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Research paper

A two-layer diffusive model for describing the variability of transdermal drug permeation

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ABSTRACT

There is mounting evidence that the permeability coefficients (k_p) that describe any given transdermal drug permeation process generally follow some form of positively skewed, non-symmetrical distribution rather than a simple normal distribution. Yet a suitable theoretical treatment of this area has not been undertaken to date. In this paper, we describe a two-layer model that can explain five drugs' k_p variabilities as measured in two previously published papers. The model shows why rapidly permeating drugs would tend to exhibit more symmetrical k_p distributions while progressively more slowly permeating drugs would tend to exhibit progressively more positively skewed k_p distributions. Future research should take this effect into account when comparing the flux variabilities of hydrophilic and lipophilic drugs.

1. Introduction

There is accumulating evidence that the permeability coefficients (k_p) that describe any given in vitro transdermal drug permeation process tend to follow a positively skewed, non-symmetrical distribution rather than a simple Gaussian normal (i.e. symmetrical bell-shaped) distribution. For example, Barry's team [1,2] analysed the data describing both 5-fluorouracil and estradiol flux through human epidermal membranes. In general, both drugs' k_p values could be more closely fitted to log-normal than to normal frequency distributions. Even in the case of tritiated water, recent analysis of 2400 in vitro k_p values, representing skins derived from 112 human volunteers, indicated that the data were positively skewed and followed a non-normal distribution [3]. Similarly, in vivo, each of the k_p databases describing the dermal penetration of ten non-steroidal anti-inflammatory drugs was positively skewed, correlating well with a log-normal but not a normal distribution [4]. In contrast, there are a few studies that have demonstrated that sometimes transdermal k_p data can be normally distributed [5,6]. There is also evidence that flux variability is greater for hydrophilic drugs than for lipophilic drugs [7].

In general terms, it is clear that k_p positive skewness is caused by the presence of defects or reduced barrier function in a small fraction of skin samples, causing such affected samples to be much more drug-permeable than the other replicate samples. Yet a deeper and more comprehensive understanding of transdermal permeation variability has not been achieved, to date. This is unfortunate since this area is crucial for facilitating correct statistical analysis of the data as well as for quality control purposes.

The aim of the current paper is to shed more light on the topic of permeation variability. To this end, we describe a theoretical two-layer diffusion model that explains, at least at a qualitative indicative level, the k_p data variations uncovered in two previously published papers. One paper collated the k_p data ($n = 63$) describing the flux of each of five different drugs across synthetic poly(dimethylsiloxane) (PDMS) membranes [8]. The other paper collated the k_p data ($n = 63$) describing the flux of each of the same five drugs across full-thickness pig skin samples [9]. Crucially, the selected conditions and methodologies in both studies were strictly identical, apart from the use of different barrier membranes. Our approach starts by analysing the skewness statistic of each drug's k_p distribution and its relationship to that drug's mean k_p.

2. Experimental data

Table 1 lists the candidate molecules tested in our previously published experiments [8,9]. It can be seen that these exhibited a

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Table 1
Table listing the partition coefficients and molecular weights of each of the candidate drugs.

Test drug	Log K(o/w) [a]	Molecular weight (Da)
Sucrose	−3.70	342
Adenosine	−1.05	267
Aldosterone	1.08	360
Corticosterone	1.94	346
Estradiol	2.29[b]	272

[a] Log K(o/w) indicates log octanol–water partition coefficient values.
[b] Estradiol partition coefficient values vary tremendously between different sources. We have used a value of 2.29 as reported by [1].

range of partition coefficient values but relatively comparable molecular weights. The graph shown in Fig. 1 was derived by combining data derived from each of these aforementioned studies. The plot is that of the skewness of each k_p database as a function of its mean k_p. Sample skewness is given by

$$Sk_{\text{sample}} = \frac{n}{(n-1)(n-2)} \sum_{i=1}^{n} \left[\frac{x_i - \bar{x}}{s}\right]^3, \quad (1)$$

where n is the sample size, x_i represents the ith value, $\bar{x}$ denotes the sample mean and s is the representative of the sample standard deviation. The skewness statistic essentially quantifies the symmetry of the underlying distribution: a zero value indicates a perfectly symmetric distribution, while positive values and negative values, respectively, indicate right-hand tailing and left-hand tailing of the distribution.

