.

Keywords

Transdermal flux; solubility; permeability coefficient; mathematical model

Introduction

Skin has evolved to provide an efficient barrier at the interface of the external environment and the body. The formidable skin barrier properties greatly limit the permeation of xenobiotics^{1–5}. An advantage in terms of the protection against environmental toxicological agents is also a drawback from the perspective of percutaneous drug delivery. In both respects, the ability to identify the key physicochemical properties of xenobiotics that determine their skin permeation potential is very attractive. A reliable estimation of the maximum transdermal flux for new compounds affords a quick method of recognizing those with high potential for percutaneous permeation.

A large body of literature has been published about skin permeability to drugs^{6–23}. The description of percutaneous transport across skin usually comprises several assumptions about the nature of the barrier and the nature of the drug penetrating this barrier. The barrier properties of the skin for a moderately lipophilic drug are typically well-described by accounting for the barrier properties of stratum corneum (SC) lipid domain alone^{24, 25}. While some studies focused on the investigation of the permeability coefficient (P) others emphasized the maximum transdermal flux ($J_{\max}$). From the therapeutic and toxicological

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point of view it is often the maximum transdermal flux that is of critical importance. Such flux is normally attained by the use of a drug-saturated vehicle.

Models estimating the permeability coefficient

The permeability coefficient is often seen as a parameter describing the intrinsic, concentration-independent, ability of a molecule to cross the SC barrier. The majority of mathematical models used to estimate drugs' permeability coefficients recognize the importance of the drug partitioning into the SC lipids and drug molecular size. Physicochemical properties frequently used to estimate the permeability coefficients of drugs include MW, $\log K_{o/w}$ and hydrogen bonding potential^{11–20}. The direct assessment of a drug concentration in the lipid domain of the SC is typically inconvenient and often replaced by a product of a drug aqueous-vehicle concentration and a partition coefficient between the SC lipids and the vehicle ($K_{SC/w}$). This partition coefficient, in turn, can be related through a linear free energy relationship^{26–28} to a drug partition coefficient between octanol and water ($K_{o/w}$) e.g. $\log K_{SC/w} = a \log K_{o/w}$. In this equation, “a” stands for a coefficient accounting for the difference in the drug solubilities in SC lipids and bulk octanol, and usually is found to be in the range of 0.7 – 0.9 indicating a somewhat more hydrophilic nature of the anisotropic SC lipids as compared to the isotropic bulk octanol^{11, 13, 14, 17}. Additionally, the diffusivity of a drug molecule in the SC lipid domain (D) can be linked to its size through an inverse power function^{29, 30} or a free volume theory^{21, 31–33}. In the free-volume theory, molecular volume is habitually substituted with MW for simplicity and without loss of prediction accuracy e.g. $D = D_0 \cdot 10^{-\beta \cdot MW}$, where D_0 is the diffusivity of a hypothetical molecule having MW of zero, and β is a coefficient relating the MW to a drug's diffusivity in the SC lipid domain. This relationship predicts a sharp drop in the drug diffusivity within the SC's lipid bilayers with increasing molecular size, where β values typically vary in the range of 0.006–0.012^{11, 12, 14, 15}. The accessibility and ease of interpretation of the $\log K_{o/w}$ and the MW makes them very popular determinants in skin permeability equations. The number of equations estimating P based, among others, on $\log K_{o/w}$ and MW is above 20 and still growing³⁴. It is worth noting that most models strive to use a single equation to describe the skin permeability for molecules spanning a broad range of physicochemical properties which implicitly assumes that the same permeation pathway across the SC is involved and no shift in the rate-limiting step in drug transport across skin occurs. One of them, arguably the most widely used, was derived by Russel Potts and Richard Guy (P&GE)¹⁴. These authors used a multiple regression analysis of the Flynn permeation database³⁵ containing human epidermal permeability data of about 90 compounds to obtain the following relationship:

$$\log P = -2.72 + 0.71 \log K_{o/w} - 0.0061 \text{ MW} \quad [\text{cm/h}] \quad (1)$$

This model explained 67% of the variability in the dataset¹⁴. The popularity of this model can be, at least to some extent, explained by the choice of just two easily-accessible determinants: $\log K_{o/w}$ and MW.

Models estimating aqueous solubility of nonelectrolytes

According to Fick's first law of diffusion the maximum flux can be achieved by using a drug-saturated vehicle. Since the P estimates are often obtained with the use of the logarithm of octanol and *water* partition coefficient (as it is in the P&GE), the knowledge of the drug's *aqueous* solubility becomes important for finding the maximum percutaneous flux. A number of equations predicting solubility of nonelectrolytes in non-aqueous^{36–39} and aqueous media have been published^{40–45}. Many of them take a theory-based approach to the solubility estimation and typically recognize the importance of determinants such as heat of fusion, experimental temperature, MP, heat capacity, cohesive energy density, molecular

volume, dispersion forces, dipolar forces and hydrogen bonding potential. However, some of the above properties are not easily accessible and their estimation requires additional experimental or calculation work. One way to circumvent this hurdle is to introduce reliable assumptions about the solute's nature and simplify the model so that it is based solely on more readily accessible determinants. One of the most widely known semi-theoretical models estimating aqueous solubility of nonelectrolytes which uses only two determinants, MP and $K_{o/w}$, is the General Solubility Equation (GSE) introduced by Samuel Yalkowsky^{42, 43}. Parameter values obtained by a multiple regression analysis on the database of 580 nonelectrolytes were found to agree very closely with those derived theoretically and accounted for 97% of the variability in the dataset. The regression form of the model is as follows:

