10 Evaluation of Stratum Corneum Heterogeneity

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When confronted with an organ as complex as skin, a biologist tends to want to relate structure to function at the most fundamental level, and indeed an enormous amount of complexity may be found. A physical scientist, on the other hand, looks for simplifying assumptions that allow him to describe the system within a mathematical framework and to make quantifiable predictions about its behavior. There is often a credibility gap between the two approaches, and the appropriate balance point moves as different problems are addressed. There is little doubt that the elegant work of Elias (1, 2), Steinert (3, 4), Wertz (5, 6), and many others in the chemistry and structural biology of the stratum corneum (SC) has enormously increased our understanding of skin barrier function; however, the simplifying framework introduced by Scheuplein and Blank (7) and advanced by others including Flynn (8), Roberts (9, 10), Cooper (11), and Potts and Guy (12) has had a comparable impact on quantifying its properties. The Potts–Guy model for steady-state skin permeability (12) and extensions thereof (13) are arguably the most widely used predictive tools in transdermal drug delivery and dermal risk assessment (14).

Potts and Guy treated skin as a homogeneous lipid membrane, arguing against the need for additional features to explain the steady-state absorption of many organic compounds from aqueous solution (12). The molecular properties determining absorption were molecular weight and octanol–water partition coefficient (K_{oct}). Elaborations on this scheme have included an aqueous barrier in series with the SC (14, 15), a polar pathway in parallel with the lipid pathway (16–18), or both (13, 19), providing reasonable limits to skin permeability for extremely hydrophilic and lipophilic compounds. Other descriptors, notably hydrogen bond donor and acceptor strength (20, 21), have been proposed, as well as quantitative structure-permeability relationships (QSPRs) (22, 23) and neural network approaches (24), yet it is not clear that significant improvements to the basic model have been achieved. Some investigators have considered the tortuosity of the lipid pathway in deriving SC barrier properties (16, 25–27) under the assumption that corneocytes are impermeable. Due to the longer path length, these models yield higher effective diffusivities for permeants in the SC than do homogeneous membrane models. However, Frasch and Barbero's notable analysis (27) shows that diffusion via a tortuous pathway and that through a homogeneous slab cannot be distinguished