and co-workers described the absorption of alkanoic acids through skin in terms of the solubility parameters of the acids (18). Shortly after the publication of the 1984 paper, Sloan, Sherertz, and co-workers published a series of eight articles (19–26), starting in 1986, that used regular solution theory to explain the effects of vehicles and the effect of changes in the physicochemical properties of drugs caused by their transient chemical modification (prodrugs) on the delivery of drugs through skin. The articles by Sloan, Sherertz, and co-workers will be discussed first, then the initial article by Cohen and co-workers, along with two very recent articles that have appeared from that group, will be discussed.

The experimental designs used in the work reported by Sloan et al. (19–26) were somewhat different from the previous designs used in similar experiments (18). First, only saturated solutions of drug–vehicle were applied to the membranes in the diffusion cells as the initial part of each experiment. Second, after the initial part of each experiment a "second" application of a standard solute–vehicle was made onto the membranes.

This second application part of each experiment enabled the investigators to determine whether or not the membranes were damaged by the initial treatment of drug–vehicle by comparing the rate of delivery (flux) of the standard solute through skin after an initial application (pretreatment) of drug–vehicle, with the rate of delivery of the standard solute without pretreatment. The higher the ratio between the two fluxes, the greater the degree of damage to the skin and the greater the degree of deviations of the experimental flux of drug–vehicle from the theoretical flux predicted by regular solution theory. In this way, it was possible to separate the thermodynamic effects (1) of the drug-vehicle interaction or (2) of the physicochemical properties of the prodrug on the partitioning process from the chemical or physical effects of the vehicles themselves on the integrity of the membranes.

Saturated solutions of drug–vehicle were used to ensure that the drugs were being tested at their maximum activity. In addition, only at saturation, on a mole fraction concentration basis, does $\alpha_i^v = \alpha_i^s$, where α_i^v and α_i^s are the activities of the drug (i) in vehicle (v) and skin (s), respectively. Hence, $K_i^{s,v}$ from Eq. 5 can be calculated using Eq. 6, but only if saturated solutions of the solute in the two phases of interest are being evaluated.

The effect of vehicles on flux of a drug through skin can be correlated with regular solution theory through the relationship between permeability coefficient ($P_i^{s,v}$) and partition coefficient ($K_i^{s,v}$). Flux ($J_i^{s,v}$) is equal to the product of $P_i^{s,v}$ and C_i^v, so from Eq. 4, $P_i^{s,v}$ is equal to the product of the partition coefficient and the diffusion coefficient (D_i^s) divided by the thickness of the