$$\log S_w = -0.0102 (MP - 25) - 1.031 \log K_{o/w} + 0.424 \quad [\text{mol/l}] \quad (2)$$

where $\log S_w$ is solute aqueous solubility, MP is solute melting point [°C] and $\log K_{o/w}$ is the logarithm of the solute octanol-water partition coefficient. The first term is derived from the ideal solubility equation. The ideal solubility is solvent-independent and the solubility estimate relies on the knowledge of the enthalpy of fusion, MP of the solute and the experimental temperature⁴³. The introduction of a molecular-independent estimate of enthalpy of fusion and a set temperature of 25°C allows a substantial simplification of the original equation and shows a negative dependence of the aqueous solubility on the MP of the solute. The second term addresses the non-ideality concerns by directly relating solute activity coefficient in water to solute $K_{o/w}$. This transformation reveals a strong inverse relationship between aqueous solubility of a nonelectrolyte and its $\log K_{o/w}$.

Models estimating maximum percutaneous flux

From the therapeutic and toxicological point of view the $J_{\max}$ is usually of higher importance than the P because it correlates directly with the maximum dose deliverable over a given period of time. Relatively few mathematical models have been proposed for the purpose of $J_{\max}$ estimation^{21–23}. They employ parameters such as drug solubility in octanol, S_w , solubility in isopropyl myristate, and MW. Kasting et al. proposed a semi-theoretical model for moderately lipophilic permeants based on the drug octanol solubility and MW²¹. Magnusson et al. found by statistical analysis that MW was the single major determinant of $J_{\max}$ in the database tested by the authors. It was shown that the addition of extra determinants such as solute solubility in octanol, MP and hydrogen bonding potential only improved the predictive ability of the model marginally²². Also, Sloan et al. postulated a model using drug solubility in isopropyl myristate (or octanol), S_w and MW^{23, 46, 47}. Each of those models showed reasonable performance in their $J_{\max}$ predictive ability. However, drawbacks include the use of parameters that are not easily determined, such as octanol or isopropyl myristate solubility. Also, the statistical model based on MW alone, although extremely simple and user-friendly, lacks theoretical backing. We believe that the introduction of a new semi-theoretical model based solely on easily-accessible molecular descriptors will be useful for the quick estimation of $J_{\max}$. The model reported herein may be seen as a close relative to the one reported by Kasting et al.²¹ in which the drug MP and $\log K_{o/w}$ are surrogates for drug octanol solubility. Octanol solubility, in turn, approximates drug solubility in the SC lipid barrier.

We hypothesize that the combination of two well-established, predictive models estimating drug skin permeability coefficients¹⁴ and aqueous solubility of nonionic compounds (S_w)^{42, 43} will afford a straightforward method for assessing the percutaneous absorption potential of new compounds in terms of the maximum flux. The purpose of this article is to report a simple and easy-to-use predictive mathematical model for estimation of the

maximum transdermal flux of xenobiotics based on three easily accessible molecular descriptors: logarithm of octanol-water partition coefficient ($\log K_{o/w}$), molecular weight (MW) and melting point (MP). The model provides simple mechanistic interpretation of the influence of each determinant on $J_{\max}$. When skin permeation measurements are not readily available or a quick screening of a database of compounds is required, this model can readily provide initial estimates of maximum transdermal flux.

Materials and methods

Mathematical modeling

Multiple linear regression analysis was performed using Scientist® 1.0 software for Windows (MicroMath, Saint Louis, MO). Maximum flux ($J_{\max}$) was the dependent variable in all analyses, while $\log K_{o/w}$, MW and MP were the independent variables. First, in order to obtain the model (Eq. 5) least squares parameter estimates from a training set ($n=87$, Table 1), the initial parameter estimates were taken directly from Eq. 4. Due to a high inverse correlation between parameters c and d , the parameter d preceding the (MP-25) term was fixed in all regression analyses at 0.0102, the value estimated *a priori* by the GSE. Parameter d was kept constant over parameter c based on the facts that 1) its regression estimate was obtained from a very large solubility database and deemed reliable ($n=580$), 2) the “best fit” value was in excellent agreement with the theoretically derived value of 0.01. Secondly, the model with parameter estimates obtained through a regression analysis on a training set (Eq. 6) was tested against a validation set ($n=121$, Table 2). Finally, both sets were combined and another regression analysis was carried out on the whole permeation dataset ($n=208$) with parameter values from Eq. 6 used as initial parameter estimates.

Permeation database – training set (Table 1)

The training set database ($n=87$) was adopted without any changes from Magnusson et al. “Molecular size as the main determinant of solute maximum flux across the skin” (supplement, originally named “set t”)²² and is compiled in terms of the $J_{\max}$ of various solutes obtained from aqueous vehicles. The inclusion criteria for this database were: the use of human SC or epidermal membrane, no organic liquids present either in donor or receiver solutions, no pure liquid permeants applied to the membrane, ionization less than 10% at the experimental pH, and the knowledge of MP, S_w and either $J_{\max}$ or P . The compounds included in the database span over a broad range of physicochemical properties, $\log K_{o/w}$ (−4.67 – 4.52), MW (18 – 477) and MP (liquids – 293 °C). The maximum flux was either experimentally measured or calculated from the product of the reported drug aqueous solubility and its permeability coefficient. No theoretically estimated aqueous solubility was allowed for calculation of $J_{\max}$ from P in this set. The compounds included in the training set partly overlap with the entries included in the Flynn database³⁵.

