the skin's hydration, and (3) vehicle effects on the local vasculature, which alter drug clearance and skin temperature, in either case, subtly influencing permeability. Drug–vehicle interactions are those in which physicochemical interactions between the drug and the vehicle kinetically or thermodynamically govern the release of the drug into the skin. Such interactions can become the rate-controlling factors and be clinically highly important when the stratum corneum is impaired as the consequence of disease or injury, for, when the skin is damaged, solution and diffusion in the vehicle may be relatively slow relative to skin permeation. Here, one is concerned about the solubility of the drug and its diffusive mobility within the vehicle, as each is a factor influencing the rate of presentation of the drug to the vehicle–skin interface. For the more usual case, in which the permeability of the intact stratum corneum is low, partitioning of the drug into the skin can still exert a profound, if not dominant, influence on the rate of delivery.

As one critically reviews the literature dealing with vehicle effects in transdermal drug delivery, a confused state of affairs about the theory of topical drug delivery is apparent. In a review of the subject, Idson (3) has cited several reasons for this confusion: (1) Experiments have been performed on a large variety of animals; (2) different methods have been used to estimate skin penetration; (3) there has been a lack of awareness of possible drug–vehicle interactions; and (4) there has been a lack of consideration of thermodynamic factors in the interpretation of results. Although all the possible types of interactions between drug, vehicle, and skin mentioned here are important to topical bioavailability, this paper mainly focuses on drug–vehicle and drug–vehicle–skin (membrane) interactions.

II. IN VITRO RELEASE FROM VEHICLES

A. Theoretical Background

As part of the assessment of a vehicle's potential for delivering a drug to the skin for topical absorption, researchers have long sought methods to determine a drug's release rate from its vehicle. It is generally assumed that the results obtained in such experiments at least qualitatively relate to the release of the drug to the skin in a clinical situation. Failure to properly interpret and integrate results from such studies could lead to a substandard drug product. Thus, by necessity knowledge of the thermodynamics and kinetics involved in the in vitro situation is important if one wishes to successfully project the results to the in vivo circumstance (4).

There are several identifiable processes that, theoretically, can establish the rate at which a drug is delivered from a film into an absorbing membrane. Minimally, these include diffusion through