Dermal and subcutaneous concentrations of solutes after in vivo iontophoretic application can also be determined in terms of clearance by blood supply to the tissue, clearance to deeper tissues, and influx by iontophoresis [115].

2.6.2 Sonophoresis

The sonophoretic iontophoretic flux can also be included in pharmacokinetic models in a manner analogous to that described under "Iontophoresis." Mitragotri et al. [116] have suggested that sonophoresis induces cavitation. They have suggested that the sonophoretic permeability $k_{\mathrm{p\ sono}}$ can be defined in terms of the passive permeability coefficient k_{p} (unit: cm/hr) and the solute octanol–water partition coefficient Kow as:

$$k_{\mathrm{p\ sono}} = k_{\mathrm{p}} + 2.5 \times 10^{-5} K_{\mathrm{ow}}^{3/4} \qquad (2.104)$$

Later work examined the threshold frequency dependency [117] and transport at low frequency [118].

2.7 PRACTICAL ISSUES IN APPLYING MATHEMATICAL MODELS TO PERCUTANEOUS ABSORPTION DATA

A major limitation in a number of reported percutaneous absorption studies, including those from our laboratories, has been the assumption of a given mathematical model. Whether that model is strictly the most appropriate one is often difficult to confirm. Most studies appear to have used the simplest model, as defined by Equation (2.1), in which the steady-state flux and lag time are defined by the steady-state portion of the curve. There are a number of limitations in using such a model, as discussed by Robinson [61] and other authors.

Robinson [61] points out that errors can be made if (1) the burst influx and lag containing through flux are represented by a steady-state approximation at early times; (2) an infinite vehicle is assumed when the concentration is actually declining due to the finite volume used; (3) penetration of a solute by passive diffusion also involves modification of the skin barrier properties (solute–skin interactions); (4) vehicle effects on solute concentration, e.g., evaporation or skin permeability (vehicle–skin interactions) exist; (5) skin reservoir effects exist, as illustrated by the extensive uptake of sunscreens into, but not necessarily through, the skin [119]; (6) discrepancies exist between in vitro and in vivo absorption due to the role of capillaries in absorption in vivo; and (7) the resistance barrier of the skin is compromised.

The expressions for a number of the more complex models contain the necessary correction factors to overcome some of the inherent limitations in the simplest model representation of data. For instance, the steady-state flux may be affected by the sampling rate from the receptor compartment, as defined by Equation (2.34). The lag time will be dependent on both this clearance and the volume ratios of the membrane and receptor phases, corrected for partitioning effects, as defined by Equation (2.35). A different set of correction factors apply if an interfacial barrier or desorption rate constant exists [Equations (2.39) and (2.40)]. As Kubota et al. [46, 47] point out, although a simple compartmental model may describe percutaneous penetration kinetics, the parameters obtained may not necessarily represent the membrane diffusion and partition coefficient.

Relating data to a specific model using nonlinear regression techniques also requires an appropriate weighting of the data in accordance with the underlying errors associated with the data. In the absence of known error structures, a weighting of 1/$y$obs may be appropriate. This weighting assumes that the coefficient of variation (standard deviation/mean) of the data is relatively constant.

Some of the dilemmas in the mathematical modeling of percutaneous absorption are enunciated in the letters to pharmaceutical research written by Singh et al. [110] and Smith et al. [111], especially in relation to pharmacodynamic modeling of skin blanching after topical application. Issues raised include (1) reliability of visual and chromameter methods; (2) analysis of ''naive'' pool data by nonlinear regression versus mixed-effect modeling; (3) baseline correction; (4) consistency of