Permeation database - validation set (Table 2)

The validation set database ($n=121$) was adopted from Magnusson et al. “Molecular size as the main determinant of solute maximum flux across the skin” (supplement, originally named “sets vs, vp and vk”)²² and is compiled in terms of the $J_{\max}$ of various solutes. The data comes from experiments including full- and split-thickness skin, pure liquid permeants, and donor solutions containing propylene glycol. Four nicotinate entries were rejected as no $\log K_{o/w}$ values were available. Additionally, the subset of data including permeation of ionized compounds (“set vf”) was excluded since the present analysis is only for nonionized compounds. A more complicated model of skin permeation would be required to include these data. Overall, the inclusion criteria for the validation set were more liberal as compared to the training set. Non-human skin, pure liquid permeants, and addition of a cosolvent (propylene glycol) were allowed. When experimental data was not available the

authors used Solaris software V4.67 (Advanced Chemistry Development) and the SRC Interactive PhysProp database to obtain estimates. The average absolute error in the $\log K_{o/w}$ determination with use of Advanced Chemistry Development software for a dataset of 103 compounds was estimated to be approximately 0.33⁴⁸. For exact database compilation methods and references to original research articles please refer to Magnusson et al. "Molecular size as the main determinant of solute maximum flux across the skin"⁴⁹. The compounds included in the validation database span over a large range of physicochemical properties, $\log K_{o/w}$ (−4.67 to 8.70), MW (18 – 765) and MP (liquids – 295 °C).

Results

The starting point for the derivation of the model estimating the maximum transdermal flux is Fick's first law of diffusion. When skin is the rate-limiting membrane for xenobiotic permeation the maximum flux can be obtained by the use of a drug-saturated vehicle. For aqueous formulation: $J_{\max} = P * S_w$, or

$$\log J_{\max} = \log P + \log S_w \quad (3)$$

There is a multitude of approaches that can be used to estimate $\log P$ and $\log S_w$. The model we set forth is based on the combination of two semi-theoretical models – P&GE (Eq. 1) and GSE (Eq. 2). The P&GE uses two determinants, $\log K_{o/w}$ and MW, to estimate a compound's skin permeability. Similarly, the GSE uses two determinants, $\log K_{o/w}$ and MP, to estimate the aqueous solubility of a nonionic compound. The direct substitution of Eq. 1 and 2 into Eq. 3 and the unit conversion gives:

$$\log J_{\max} = 3.704 - 0.321 \log K_{o/w} - 0.0061 \text{ MW} - 0.0102 (\text{MP} - 25) \quad \left[\text{nmol h}^{-1} \text{ cm}^{-2} \right] \quad (4)$$

where $\log K_{o/w}$ is the logarithm of the permeants's octanol-water partition coefficient, MW is the permeants's molecular weight, and MP is its melting point [°C]. For liquid solutes the term (MP-25) is set equal to zero. Since the $\log K_{o/w}$ is used by both Eq. 1 and 2, Eq. 4 relies on the total number of three determinants: $\log K_{o/w}$, MW and MP.

Figure 1 shows the $\log J_{\max}$ predicted by Eq. 4 plotted against the experimental $\log J_{\max}$ reported in the training set (Table 1). The straight line depicts ideal correlation and dashed lines enclose the region of ideal correlation ± 1 log unit. Generally, the predictions fall in a reasonable range of $\log J_{\max}$ values, although a trend of overestimating $J_{\max}$ in the low-flux region and underestimating $J_{\max}$ in the high-flux region is apparent. It is noteworthy that Eq. 4 parameter values were obtained directly from Eq. 1 and 2 employing separate databases (training sets), and not through the regression analysis on the training set reported here.

In the next step, a multiple linear regression analysis on the training set (Table 1) was carried out using the following model:

$$\log J_{\max} = a + b \log K_{o/w} + c \text{ MW} + d (\text{MP} - 25) \quad \left[\text{nmol h}^{-1} \text{ cm}^{-2} \right] \quad (5)$$

The initial parameter (a,b,c, and d) estimates were taken directly from Eq. 4. The least-squares fitting yielded the following equation:

$$\log J_{\max} = 4.911 - 0.167 \log K_{o/w} - 0.0120 \text{ MW} - 0.0102 (\text{MP} - 25) \quad \left[\text{nmol h}^{-1} \text{ cm}^{-2} \right] \quad (6)$$

An improved correlation devoid of any systematic deviation between calculated and experimental $\log J_{\max}$ is demonstrated in Figure 2. The coefficient of determination ($R^2=0.90$) indicates that the model accounts for 90% of the variability in the dataset with the standard deviation of 0.72 log unit. The vast majority of the experimentally determined $J_{\max}$ values fall in the range of the predicted $J_{\max}$ values ± 1 log unit. Moreover, the difference between predicted and experimental $\log J_{\max}$'s (residuals) plotted against individual determinants: $\log K_{o/w}$, MW and MP is shown in Figures 3,4 and 5, respectively. As evident from these figures residuals oscillate around the value of zero and there are no apparent trends in residuals as the value of each determinant is varied.

