25
A random walk model of stratum corneum diffusion

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Introduction

A mathematical model has been developed that is based on the molecular mechanism of diffusion and that explicitly incorporates the nonuniform structure of the stratum corneum (SC).[1] The model is used to predict permeability coefficients of chemicals based on their molecular weight (MW) and octanol-water partition coefficient (P).

Methods

Diffusion through the heterogeneous SC is modeled as a random walk process. Particles of a diffusing substance are placed on the surface of a model SC membrane and undergo two-dimensional random walks through the transverse section of the biphasic (lipids and corneocytes) membrane. From any current location, a molecule moves randomly to a new location. The movement of molecules within the membrane is determined by two independent variables: relative diffusivity within the corneocytes and lipids, and instantaneous partitioning of the chemical between lipid and corneocyte phases.

Two variables are calculated from the random walk simulations: effective diffusivity (D^*) and effective path length (l^*). These are defined as the diffusivity and thickness of a homogeneous membrane having identical diffusion properties as the heterogeneous SC for a specific chemical. These are derived by examining the behavior of many diffusing particles under identical input conditions.

Steady-state permeability (k_p) is given by: $k_p = K_{mv}D/l$, where K_{mv} is the membrane-vehicle partition coefficient. Thus, we use D^* and l^* to estimate permeability coefficients. All variables are reduced to simple algebraic functions of MW and P.[1] Values for four variable parameters were

found by non-linear regression of the model with the Flynn[2] database of 94 permeability measurements.

Results

Figure 25.1 shows a comparison between the model predictions of k_p and experimental values reported by Flynn.[2] The correlation coefficient (R^2) is 0.84. Diameters of the circular symbols are proportional to molecular weights of the compounds. Also shown is the line of identity.

For comparisons among different models, identical regression analyses were performed on five published models that predict k_p as a function of MW and P (Table 25.1).

Discussion

The random walk model of diffusion through the SC has advantages over other approaches: this model is based on first principles - the molecular basis of diffusion – and it permits diffusion calculations in a morphologically realistic, heterogeneous SC membrane.

In this model, lipids and corneocytes are considered distinct phases with different diffusivities and different chemical affinities. Consequently, neither diffusivity nor diffusional path length of the SC membrane is a simple constant. However, comparison of model results with an appropriate solution to the classic diffusion equation for a homogeneous membrane permits the identification of an effective diffusivity (D*) and an effective path length (l*). These chemical-specific quantities are used to

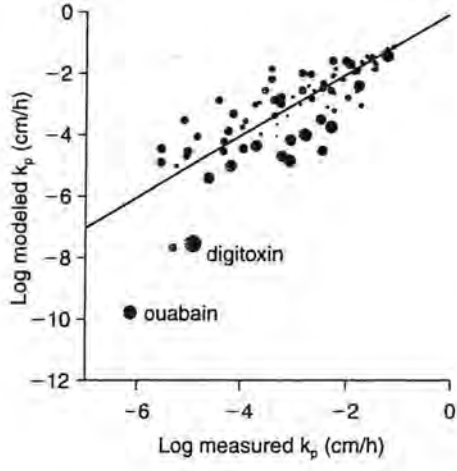

Figure 25.1

Modeled skin permeability k_p compared with experimental measurements reported by Flynn.[2] Diameters of symbols are proportional to the MW of the compounds. The two compounds with the largest MW (ouabin, digitoxin) have the largest residual differences. Line of identity is also shown.

Table 25.1 Regression statistics for six models. The models were fitted to the Flynn database[2] of 94 measurements. np: number of fitted parameters of model; R^2: correlation coefficient; SE: standard error of the model estimate; F: measure of the predictive value of the independent variables (higher F statistic indicates greater predictive value).

Model (reference)	np	R^2	SE	F
Frasch[1]	4	0.84	0.008	154
Modified Robinson[3]	4	0.80	0.009	116
McKone and Howd[3,4]	5	0.80	0.009	87
Cleek and Bunge[5]	3	0.78	0.009	158
Modified Potts and Guy[3]	3	0.73	0.653	120
Potts and Guy[3,6]	3	0.68	0.704	96

predict steady-state permeability of chemicals in an aqueous vehicle. All variables are reduced to simple algebraic functions of MW and P.

In conclusion, we have presented a novel mathematical model of skin permeation. The model is based on the fundamental molecular mechanism of diffusion and accounts for the structural and chemical heterogeneity of the SC. It provides mechanistic insight into the process of skin permeation and has excellent predictive capacity.

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The Essential Stratum Corneum

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