elimination rate constant of the solute from the body, and f_e is the fraction of the solute excreted in the urine. This plot is associated with a lag time t_L of:

$$t_L = \frac{1}{k_{el}} + \frac{t_d}{6} \tag{2.82}$$

where again $t_d = h^2_m/D$, D is the diffusivity of the solute in an SC and h_m is the distance of the pathway of diffusion. Even for multicompartmental disposition kinetics, the total lag time for elimination of a solute is uncoupled and is the sum of epidermal diffusion and pharmacokinetic lag times [86]. When only a finite dose of solute is applied to the skin, the urinary excretion rate is also a function of the vehicle thickness [17].

In practice, the direct application of Equation (2.19) to in vivo absorption may be limited. Equation (2.32), which takes into account the effectiveness of blood flow in removal of solute from the epidermis and the accumulation of solute in the epidermis in vivo, may be more appropriate. Accordingly, the actual steady-state flux is less than k_pAC_v due to this limitation in blood flow clearance, as defined by Equation (2.34). More recently, Liu et al [128] described the Laplace equivalent solution for 2.81:

$$\hat{M}_{u,sc}(s) = A\hat{J}_{sc}(s)\frac{k_u}{s(s+k_{el})} = A\frac{J_{ss,sc}}{s^2}\frac{\sqrt{st_{d,sc}}}{\sinh\sqrt{st_{d,sc}}}\frac{k_u}{(s+k_{el})} \tag{2.83}$$

Where $\hat{M}_{u,sc}(s)$ is the amount excreted in the urine over time in the Laplace domain for a stratum corneum barrier only, with a diffusion time $t_{d,sc}$ with a steady state flux $\hat{J}_{sc}(s)$ per unit area for an area A, $J_{ss,sc} = k_{p,sc}C$, and where $k_{p,sc}$ is the permeability coefficient of SC barrier only. They then went on to describe the expression for $\hat{M}_{u,epi}(s)$ is the amount excreted in the urine over time in the Laplace domain for when both the stratum corneum and viable epidermis contribute to the skin barrier:

$$\begin{aligned}\hat{M}_{u,epi}(s) &= A\hat{J}_{epi}(s)\frac{k_u}{s(s+k_{el})} \\ &= A\frac{J_{ss,sc}\sqrt{st_{d,sc}}k_u}{s^2\left(B\frac{\sqrt{st_{d,sc}}}{\sqrt{st_{d,ve}}}cosh\sqrt{st_{d,sc}}sinh\sqrt{st_{d,ve}} + sinh\sqrt{st_{d,sc}}cosh\sqrt{st_{d,ve}}\right)(s+k_{el})}\end{aligned} \tag{2.84}$$

Where Eq. 2.84 is based on the expression for epidermal flux, $\hat{J}_{epi}(s)$ defined by:

$$\hat{J}_{epi}(s) = \frac{J_{ss,sc}\sqrt{st_{d,sc}}}{s\left(B\frac{\sqrt{st_{d,sc}}}{\sqrt{st_{d,ve}}}cosh\sqrt{st_{d,sc}}sinh\sqrt{st_{d,ve}} + sinh\sqrt{st_{d,sc}}cosh\sqrt{st_{d,ve}}\right)} \tag{2.85}$$

Where the parameter B is that used by Bunge and Cleek [26] used a to define the relative permeability of the SC to the VE, as shown in Eq. 7:

$$B = \frac{D_{sc}h_{ve}K_{ce}}{D_{ve}h_{sc}} = \frac{D_{sc}K_{sc}/h_{sc}}{D_{ve}K_{ve}/h_{ve}} = \frac{k_{p,sc}}{k_{p,ve}} \tag{2.86}$$

where $k_{p,sc}$ and $k_{p,ve}$ are permeability coefficient of SC and VE, respectively

2.5.3 Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Models

A number of authors have advocated the use of physiological rather than compartmental representations of the body. McDougal [87] has summarized the modeling in this area. These models utilize the