In the following step, the regression version of the model (Eq. 6) was tested against a larger and more liberally compiled validation set of 121 permeants (Table 2). Experimental data obtained with the use of non-human skin, pure liquid permeants, and addition of a cosolvent (propylene glycol) were all included. Figure 6 demonstrates the performance of the model (Eq. 6) against the validation set (Table 2). The majority of the experimentally determined $J_{\max}$ values in the validation set falls in the range of the predicted $J_{\max}$ values ± 1 log unit. However, the model tends to underestimate the $J_{\max}$ of low-flux xenobiotics and greater scatter of the data along the ideal correlation line is observed. The coefficient of determination ($R^2=0.61$) indicates that the model accounts for 61% of the variability in the dataset with the standard deviation of 1.2 log unit.

Finally, a combined dataset containing both training and validation sets ($n=208$, Table 1 and 2 combined) was employed. A regression analysis on the whole dataset, with the initial parameter estimates taken from Eq. 6, yielded the following expression:

$$\log J_{\max} = 4.600 - 0.219 \log K_{o/w} - 0.0086 \text{ MW} - 0.0102 (\text{MP} - 25) \quad \left[\text{nmol h}^{-1} \text{ cm}^{-2} \right] \quad (7)$$

Figure 7 demonstrates the results of the least-squares fitting process. The majority of the experimentally determined $J_{\max}$ values in the combined permeation dataset falls in the range of the predicted $J_{\max}$ values ± 1 log unit. Only random deviations are observed along the ideal correlation line but greater scatter of the data is present as compared to Figure 2. The coefficient of determination ($R^2=0.81$) indicates that the model accounts for 81% of the variability in the dataset with the standard deviation of 0.89 log unit.

Discussion

According to the regression versions of the $J_{\max}$ model (Eqs 6 and 7) a decrease in a drug's $\log K_{o/w}$, MW or MP implies higher maximum percutaneous flux. While the parameters c and d preceding MW and (MP-25) terms, respectively, retain their original meaning from Eq. 1 and 2, the parameter b preceding the $\log K_{o/w}$ term reflects its influence on both P and S_w . All parameter estimates obtained here (mean $\pm$ 95% CI) agree well with previous literature reports. Specifically, the estimates obtained through regression analysis on the training set (Eq. 6) show negative dependence of $\log J_{\max}$ on the MW (-0.0120 ± 0.0015) which is somewhat steeper than that reported by Potts and Guy but falls in the range of values previously reported, such as 0.012^{11} , and is justified on the grounds of the free-volume theory. The increase in the MW of 100 Da translates, on average, into a 16-fold drop in the $J_{\max}$. The negative dependence of $\log J_{\max}$ on the drug's MP (-0.0102 , as estimated *a priori* by GSE) can be rationalized by its influence on the aqueous solubility, with an increase in the MP of 100°C translating, on average, into a 10-fold drop in the flux. Finally, the negative dependence of $\log J_{\max}$ on the drug's $\log K_{o/w}$ (-0.1666 ± 0.0801) arises from its effect on both the drug's permeability coefficient and aqueous solubility. A unit increase in the $\log K_{o/w}$ value causes roughly a 10-fold drop in the aqueous solubility of a nonionic

solute, on the other hand, it also causes around a 7-fold increase in the partitioning into the SC lipids. Overall, the permeant's concentration in the SC lipid barrier drops, on average, around 1.5-fold per unit increase in the $\log K_{o/w}$ value. Therefore, the $\log K_{o/w}$ effect on J_{max} is opposite from its effect on P. It is also true that $\log K_{o/w}$ influence on J_{max} , as compared to MW and MP, is minor since its effects on P and S_w almost cancel out. It could be argued that the presence of the $\log K_{o/w}$ parameter in the model is not necessary. However, both the non-zero parameter b estimate found here as well as a slight decrease in the Model Selection Criterion from 2.28 to 2.12, when $\log K_{o/w}$ is excluded from the model, suggest otherwise. (Model Selection Criterion is a modified Akaike Information Criterion where larger value indicates more appropriate model⁵⁰). Physically, the non-zero parameter b estimate supports the notion of SC lipids being somewhat more polar in nature as compared to the bulk octanol^{11, 13, 14, 17}.

The performance of the model obtained through regression on the training set (Eq. 6) tested against a validation set is acceptable but a non-random deviation exists in the low-flux region and data scatter is noticeable. Besides the inherent data variability related to the use of various experimental set-ups, factors such as the use of skin obtained from various animal species and cosolvent-skin interactions may add additional uncertainty. Unlike in the training set, the validation set may potentially suffer from these drawbacks. On the other hand, the limiting number of entries in the training set may not truly be representative of the whole permeant population and overestimate the effect of the molecular weight on the maximum flux. This line of reasoning seems to be supported by the fact that all of the underestimated J_{max} predictions in the low-flux region correspond to higher-MW compounds.