With respect to PDMS membranes, it should first be mentioned that there are only four data points since sucrose did not permeate across the membranes. Moreover, it can be seen that skewness did not change as a function of mean k_p in any obvious manner and was actually close to zero for all the test drugs. Such relatively symmetrical k_p distributions are consistent with the fact that the drugs in this system are permeating across a single and largely defect-free, homogenous synthetic membrane. In contrast, in the case of full-thickness skin, skewness for all five drugs had much larger positive values that tended to decrease as mean k_p increased.

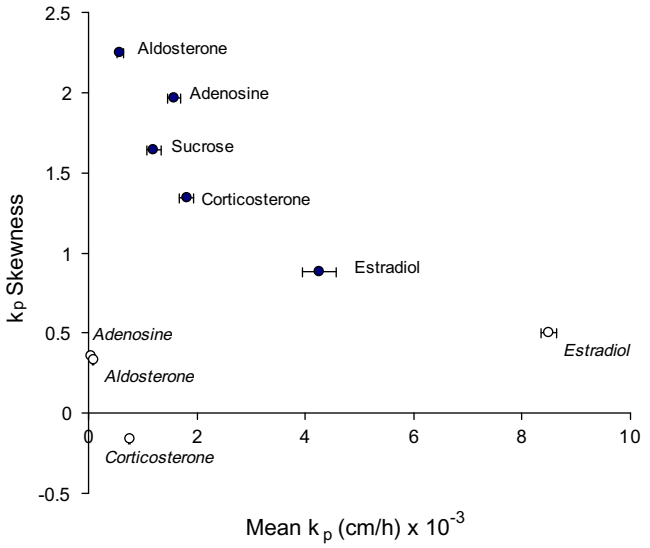

Fig. 1. The k_p sample skewness plotted as a function of mean k_p for each of the tested drugs. Empty and filled circles represent PDMS membrane and full-thickness skin data, respectively. Error bars indicate standard error of the means ($n = 63$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Theoretical development

We propose to explain the biological skin skewness paradigm by applying a two-layer diffusion model. The model consists of an upper stratum corneum and an underlying hydrophilic layer, the latter representing the combined viable epidermis and dermis. Such theoretical consolidation of the deeper strata into a single layer is a common approach [10].

The stratum corneum in any given experiment is treated as a homogeneous layer of effective thickness h, across which the drug i diffuses with effective molecular diffusivity κ_i. Since it can be expected that different individual skin samples might exhibit quite substantial variations in stratum corneum thickness, it follows that between two replicate experiments using the same drug, h varies although κ_i remains unchanged. Of course, this will be somewhat violated in practice as κ_i will vary with factors such as corneocyte morphology but any useful model must simplify reality to some extent.

With respect to the underlying hydrophilic layers, at any given site this tissue is some 2 orders of magnitude thicker than the stratum corneum. Moreover, due to its inner location and greater mechanical rigidity, it is much less susceptible than the constantly shedding stratum corneum to pronounced defects or large thickness variations induced by environmental friction and mild trauma. Moreover, in terms of barrier properties, it is thought that the stratum corneum can be potentially bypassed by hair follicles to a much more total extent than the hydrophilic layers [11]. Therefore, for the sake of simplicity, our model considers the hydrophilic tissue as a homogeneous layer of fixed thickness h_0. With regard to the diffusivities of dermally unbound drugs, these tend to depend on molecular weight (MW), as described by the Wilke–Chang correlation [12]. Specifically, Kasting's group [13] recently showed that experimental drug diffusivities varied as a function of $(\text{MW})^{-0.655}$ over the range $18 < \text{MW} < 477$. Since all our drug candidates exhibit comparable molecular weights that are well within this range (see Table 1), our model treats all drugs diffusing within the hydrophilic layer as having identical molecular diffusivity κ_0.

