

A number of theoretical plasma concentration profiles were then constructed. In reality, Michaelis–Menten kinetics may be operative for a number of solutes.

2.4.3 SOLUTE–VEHICLE, VEHICLE–SKIN, AND SOLUTE–SKIN INTERACTIONS

The practical application of mathematical models in percutaneous absorption to therapeutics or risk assessment is dependent on an understanding of solute–skin, solute–vehicle, and vehicle–skin interactions. Some aspects of each of these areas have been discussed by Roberts and Walters [2], Hadgraft and Wolff [60], Robinson [61], and Roberts et al. [45].

The present analysis has generally been limited to percutaneous absorption kinetics in which the underlying physicochemical parameters are time-independent. In practice, the application of a vehicle to the skin will lead to a time-dependent change in permeability due to either a solute–skin interaction or a vehicle–skin interaction. The solutions of the resultant concentration-dependent diffusion processes also lead to a time- and space-dependent change in solute diffusivity—these are relatively complex and are beyond the scope of this chapter.

Of critical importance in both therapeutics and toxicology is the maximum flux of a solute J_{\max} . This flux is normally attained at the solubility of the solute in the given vehicle, S_v , consistent with the solubility of the solute in the SC transport pathway S_m :

$$J_{\max} = \frac{D_m K_m S_v}{h_m} = k_p S_v = \frac{D_m S_m}{h_m} \quad (2.71)$$

The importance of J_{\max} as a parameter describing penetration through the skin is in its invariance for a given solute transport from different vehicles, unlike k_p , which is vehicle-dependent. This invariance holds unless the vehicle affects either D_m or S_m [45]. J_{\max} (in mol/cm² hr) may be expressed in terms of molecular weight (MW), melting point (Mpt), and hydrogen bonding acceptor ability (Ha) [62]:

$$\log J_{\max} = -4.35 - 0.0154\text{MW} - 0.293\text{Mp}^* + 0.371\text{Ha}, \quad n = 87, \quad r^2 = 0.937 \quad (2.72)$$

where J_{\max} is in mol/cm² hr and the dependence on Mpt is described using the Mpt term: $\text{Mp}^* = \Delta S_f (\text{Mpt} - T) u(\text{Mpt} - T)/T$, from Yalkowsky's solubility [Equation (2.63)], where T is the temperature, ΔS_f is the entropy of fusion of a solute, and $u(x)$ is the unit step function [i.e., $u(x) = 1$ for $x > 0$ and $u(x) = 0$ for $x < 0$]. Most of the regression variance for J_{\max} is defined by MW, showing the dominance of size as a determinant of maximum flux [62]:

$$\log J_{\max} = -3.90 - 0.0190\text{MW}, \quad n = 87 \quad r^2 = 0.847 \quad (2.73)$$

2.4.4 EFFECT OF SURFACE LOSS THROUGH PROCESSES SUCH AS EVAPORATION AND ADSORPTION TO SKIN SURFACE

There is a potential change in solute concentration as a consequence of surface loss during percutaneous absorption. The loss may result in (1) an effective reduction in the volume of the vehicle alone due to evaporation and an increase in solute concentration as a consequence, (2) a reduction in both solute and vehicle due to a removal process, and (3) a loss of solute only due to volatilization or adsorption to the skin surface. For instance, Reifenrath and Robinson [64] have shown that mosquito repellents may be lost due to evaporation at a rate comparable to their percutaneous absorption. The loss of vehicle at a defined rate creates a moving boundary problem and does not appear to have been considered to any great extent in the literature. Guy and Hadgraft [56, 57] examined the first- and zero-order losses of solute from the vehicle surface using diffusion and compartment models, respectively. Recently Saiyasombati and Kasting [65] examined the disposition of benzyl