Finally, the combination of the training and validation sets into one complete permeation database and subsequent regression analysis returned the following parameter estimates (mean $\pm$ 95% CI): b (-0.215 ± 0.065), c (-0.00857 ± 0.00104), and d (0.0102 as estimated *a priori* by GSE). The overall J_{max} dependence on $\log K_{o/w}$, MW and MP descriptors remains similar to the previously discussed relationship corresponding to the training set alone. For the complete database, the negative J_{max} dependence on $\log K_{o/w}$ is slightly more pronounced, on the other hand, the MW importance is somewhat depreciated. Overall, however, findings based on the training set alone and complete permeation database are in very good agreement. As to judgment of which approach (training set vs. whole permeation database) gives more reliable parameter estimates, the answer is: it depends. The training set alone has the advantage of containing a very carefully selected spectrum of compounds permeating from aqueous solutions through human skin exclusively, but at the same time, suffers from a relatively low number of entries (n=87). Conversely, the whole permeation database (training and validation sets combined) encompasses a broader spectrum of permeants diffusing across skin of various species-origin and some of which contain cosolvent in the donor solution, but at the same time, offers a large number of entries (n=208).

Limitations of the model proposed here are related to the fact that it uses a single equation to predict the maximum transdermal flux. Therefore, it is implicitly assumed that all permeants cross the skin barrier by the same pathway and no shift in the rate-limiting step of the drug transport occurs. Also, the GSE predicts aqueous solubility of the nonionic compounds at 25°C while *in vitro* skin diffusion experiments are typically carried out at higher temperature. However, given the different experimental conditions (temperature in the range 22 – 39°C) used by authors whose data is included in the permeation databases and for the sake of simplicity of the final model the temperature difference was not explicitly considered.

The model that we propose represents a valuable tool that has theoretical backing while retaining simplicity. It is based on two widely-approved models for estimation of aqueous solubility of nonelectrolytes (GSE) and skin permeability of drugs (P&GE). Its regression version is in good agreement with the expected theoretical considerations and former literature reports. The only inputs it requires are easily-obtainable molecular descriptors. Yet it allows a meaningful analysis of the impact of each predictor on the maximum flux through skin on the theoretical basis. While the flux dependence on MW through free-volume theory is not a surprise, the effect of the $\log K_{o/w}$ on the maximum flux is interesting. The beneficial effect of high lipophilicity on the permeability coefficient is more than compensated for by its negative effect on the decreased aqueous solubility. As a result the maximum flux shows a weak negative dependence on $\log K_{o/w}$. Next, even for non-aqueous vehicles this relationship holds due to the fact that the product of permeant solubility in a vehicle and the corresponding partition coefficient between this vehicle and stratum corneum lipids is a constant across different vehicles. This manifests itself as a good fit of the model to the wide database of solutes including non-aqueous vehicles. Finally, a quantitative dependence of maximum flux on the melting point is not widely recognized and the proposed model incorporates this relationship. Hence, the model reported herein provides theoretical and quantitative mechanistic explanation of the impact of all three predictors it employs on the maximum skin flux. No predictive model has directly combined the concepts from GSE and skin permeability prediction by P&GE to elucidate the effect of simple molecular descriptors on the maximum transdermal flux.

Alternative models allowing estimation of the J_{max} , although useful, may not have the same advantage of being user-friendly and theoretically sound. For example, the theory-backed and elegant model set forth by Kasting²¹ requires the knowledge of drug octanol solubility which may not be readily available or requires additional calculation. Next, the model reported by the Sloan group^{23, 46, 47, 51}, despite its good predictive power (as judged by R^2 value), also requires either isopropyl myristate or octanol solubility input. Additionally, the authors claim that the “model takes into account the apparent biphasic nature of the barrier to permeation” by inclusion of a term corresponding to drug aqueous solubility in addition to the octanol solubility and MW⁴⁶. However, we argue that this statement is not justified. The importance of aqueous and lipid solubility of a permeant, cited by the above model, does not correspond to the “lipid-only pathway”⁴⁶ and “lipid-aqueous series pathway”⁴⁶ in the stratum corneum. In the derivation process, what had initially been an octanol-water partition coefficient (mimicking drug partitioning between aqueous vehicle and “lipid-only pathway” in the stratum corneum) was split into two interrelated solubility terms (octanol and water). The aqueous solubility term was then linked to the “lipid-aqueous series pathway” while, in fact, the aqueous solubility term refers to the permeant solubility in the aqueous vehicle and not to the “lipid-aqueous series pathway” across stratum corneum. Hence, we believe that the data interpretation based on the above model is not sound. On the other hand, the model presented by the Roberts group⁴⁹ is extremely simple and easy-to-use. Its final shape was dictated by the stepwise regression statistical analysis which revealed that MW is the single most important predictor to consider when estimating the maximum transdermal flux of a permeant. However, the model does not elucidate, on theoretical grounds, the role of molecular size in the permeation process nor does it exclude the possibility that the use of other predictors may be theoretically justified.

Conclusions

There are few mathematical models that can be used to estimate maximum transdermal flux of xenobiotics. We believe that the major advantage of the model reported herein comes from the fact that it requires little or no experimental data to provide valuable information with respect to the percutaneous permeation potential of a new compound in terms of the

maximum flux. While many models estimating drug skin permeability coefficient use two determinants – $\log K_{o/w}$ and MW, with the cost of one additional determinant – MP, the maximum percutaneous flux can be estimated. Also, all three parameters are typically easily accessible and their use can be rationalized based on scientific theory. The model provides simple mechanistic interpretation of the influence of each determinant on J_{max} . When skin permeation measurements are not readily available or a quick screening of a database of compounds is required, this model can readily provide initial estimates of maximum transdermal flux.

Acknowledgments

This research was supported by NIDA R01 DA13425.