Considering the skin bilayer model as a whole, it can be shown that at steady state, there are linear gradients of concentration throughout each layer. In this situation, it can be shown that the resulting permeability coefficient is given by

$$k_{pi} = \frac{\kappa_i \kappa_0}{\kappa_i h_0 + \kappa_0 h}. \quad (2)$$

We assume that the distribution of h can be characterised by some typical (e.g. median) value $\bar{h}$, so that $h = \bar{h}H$, where H is a dimensionless random variable that may depend on other parameters and which takes typical values of order 1. This allows us to somewhat condense the problem and reduce the number of parameters to derive

$$k_{pi} = \frac{\kappa_i \kappa_0}{\kappa_i h_0 + \kappa_0 \bar{h} H} = \frac{\kappa_0}{h_0} \frac{\varepsilon_i}{(\varepsilon_i + H)}, \quad \text{where } \varepsilon_i = \frac{h_0 \kappa_i}{\kappa_0 \bar{h}}. \quad (3)$$

The advantage of this approach is that it expresses the variation of κ_i relative to all other quantities as a single dimensionless parameter ε_i. Since diffusion through the stratum corneum will typically be the rate-limiting step in the process, we expect that $\varepsilon_i \ll 1$. It is convenient to define the normalised quantity

$$K^*_{pi} = \frac{k_{pi} h_0}{\kappa_0} = \frac{\varepsilon_i}{\varepsilon_i + H}. \quad (4)$$

This allows us to ignore the dimensional prefactor in k_{pi}, which has in any case been assumed to be the same for all the test drugs.

To proceed further, we need to specify a distribution for H. For simplicity, it can be assumed that h follows a log-normal distribution with median $\overline{h}$, so H follows a log-normal distribution $\log N(\mu, \sigma)$ with $\mu = 0$ and the remaining parameter σ unspecified. (Appendix A considers the alternative of a Gamma distribution for h.) Higher values of σ correspond to a wider variation in the values of H, as well as to a slightly higher mean value. Some straightforward but tedious calculations, following the procedure of [14], yield the probability density function $f_i(t)$ for the random variable K^*_{pi}. It is given by

$$f_i(t) = \frac{1}{\sigma\sqrt{2\pi}(1-t)t}\exp\left(-\frac{1}{2\sigma^2}\left(\ln\left(\frac{\varepsilon_i(1-t)}{t}\right)\right)^2\right) \quad \text{for } 0 < t < 1. \tag{5}$$

(Note that from Eq. (4) and from the fact that $\varepsilon_i > 0$ and $H > 0$ by construction, K^*_{pi} must lie in the range $0 < K^*_{pi} < 1$.)

The distribution skewness $Sk(K^*_{pi})$ can now be calculated directly from the definition

$$Sk(K^*_{pi}) = \frac{\int_0^1 (t - E(K^*_{pi}))^3 f_i(t)dt}{\left[\int_0^1 (t - E(K^*_{pi}))^2 f_i(t)dt\right]^{3/2}}. \tag{6}$$

As there do not appear to be any convenient analytical expressions for $E(K^*_{pi})$ or $Sk(K^*_{pi})$, these were calculated numerically for given values of σ and ε_i using the 'Maple 12' software package.

4. Results

The theoretical model described earlier was used to generate a graph of $Sk(K^*_{pi})$ plotted as a function of $E(K^*_{pi})$. This is presented in Fig. 2. It can be seen that as ε_i is increased while holding σ constant, the mean $E(K^*_{pi})$ increases while the skewness $Sk(K^*_{pi})$ decreases. This corresponds to varying the penetrants but assuming that the transport of every penetrant is controlled by the same geometrical properties of the stratum corneum sample. It can be seen that the theoretical curves in Fig. 2 do indeed trace a similar profile to the biological skin data points presented in Fig. 1. Appendix A demonstrates that similar results can be obtained by taking a different underlying distribution for h, suggesting strongly that this result is not an artefact of the details of our model.

