Predicting Diffusion in the Dermis: a Physiologically Based, Bottom-up Approach

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Background

A mechanistic Physiologically Based Pharmacokinetic (PBPK) Model describing diffusion and absorption processes in the dermis has been presented previously (Clarke 2018). The Depth Resolved Dermis Model (DRDM) has been verified for six compounds in the literature for which depth-resolved concentration profiles in the dermis were available. One important aspect of this model is its ability to accurately predict the diffusion of small drug molecules in the dermis. As part of the model development, a new physiologically based, bottom-up approach for predicting the effective diffusivity in the dermis was developed.

Methods

The effective diffusion of a molecule can be described by the weighted sum of the diffusion of its unbound form, and that of its bound form. Therefore this model requires three pieces of information:

$D_{unbound}$ = The diffusivity of the unbound drug in dermis interstitial fluid

D_{bound} = The diffusivity of albumin bound drug in dermis interstitial fluid

fu_{ISF} = Fraction unbound to albumin in the dermis interstitial fluid

These parameters can then be used to predict the effective diffusivity of the drug in the dermis using Equation 1.

$$D_{Dermis} = fu_{ISF} * D_{unbound} + (1 - fu_{ISF}) * D_{Bound} \qquad (1)$$

$D_{unbound}$

The diffusivity of an unbound molecule in the interstitial fluid (ISF) can be predicted using the Wilke-Chang equation (Equation 2).

$$D_{unbound}(cm^2/s) = \left(\frac{7.4 * 10^{-10} * T_{Dermis} * (MW\emptyset_{ISF})^{0.5}}{\eta_{ISF} * V_A{}^{0.6}}\right) \qquad (2)$$

Where:

T_{Dermis} = *Absolute Temperature in the Dermis Value* = 310.15 K

$MW\emptyset_{ISF}$ = Solvent Molecular Weight * *Association parameter (assumed the same as water);*
Value = 40.68 Da

η_{ISF} = *Viscosity of ISF (assumed the same as lymph measured by* Bouta et al., 2014);
Value = 0.0181 dyne × s/cm^2

V_A = *Molar Volume of the Molecule (predicted from MW by method described in* Ibrahim et al., 2012).

Methods

D_{Bound}

The diffusion of bound drug was taken to be the same as the effective diffusivity of albumin through insterstitium (Nugent and Jain, 1984)(Nugent and Jain, 1984)(Fox and Wayland, 1979). Crucially this effective diffusivity is around 13-fold slower than the aqueous diffusivity of albumin.

Under the assumption that the molecule is sufficiently small that the effect on diffusion caused by its binding is negligible; Value = 0.000216 cm^2/h

fu_{ISF}

The fraction of drug unbound to albumin in the interstitial fluid of the dermis can be predicted by Equation 3.

$$fu_{ISF} = \frac{1}{1 + \frac{[P]_{Dermis}}{K_D}} \qquad (3)$$

$[P]_{Dermis}$ = *The abundance of albumin in the dermis ISF;* Value = 458.1 µM (Bert et al., 1986)

K_D = *The affinity constant between the drug and albumin. This can be calculated by rearranging Equation 3 and replacing* fu_{ISF} *and* $[P]_{Dermis}$ *with values for plasma, where measured values of* fu_{Plasma} *are available.*

Data on fraction unbound to albumin for the relevant drugs was collected, where multiple measurements were available, preference was given as such:

$$fu_{Dermis} > fu_{2\%\,solution} > fu_{4\%\,solution} > fu_{plasma} > fu_{predicted}$$

For the latter three cases, fu values were converted to fu_{Dermis} using Equation 3.

A database of effective diffusivity values estimated experimentally was collated (Kretsos et al., 2008)(Anissimov and Roberts, 2011)(Ibrahim and Kasting, 2010) which included 34 observations.

These values were compared against the values predicted with this bottom-up approach. The quality of prediction was assessed by linear regression and Normalised root mean square error (NRMSE), normalised by max-min of the observed data.

Results

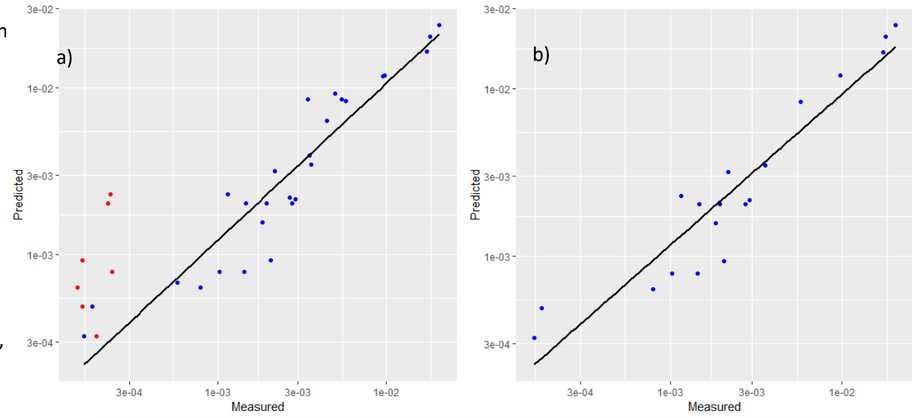
A plot of Measured vs Predicted effective diffusivity values with a regression line can be seen in Figure 1.

Figure 1(a) shows the full data set of 34 observations, Points in Red represent data from (Tojo et al., 1987), which were excluded from the analysis because these values were obtained from 'stripped skin' i.e., skin that still had a large portion of viable epidermis intact. It is clear that these data points are not representative of diffusion in the dermis, therefore they were not included in the analyses, leaving 27 observations. A linear regression analysis found an R^2 of 0.94 with a slope 1.12. The NRMSE was 9.4%.

Results

Figure 1(b) shows a dataset subset to only include observations for which a measured value of fraction unbound to albumin was available. A linear regression analysis found an R^2 of 0.98 with a slope 1.12. The NRMSE was 6.6 %.

Figure 1 – Measured vs Predicted diffusivity values. Red points were not included in the regression analysis



Conclusions

This bottom-up approach to predicting drug diffusion in the dermis showed good predictive power.

This work suggests that a major determinant of drug diffusion in the dermis is its albumin binding affinity.

This model, due to its physiologically based methodology could be leveraged to predict the effect of skin disease upon the diffusion of drugs in the dermis. For example in psoriasis where the albumin content of the dermis ISF has been shown to be decreased (Staberg et al., 1983).

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