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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 $i$th 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.

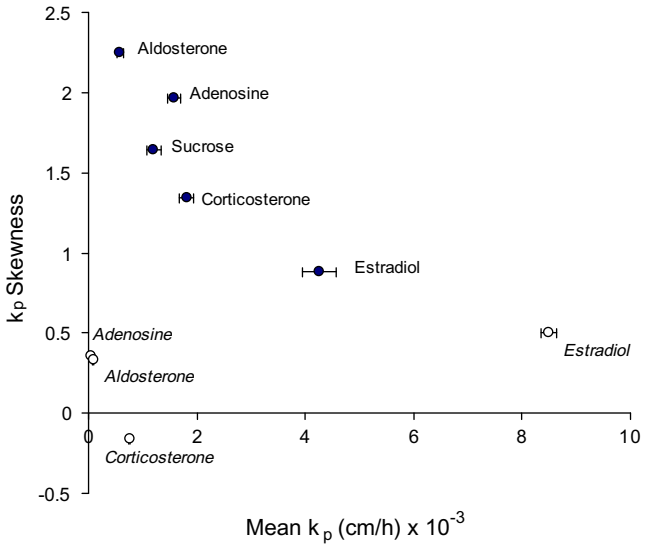


**Fig. 1.** The $k_p$ sample skewness plotted as a function of mean $k_p$ for each of the tested drugs. Empty and filled circles represent PDMS membrane and full-thickness skin data, respectively. Error bars indicate standard error of the means ($n = 63$). (For interpretation of the references to color 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 $\kappa_i$. 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 $\kappa_i$ remains unchanged. Of course, this will be somewhat violated in practice as $\kappa_i$ 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 $\kappa_0$.

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 $\kappa_i$ relative to all other quantities as a single dimensionless parameter $\varepsilon_i$. 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.