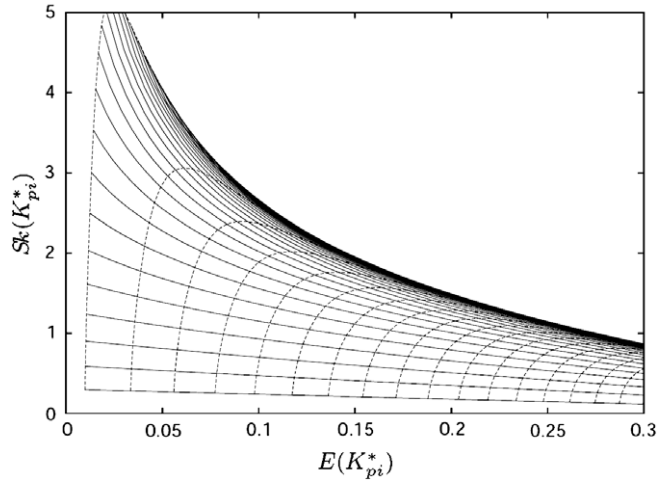

Fig. 2. The variation of $Sk(K^*_{pi})$ as a function of $E(K^*_{pi})$ when H follows a log-normal distribution. Solid lines show the effect of varying the diffusivity parameter ε_i, while holding the distribution parameter σ constant. (Values of σ are evenly spaced in the range $0.1 \leqslant \sigma \leqslant 3$, with $\sigma = 0.1$ the lowest and $\sigma = 3$ the highest line.) The dashed lines show the effect of varying σ, while ε_i is constant. (Values of ε_i are evenly spaced in the range $0.01 \leqslant \varepsilon_i \leqslant 0.5$, with $\varepsilon_i = 0.01$ the leftmost and $\varepsilon_i = 0.5$ the rightmost line.)

It is important to note that this systematic variation of skewness with mean permeability depends on the presence of the lower layer representing the viable dermis and epidermis. If instead of the two-layer model presented here we were to consider a single-layer diffusive model, then regardless of the distribution of h, we would not expect any variation of $Sk(k_p)$ with $E(k_p)$. This is easy to demonstrate. Consider two penetrants labelled by $i = 1$ and $i = 2$, so $k_{p1} = \kappa_1/h$ and $k_{p2} = \kappa_2/h$. The random variables k_{p1} and k_{p2} are then simply related by $k_{p2} = \frac{\kappa_2}{\kappa_1}k_{p1}$, and their probability density functions are related by $f_2(t) = \frac{\kappa_2}{\kappa_1}f_1\left(\frac{\kappa_2 t}{\kappa_1}\right)$. It is therefore simple to show from the definitions of mean and of distribution skewness that $E(k_{p2}) = \frac{\kappa_2}{\kappa_1}E(k_{p1})$ but that $Sk(k_{p2}) = Sk(k_{p1})$, so this model cannot explain any systematic change of skewness with the properties of the penetrant. In mechanistic terms, this failure occurs because single-layer diffusion is a linear process. Thus, the presence of flaws (low values of h) in some samples speeds up the permeation of both penetrants by the same factor without preferentially affecting the slower-diffusing penetrant.

Returning to Fig 2, it is also of interest to consider the role of σ, which describes the variability in the effective thickness of the stratum corneum. The higher its value, the higher the maximum skewness and the more strongly the skewness varies with mean. Yet it should be noted that there is clearly some limit above which the skewness cannot increase for a given value of $E(K^*_{pi})$, no matter how high σ is taken to be.

