The human skin–blanching assay for evaluating the bioequivalence of topical corticosteroid products should follow standardized guidelines as developed by the U.S. Food and Drug Administration (FDA) in 1995. Demana et al. [109] evaluated the area under the effect curve (AUEC), also called the effect (*E*), for both visual and chromameter-derived data. The visual data were best described by a sigmoidal E_{max} model [Equation (2.101)] while the chromameter data were described by a simple E_{max} model [Equation (2.102)]:

$$E = E_0 \pm \frac{E_{\text{max}} D}{D + ED_{50}} \tag{2.101}$$

$$E = E_0 \pm \frac{E_{\text{max}} D^{\gamma}}{D^{\gamma} + ED^{\gamma}{}_{50}} \tag{2.102}$$

where E_{max} is the maximal AUEC, *D* is the dose duration, ED_{50} is the dose duration for half- maximal *E*, and g is a sigmoidicity factor related to the shape of the curve. The parameter E_0, not explicitly stated in the modeling by Demana et al. [109], should be included in the model fitting to correct for baseline readings [110]. Smith et al. [111] have pointed out that they had corrected for E_0 using unmedicated site values in their earlier work [109]. A key aspect in this mathematical modeling is varying the dose administered by varying the duration of application. Varying dose duration is then used to relate the vasoconstrictor response to a range of corticosteroid amounts. Demana et al. [109] used a weighting of 1/AUEC and a number of goodness-of-fit criteria in their analyses.

More recently, Cordero et al. [112] developed an index to predict topical efficiency of a series of nonsteroidal antiinflammatory drugs. This index took into account both the biopharmaceutical aspect, based on the maximal flux, and the pharmacodynamic aspect, based on the ability to inhibit cyclooxygenase-2 in vitro.

2.6 MODELING WITH FACILITATED TRANSDERMAL DELIVERY

2.6.1 IONTOPHORESIS

A number of mathematical models are used in iontophoresis. As described by Kasting [113], these are generally defined by the Nernst Planck and Poisson equations. Of particular practical usefulness is the iontophoretic flux of a solute through the epidermis. This flux can be incorporated into various pharmacokinetic models for the body to enable the description of plasma concentration and urinary excretion–time data. Singh et al. [82] examined in vivo plasma data after iontophoretic transport with simple pharmacokinetic models. In vivo blood concentrations for most solutes delivered by iontophoresis appear to be able to be described by zero-order input into a one-compartment model [Equations (2.76) and (2.79)] [82].

The iontophoretic flux depends on a number of factors, including solute ionization, interaction of solutes with pore walls, solute size, solute shape, solute charge, Debye layer thickness, solute concentration, and presence of extraneous ions, which are all accounted for. We have recently proposed an integrating expression for the flux of the *j*th solute [114]:

$$J_{j\text{iont}} = C_j \left[\frac{2\mu_{\text{j}} fi_{\text{j}} F z_{\text{j}} I_{\text{T}} \Omega \text{PRT}_{\text{J}}}{(k_{\text{s,a}} + k_{\text{s,c}}) \left[1 + fu_{\text{i}} \theta_{\text{ju}} + fi_{\text{j}} \theta_{\text{ji}} \right]} \pm (1 - \sigma_{\text{j}}) \upsilon_{\text{m}} \right] \tag{2.103}$$

where *Cj* is the concentration of the *j*-th solute, m*j* is its mobility, fi_j and fu_i are ionized and unionized fractions of the solute (respectively), z_j is its charge, PRT_j is a partial restriction term, s_j is the reflection coefficient term, v_{m} is the velocity of water flow across the membrane, *I*T is the total current across the membrane, O is the permselectivity for cations, $k_{\text{s,a}}$ and $k_{\text{s,c}}$ are conductivities of the anode and cathode solutions (respectively), y_{ju} and y_{ji} are parameters describing the interaction of unionized and ionized fractions of the solute with the pore, and *F* is Faraday's constant.