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A random walk model of stratum corneum diffusion

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Aims: Chemicals penetrate the skin through passive diffusion, a mass transfer process that arises from random molecular motions. Transdermal penetration is governed by the skin's specific morphological structure and biochemical composition. In order to account for the complex "brick-and-mortar" structure of the stratum corneum, a mathematical model has been devised that explicitly incorporates this non-uniform structure.

Methods: Diffusion through the stratum corneum is modeled as a random walk process. Particles of a diffusing substance are placed on the surface of a model stratum corneum membrane and undergo 2 dimensional random walks within a transverse section of the membrane. Random thermal motion of molecules is modeled as a "random walk": from any current location, a molecule moves randomly to a new location. At each time step, 2 random numbers are generated to determine the relative magnitudes of a particle's displacement in the lateral and transverse directions. Within a particular phase--corneocyte or lipid--the magnitude of the movement is determined by the molecule's mobility within that phase. Whenever a particle reaches a boundary between lipid and corneocyte, an attempt is made to jump between the phases. The probability of a successful jump is determined by the chemical's corneocyte-lipid partition coefficient, which relates the steady-state chemical concentration in the cellular phase relative to the lipid phase, and is considered to be an independent variable of the model. Model results lead to closed form mathematical expressions for "effective diffusivity" (D*) and "effective path length" (l*) . These concepts (D* and l*) are crucial to the model development. They refer to the diffusivity and thickness of a homogeneous membrane having identical properties as the heterogenous stratum corneum for a particular chemical of interest–D* and l* will vary depending on the chemical properties of the permeant. By applying "free volume theory" and an SC lipid-octanol analogy, these two model variables were related to the chemical properties molecular weight and octanol-water partition coefficient for any given diffusing chemical. Along with an expression for membrane-vehicle partition coefficient, these variables are used to calculate the permeability coefficient. Model results have been compared with experimental data published in the literature. The Flynn (1990) data set is a collection of human skin permeability coefficients from an aqueous vehicle, derived primarily from in-vitro measurements. The data include 97 measurements of 94 chemicals made in a variety of labs under a variety of conditions. This data base has been widely used in the development of skin permeability correlations. We have regressed the model against this data base.

Results and conclusions: The correlation (R2) between model permeability predictions and the Flynn data base of measured permeability coefficients is 0.84. This compares with R2 of 0.68 for the Potts and Guy (1992) equation. We conclude that the present approach provides mechanistic insight into the diffusion process and superior predictive capacity. The concepts of effective diffusivity and effective path length appear to be valid and useful.

References

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