5. Discussion

The salient finding is that we can indeed use a simple two-layer model to explain, in general terms, the observed variation of permeability skewness with mean permeability for biological skins. The essential mechanism is that the faster a drug diffuses across the stratum corneum, the greater the role that the lower layer (the viable dermis and epidermis) plays in determining the overall permeability, and thus the less sensitive the permeability becomes to the variations in the stratum corneum. As discussed in Section 4, a single-layer diffusive model would not exhibit this behaviour, as such a model would not contain a secondary process to control the permeability of the more rapid penetrants.

No doubt, the mathematical model could be refined, for example by considering other distributions of h, treating the viable epidermis and dermis as separate compartments and/or incorporating drug–tissue partitioning steps, etc. However, we feel that any such model can only give a qualitative indication of the principles at play, and it would be very difficult to develop a model that could be used to predict actual data. For that purpose, the model would have to be greatly expanded to include elements such as penetrant-dependent variations in stratum corneum transport route and site-dependent variations in corneocyte morphology.

The main contribution of this study is the finding that rapidly permeating drugs would tend to exhibit more symmetrical k_p distributions, while progressively more slowly permeating drugs would tend to exhibit progressively more positively skewed, asymmetric distributions. The key is to use skewness to measure variability rather than other mathematically related parameters such as the coefficient of variation, fit to normality, and fit to log-normality. Some past studies have focused on hydrophilic versus lipophilic drugs, applying one of the other parameters to evaluate flux variability. In some studies, it was reported that hydrophilic drugs showed more variability than lipophilic drugs while others have found no difference. It is possible that in many cases, the hydrophilic drugs were simply the slower permeants producing more asymmetrical flux distributions. This will often result in greater

variability, but it depends upon the parameter being used as the end point in that study. It follows that if hydrophilic and hydrophobic drugs are being compared in terms of their flux variability, a well-designed study should involve use of candidate drugs that exhibit similar k_p values. Such an approach may yield further mechanistic insights.

Appendix A. Results employing an alternative underlying distribution for *H*

A natural concern about the results presented earlier is that they may not be generic, but may depend critically on our choice of a log-normal distribution for the rescaled stratum corneum thickness *H*. This appendix demonstrates that the same quantitative trends can be found if a different underlying distribution is chosen.

Any suitable distribution for *H* must not permit it to take zero or negative values, and this immediately rules out choices such as the normal distribution. An artificially truncated normal distribution could be employed instead, but this lacks the simplicity that generally makes the normal distribution a natural choice. However, there are several standard probability distributions that are supported only on the interval $(0, \infty)$, and which are therefore appropriate choices.

Specifically, we consider here the Gamma distribution with a "scale parameter" S and a "shape parameter" n. The probability density function for H is then given by

$$f(t) = \frac{1}{S\Gamma(n)}\left(\frac{t}{S}\right)^{n-1} e^{-t/S}, \tag{7}$$

where $\Gamma(n)$ is the standard gamma function. The distribution has mean Sn and variance S^2n. Higher values of n lead to a distribution which is centred further away from zero, i.e. to a lower probability of very small thicknesses.

Assuming such a distribution for H, we may calculate the probability density function for K^*_{pi} as

$$f_i(t) = \left(\frac{\varepsilon_i}{S}\right)^n \frac{(1-t)^{n-1}}{t^{n+1}} \frac{\exp\left(\frac{\varepsilon_i}{S}\frac{(t-1)}{t}\right)}{\Gamma(n)}, \quad \text{where } 0 \leqslant t \leqslant 1. \tag{8}$$

The distribution mean and skewness can now be evaluated as before. In fact, both have closed-form representations. Since these are somewhat cumbersome, especially in the case of $Sk(K^*_{pi})$, we do not include them here. However, it is worth noting that both the mean and skewness are functions only of the quantity ε_i/S rather than of ε_i and of S independently.

Fig. 3 illustrates the variation of the distribution skewness $Sk(K^*_{pi})$ with the distribution mean $E(K^*_{pi})$ for several values of n. The qualitative result is very similar to that for the log-normal distribution, in that the skewness decreases as the mean increases. This suggests that this behaviour is, as the mechanism described in Section 5 suggests, generic rather than an artefact of assuming log-normal behaviour for H.