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Figure 1. Maximum transdermal flux calculated from Eq. 4 (J_{pred}) plotted against the experimental maximum transdermal flux (J_{exp}) of solutes included in the training set (Table 1). The solid line indicates ideal correlation while dashed lines enclose the region of ideal correlation ± 1 log unit.

Figure 2.

Maximum transdermal flux calculated from eq. (6) (J_{pred}) plotted against the experimental maximum transdermal flux (J_{exp}) of solutes included in the training set (Table 1). The solid line indicates ideal correlation while dashed lines enclose the region of ideal correlation ± 1 log unit.

Figure 3.
Regression analysis residuals $\log(J_{\text{pred}}/J_{\text{exp}})$ plotted against $\log K_{o/w}$ of permeants

Figure 4.
Regression analysis residuals $\log(J_{\text{pred}}/J_{\text{exp}})$ plotted against MW of permeants

Figure 5.
Regression analysis residuals $\log(J_{\text{pred}}/J_{\text{exp}})$ plotted against MP of permeants

Figure 6. Maximum transdermal flux calculated from eq. (6) (J_{pred}) plotted against the experimental maximum transdermal flux (J_{exp}) of solutes included in the validation set (Table 2). The solid line indicates ideal correlation while dashed lines enclose the region of ideal correlation ± 1 log unit.

Figure 7. Maximum transdermal flux calculated from eq. (7) (J_{pred}) plotted against the experimental maximum transdermal flux (J_{exp}) of solutes included in the training and validation sets (Table 1 and 2 combined). The solid line indicates ideal correlation while dashed lines enclose the region of ideal correlation ± 1 log unit.

Training set comprised of 67 compounds, 87 entries. The database was obtained from Magnusson et al. "Molecular size as the main determinant of solute maximum flux across the skin" (supplement, originally named "set t")²².

Table 1

#	Compound	logJ _{max} [nmol h ⁻¹ cm ⁻²]	MW [Da]	logK _{ow}	MP [°C]*
1	17-alpha-Hydroxyprogesterone	-1.77	330.5	2.89	223
2	2,3-Butanediol	2.75	90.1	-0.99	25
3	2,4,6-Trichlorophenol	2.43	197.5	3.58	69
4	2,4-Dichlorophenol	3.27	163	3	45
5	2-Butanone	4.14	72.1	0.37	25
6	2-Ethoxy ethanol	3.42	90.1	-0.27	25
7	2-Phenylethanol	3.14	122.2	1.36	25
8	3,4-Xylenol	3.17	122.2	2.4	61
9	4-Hydroxybenzyl alcohol	2.03	124.1	0.3	120
10	5-Fluorouracil	0.43	130.1	-0.78	283
11	alpha-(4-Hydroxyphenyl)acetamide	1.63	151.2	-0.29	177
12	Benzene	3.39	78.1	2.22	25
13	Benzoic acid	3.1	122.1	1.9	122
14	Benzoic acid	3.1	122.1	1.9	122
15	Benzyl alcohol	3.38	108.1	1.04	25
16	beta-Estradiol	-0.89	272.4	4.13	176
17	beta-Estradiol	-2.88	272.4	4.13	176
18	beta-Estradiol	-1.2	272.4	4.13	176
19	Betamethasone-17-valerate	-1.65	476.6	3.98	184
20	beta-Naphthol	2.29	144.2	2.71	123
21	Butanol	3.41	74.1	0.88	25
22	Butanol	3.33	74.1	0.88	25
23	Chlorocresol	3.28	142.6	2.89	67
24	Chloroxylenol	2.05	156.6	3.35	116
25	Cortexone	-0.87	330.5	3.41	142
26	Corticosterone	-0.51	346.5	1.76	181
27	Corticosterone	-1.54	346.5	1.76	181

#	Compound	$\log J_{\max}$ [nmol h ⁻¹ cm ⁻²]	MW [Da]	$\log K_{ow}$	MP [°C] ^a
28	Corticosterone	-1.89	346.5	1.76	181
29	Corticosterone	0.17	346.5	1.76	181
30	Cortisone	-2.19	360.5	1.24	222
31	Decanol	1.27	158.3	4.06	25
32	Estril	-2.23	288.4	2.94	282
33	Estrone	-1.76	270.4	3.69	255
34	Ethanol	4.13	46	-0.19	25
35	Ethyl ether	4.12	74.1	0.98	25
36	Heptanol	2.73	116.2	2.47	25
37	Heptanol	2.66	116.2	2.47	25
38	Hexanol	2.87	102.2	1.94	25
39	Hydrocortisone (HC)	-2.64	362.5	1.43	220
40	Hydrocortisone (HC)	-2.6	362.5	1.43	220
41	Mannitol	1.95	182.2	-4.67	167
42	Mannitol	1.74	182.2	-4.67	167
43	Mannitol	2.07	182.2	-4.67	167
44	m-Cresol	3.55	108.1	1.94	25
45	Methanol	4.19	32	-0.72	25
46	Methanol	4.7	32	-0.72	25
47	Methyl-4-hydroxy benzoate	2.08	152.1	1.87	128
48	m-Nitrophenol	2.72	139.1	1.93	97
49	Nicotinate, ethyl	3.35	151.2	1.41	25
50	Nicotinate, methyl	3.03	137.1	0.88	43
51	Nonanol	1.77	144	3.53	25
52	o-Chlorophenol	3.75	128.6	2.04	25
53	o-Cresol	3.56	108.1	1.94	30
54	Octanol	2.33	130.2	3	25
55	Octanol	2.4	130.2	3	25
56	o-Phenylenediamine	2.26	108.1	0.05	104
57	p-Bromophenol	3.5	173	2.49	64
58	p-Chlorophenol	3.83	128.6	2.43	44

