One way to model the drug uptake from the capillary loops is through the implementation of a two-layer distributed-elimination model [132]:

$$\frac{\partial C_{ve}}{\partial t} = D_{ve}\frac{\partial^2 C_{ve}}{\partial x^2} \tag{2.96}$$

$$\frac{\partial C_{d}}{\partial t} = D_{d}\frac{\partial^2 C_{d}}{\partial x^2} - k_e C_d \tag{2.97}$$

Where C_{ve} and C_d are solute concnetrations in the viable epidermis and dermis and D_{ve} and D_d is the diffusion coefficient in the epidermis and dermis, k_e is the elimination rate and x is the depth within the dermis.

In previous models, the drug uptake was usually depicted via a sink condition that was placed at an arbitrary depth in the dermis. However, the distributed-elimination model incorporates the capillary network via an elimination rate constant. Solving the two-layer model in the Laplace domain gives the following expressions:

$$C_{ve}^{ss}(x) = \frac{J_{sc}}{\sqrt{D_{ve}k_e}} + \frac{J_{sc}h_{cl}}{D_{ve}}\left(1 - \frac{x}{h_{cl}}\right) \tag{2.98}$$

$$C_{d}^{ss}(x) = \frac{J_{sc}}{\sqrt{D_{d}k_e}}\exp\left(\sqrt{\frac{k_e}{D_d}}\left(h_{cl} - x\right)\right) \tag{2.99}$$

where J_{sc} is the flux from the SC, h_{cl} is the depth of the capillary loops and ss represents the steady-state.

A three-dimensional capillary loop model that explicitly considers the geometry and spacing of the capillary loops was developed [133]. The capillary loops in this model were presented to give an in silico simulation of typical drug transport in the viable skin. The results of this model were compared to both the distributed elimination model and the sink condition case and showed that the capillary model much more effectively modelled viable skin concentration. This model has now been further developed in a computational form to better understand the impact of elevated skin temperatures on transdermal drug delivery and dermal clearance [63].

2.5.6 Pharmacodynamic Modeling

In principle, established pharmacodynamic models used in whole-body pharmacokinetic modeling can be directly used when solutes are delivered by the skin. Complexities can exist when the site of drug targeting is the skin itself. Imanidis et al. [83] showed that the antiviral efficacy to HSV-1 skin infections of acyclovir was directly related to the logarithm of the flux from transdermal patches—consistent with classical log dose–response relationships. However, an equivalent systemic dose was relatively ineffective.

Beastall et al. [108] examined the onset of erythema (t_E) as a function of solute concentration (C_o). Applying Fick's law of diffusion, they obtained the expression:

$$\log\frac{n_E}{h_m} = \log\left(C_v t_E^{3/2}\right) + \log\left[\frac{K_m}{1 + K_m / p^{1/2}}\right] + \log\left[\frac{8D_{sc}^{3/2}}{\pi^{1/2}h_m^3}\right] - \frac{h_m^2}{9.2D_{sc}t_E} \tag{2.100}$$

where D_{sc} is the diffusion coefficient of nicotinate in the SC, K_m is its partition coefficient between vehicle and skin, h_m is the diffusion path length, p is the ratio of the diffusion coefficients of the nicotinate in the vehicle and the skin, and n_E is the concentration of nicotinate required to trigger erythema. This expression showed a linear relationship should and did exist between $\log C_v t^{2/3}{}_E$ and $1/t_E$. The gradient of the relationship $D_{sc}/h^2{}_m$ was greatly affected by the co-administration of the enhancer urea.