Appendix B. Distribution variance

Although the emphasis of the study has been on the variation of permeability skewness with mean permeability, the data plotted in Fig. 1 also indicate a secondary trend. This trend is that the variance of k_p increases with the mean value, in contrast to the decreasing trend in skewness. This feature can also be predicted, qualitatively at least, by the two-layer model presented here. It is simple to evaluate the variance of the K^*_{pi} distribution given the probability density function $f_i(t)$, using the definition

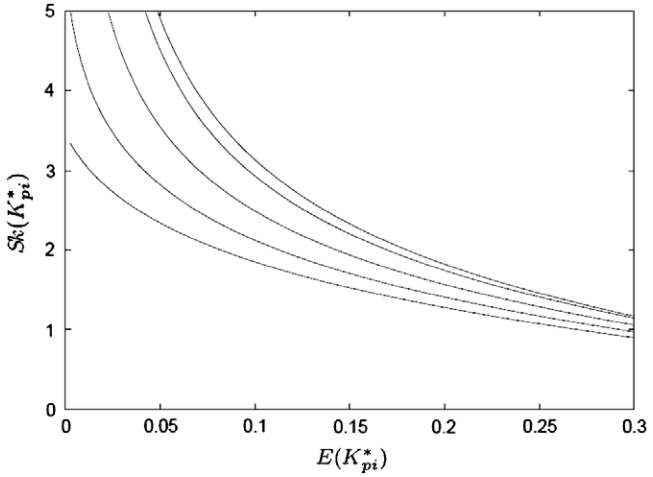

Fig. 3. The variation of $Sk(K^*_{pi})$ as a function of $E(K^*_{pi})$ when H follows a Gamma distribution. Solid lines show the effect of varying the quantity ε_i/S, while holding the distribution parameter n constant. Values of ε_i/S ranged from 0.002 to 1; values of n were $n = 1$ (uppermost), 2, 3, 4 and 5 (lowest line).

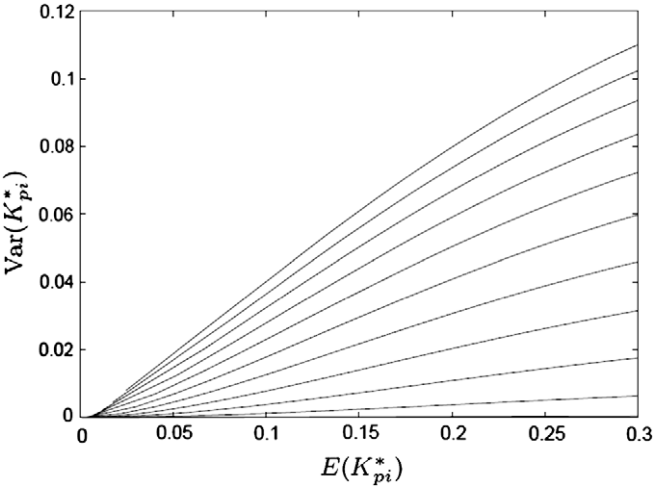

Fig. 4. The variation of $Var(K^*_{pi})$ as a function of $E(K^*_{pi})$ when H follows a log-normal distribution. Different lines show the effect of varying the diffusivity parameter ε_i, while holding the distribution parameter σ constant. (Values of σ are evenly spaced in the range $0.1 \leqslant \sigma \leqslant 3$, with $\sigma = 0.1$ the lowest and $\sigma = 3$ the highest line.)

$$Var(K^*_{pi}) = \int_0^1 (t - E(K^*_{pi}))^2 f_i(t)dt.$$

Fig. 4 shows the variance calculated using the log-normal distribution model, for the same range of ε_i and S as in Fig. 2. It is clear that as the mean increases, so does the variance. This provides further support for the use of such a model as a first step to understanding the mechanisms behind the permeability data presented in Fig. 1.

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