#	Compound	logJ _{max} [nmol h ⁻¹ cm ⁻²]	MW [Da]	logK _{ow}	MP [°C] [*]
59	p-Cresol	3.53	108.1	1.94	36
60	p-Cresol	4.38	108.1	1.94	36
61	Pentanol	3.18	88.2	1.41	25
62	p-Ethylphenol	3.15	122.2	2.47	45
63	Phenol	4.23	94.1	1.48	41
64	Phenol	2.12	94.1	1.48	41
65	Phenol	3.83	94.1	1.48	41
66	p-Nitrophenol	2.75	139.1	1.57	114
67	p-Phenylenediamine	1.91	108.1	-0.85	146
68	Prednisolone	-1.56	360.4	1.69	241
69	Pregnenolone	-1.09	316.5	4.52	193
70	Progesterone	-1.37	314.5	4.04	121
71	Propanol	4.35	60	0.34	25
72	Propanol	4.2	60	0.34	25
73	Resorcinol	3.19	110.1	0.76	111
74	Sucrose	1.76	342.3	-3.85	186
75	Testosterone	-1.46	288.4	3.48	155
76	Testosterone	-1.16	288.4	3.48	155
77	Thymol	2.55	150.2	3.28	52
78	Toluene	3.68	92.1	2.68	25
79	Triamcinolone	-3.09	394.5	1.03	270
80	Triamcinolone acetamide	-3.01	434.5	2.6	293
81	Urea	3.4	60.1	-2.11	133
82	Urea	3.24	60.1	-2.11	133
83	Urea	3.13	60.1	-2.11	133
84	Water	4.94	18	-1.38	25
85	Water	4.93	18	-1.38	25
86	Water	4.68	18	-1.38	25
87	Water	4.44	18	-1.38	25

* For liquid permeants the MP was set to 25 °C

Table 2

Validation set comprised of 121 entries. The database was obtained from Magnusson et al. "Molecular size as the main determinant of solute maximum flux across the skin" (supplement, originally named "sets vs, vp and vk")²².

#	Compound	logI _{max} [nmol h ⁻¹ cm ⁻²]	MW [Da]	logK _{ow}	MP [°C]*
1	2-Ethylhexanol	2.47	130.23	2.82	25
2	2-Phenylethanol	3.73	122.2	1.36	25
3	2-Phenylethanol	3.33	122.2	1.36	25
4	2-Propoxyethanol	3.75	104.2	0.27	25
5	5-Fluorouracil	1.39	130.1	-0.78	283
6	5-Fluorouracil	0.34	130.1	-0.78	283
7	5-Fluorouracil	0.82	130.1	-0.78	283
8	Acetaminophen	1.48	151.2	0.46	170
9	Aminopyrine	2.40	231.3	0.76	108
10	Aniline	4.30	93.1	0.94	25
11	Aniline	3.91	93.1	0.94	25
12	Anisole	3.96	108.1	2.13	25
13	Anisole	3.11	108.1	2.13	25
14	Antipyrine	2.47	188.2	0.27	112
15	Benzaldehyde	4.27	106.1	1.64	25
16	Benzaldehyde	3.63	106.1	1.64	25
17	Benzene	4.38	78.1	2.22	25
18	Benzene	3.10	78.1	2.22	25
19	Benzene	3.51	78.1	2.28	25
20	Benzoic acid	3.77	122.1	1.9	122
21	Benzoic acid	3.14	122.1	1.9	122
22	Benzyl alcohol	3.99	108.1	1.04	25
23	Benzyl alcohol	3.70	108.1	1.04	25
24	Benzyl alcohol	3.75	108.1	1.04	25
25	beta-Estradiol	1.61	272.4	4.13	176
26	beta-Estradiol	-1.23	272.4	4.13	176
27	beta-Estradiol	-1.24	272.4	4.13	176

#	Compound	$\text{IOgl}_{\text{max}}[\text{nmol h}^{-1} \text{cm}^{-2}]$	MW [Da]	$\log K_{\text{ow}}$	MP [$^{\circ}\text{C}$]*
28	Betamethasone	-1.41	392.5	2.06	233
29	Betamethasone-17-valerate	-0.92	476.6	3.98	184
30	Butanol	2.81	74.1	0.88	25
31	Butobarbitone	0.65	212.3	1.75	127
32	Caffeine	0.89	194.2	-0.08	238
33	Chloroform	3.97	119.4	1.76	25
34	Chlorpheniramine	1.11	274.8	3.39	25
35	Clonidine	1.78	230.1	1.59	130
36	Coumarin	2.07	146.1	1.39	71
37	Cyclobarbitone	1.01	236.3	2.13	173
38	Decanol	0.62	158.3	4.06	25
39	Dexamethasone	-0.76	392.5	2.06	262
40	Dextromethorphan	1.57	271.4	4.13	110
41	Dextromethorphan HBr	1.52	271.4	-0.05	125
42	Di(2-ethylhexyl)phthalate	-0.59	390.56	8.7	25
43	Diazepam	1.22	284.7	2.82	132
44	Diethylcarbamazine	2.70	199.3	1.14	48
45	Diethylene glycol monobutyl ether	3.26	162.23	0.44	25
46	Digitoxin	-3.77	764.9	2.73	256
47	Ephedrine	3.26	165.2	1.05	34
48	Ethacrynic acid	3.39	303.1	3.69	123
49	Ethanol	4.09	46	-0.19	25
50	Ethanol	3.73	46	-0.19	25
51	Ethanol	3.70	46	-0.19	25
52	Ethoxyethyl acetate	4.03	132.16	0.72	25
53	Ethyl-3-ethoxypropionate	3.70	146.18	1.25	25
54	Ethylene glycol	3.28	62.07	-1.36	25
55	Formaldehyde	4.18	30	0.35	25
56	Furosemide	-0.20	330.8	2.03	295
57	Glycolic acid	3.85	76.1	-1.05	80
58	Griseofulvin	-0.17	352.8	2.36	220

