

all of the models examined occasionally predicted transdermal fluxes that were unacceptably high or low when compared with experimentally determined data. It was hoped that insight into these discrepancies could be gained by obtaining additional experimental transdermal flux values from the literature for comparison with predicted values. Thus, an appropriate combination of the predicted values from each of the models might provide a more reliable overall predicted flux.

Another application for these computational methods becomes apparent by realizing that a reasonable transdermal flux value for a drug can be predicted with knowledge of the molecular weight and two readily calculable physicochemical drug properties (8,9). Because group contribution methods allow the calculation of both partition coefficient and water solubility, it becomes possible to predict a transdermal flux value for any liquid drug molecule whose structure can be drawn, regardless of whether or not the drug has actually been synthesized. For crystalline drugs, knowledge of the melting point is required in addition to the structure of the molecule. This could be of particular value when designing analogues to existing drugs or prodrugs in hopes of obtaining increased systemic breakthrough after topical administration. Indeed, by calculating flux values over a full range of water solubilities and partition coefficients, particularly useful insight into how to alter drug structure can be obtained.

II. DESCRIPTION OF THE MODELS

Because the models have been described in detail in both the original publications and in the previous technical update, only a brief description will be presented here. Model 1, the two-parallel-pathway model for skin permeation proposed by Berner and Cooper, (4) separates permeation through the skin's barrier function into two paths, a *polar* (aqueous) path and a *nonpolar* (lipophilic) path. The diffusion constants for the polar, D_p , and lipophilic, D_L , pathways are calculated using the equations

$$D_p = (3.8 \times 10^{-5})e^{-0.016(M)} \quad [1]$$

$$D_L = (1.7 \times 10^{-5})e^{-0.016(M)} \quad [2]$$

where M is the molecular weight of the drug, and the resulting diffusion constants are given in cm^2/hr . Because the fluxes of the polar and lipophilic pathways are considered additive, the total flux