#	Compound	log ₁₀ K _{max} [nmol h ⁻¹ cm ⁻²]	MW [Da]	logK _{ow}	MP [°C] ^a
59	Griseofulvin	-1.50	352.8	2.36	220
60	HC-yI-propionate	-1.12	418.5	2.51	196
61	Heptanol	2.26	116.2	2.47	25
62	Hexanol	2.63	102.2	1.94	25
63	Hexanol	3.20	102.2	1.94	25
64	Hyalazine HCl	2.10	160.2	-1.53	275
65	Hydrocortisone	0.06	362.5	1.43	220
66	Hydrocortisone (HC)	-0.98	362.5	1.43	220
67	Ibuprofen	3.32	206.3	3.72	76
68	Indolyl-3-acetic acid	1.80	175.2	1.41	169
69	Indomethacin	-0.16	357.8	3.11	158
70	Isoquinoline	2.77	129.2	1.96	26
71	Isosorbide dinitrate	1.31	236.1	0.9	70
72	Isosorbide dinitrate	1.97	236.1	0.9	70
73	Ketoprofen	1.67	254.3	2.81	94
74	Ketorolac (R)	0.29	255.3	2.08	176
75	Ketorolac (S)	0.20	255.3	2.08	176
76	Ketorolac (SR 50:50)	0.71	255.3	2.08	156
77	Mannitol	1.75	182.2	-4.67	167
78	Methanol	5.41	32	-0.72	25
79	Methyl salicylate	3.95	152.1	2.55	25
80	Minoxidil	0.59	209.3	1.24	248
81	Morphine hydrochloride (+)	1.83	339.4	-2.53	200
82	Morphine sulfate	-0.18	285.3	-1.76	254
83	Naproxen	1.32	230.3	3	153
84	n-Hexane	0.98	86.2	3.9	25
85	Nicorandil	1.53	211.2	-1.02	85
86	Nicorandil	1.69	211.2	0.72	93
87	Nicotinate, benzyl	1.98	213.2	2.66	25
88	Nicotinate, butyl	2.64	179.1	2.48	25
89	Nicotinate, ethyl	3.15	151.2	1.41	25

#	Compound	$\log I_{\max} [\text{nmol h}^{-1} \text{cm}^{-2}]$	MW [Da]	$\log K_{ow}$	MP [$^{\circ}\text{C}$]*
90	Nicotinate, hexyl	1.77	207.3	3.54	25
91	Nicotine	5.11	162.2	0.72	25
92	Nicotinic acid	1.25	123.1	0.82	237
93	Nifedipine	-0.69	346.3	2.2	173
94	Nitroglycerine	1.76	227.1	2.22	25
95	Nonanol	1.23	144	3.53	25
96	Octanol	1.80	130.2	3	25
97	Octanol	2.33	130.2	3	25
98	Ouabain	-1.86	584.7	-1.35	190
99	Ouabain	-1.09	584.7	-1.35	190
100	Parathion	-2.59	291.3	3.84	25
101	Pentanol	2.67	88.2	1.41	25
102	Pentanol	3.18	88.2	1.41	25
103	Pentazocine	0.38	285.4	4.64	146
104	Pentazocine HCl	0.35	285.4	-1.7	254
105	Piroxicam	0.32	331.4	1.71	199
106	Propanol	3.33	60	0.34	25
107	Propanol	4.12	60	0.34	25
108	Propranolol HCl	1.41	259.4	-0.45	163
109	Salicylamide	2.59	137.1	0.89	142
110	Salicylic acid	4.14	138.1	2.06	159
111	Sucrose	1.50	342.3	-3.85	186
112	Sulindac	-1.07	356.4	3.42	183
113	Terbutaline sulfate	-0.75	225.3	-1.9	247
114	Testosterone	2.08	288.4	3.48	155
115	Tetrachloroethylene	1.34	165.9	2.95	25
116	Triamcinolone acetamide	-0.38	434.5	2.6	293
117	Trichloroethylene	3.00	131.4	2.26	25
118	Water	4.89	18	-1.38	25
119	Water	4.94	18	-1.38	25
120	Water	4.55	18	-1.38	25

#	Compound	$\text{IOgl}_{\text{max}} [\text{nmol h}^{-1} \text{cm}^{-2}]$	MW [Da]	$\log K_{\text{o/w}}$	MP [$^{\circ}\text{C}$] [*]
121	Water	5.19	18	-1.38	25

^{*} For liquid permeants the MP was set to 25 $^{\circ}\text{C}$