

where K_p is the permeability coefficient of the permeant in the skin and C is the concentration of the permeant in the applied formulation vehicle. The permeability coefficient is a composite parameter:

$$K_p = P \cdot D/h \quad (17.2)$$

where P is the partition coefficient of the permeant between the skin and the applied formulation vehicle, D , is the diffusion coefficient of the permeant in the skin, and h is the skin thickness (or, more accurately, the length of the diffusional pathway through the stratum corneum intercellular route).

Although the mathematical modeling of skin diffusion can be considered in far more complex ways (Chapter 2), this simple form of Fick's law is useful to illustrate that percutaneous permeation through the stratum corneum can be enhanced by increasing partitioning or diffusivity, and forms the basis of the range of formulation approaches to skin drug delivery. For example, chemical permeation enhancers that disrupt the stratum corneum intercellular lipid packing will increase diffusivity, whereas solvents present in a formulation vehicle may permeate with the permeant into the stratum corneum to promote partitioning from the vehicle to the skin.

17.3 SKIN PERMEANT PROPERTIES

The ideal physicochemical properties for passive skin delivery are low molecular weight (<500 daltons), moderate lipophilicity ($\log P_{o/w}$ 1–4), melting point <200°C, and good potency (daily systemic dose ≤ 20 mg). Quantitative structure permeation relationships (QSPR) studies [4, 5] have shown that small solute size is important for facilitating the diffusion process, while adequate lipophilicity is required to provide sufficient solubility in the stratum corneum. Drug potency is an important consideration, as demonstrated for a series of antiinflammatory drugs [6]. Although the maximum flux of diclofenac (with a $\log P > 4$) was lower than other antiinflammatory drugs, with $\log P$ in the range of 2.7 to 3.1, it had the highest efficacy coefficient ratio (the ratio of maximum flux and drug potency dose), since the antiinflammatory effect of a drug also depends on lipophilicity, thus providing higher potency. Permeant solubility is an important consideration in flux and in formulation design. Although lipophilicity is required for uptake into the stratum corneum and diffusion within the intercellular lipid domains, there is a need to ensure sufficient aqueous solubility to minimize donor depletion from an aqueous-based formulation over the period of application to the skin.

Permeants that are weak acids or bases can dissociate depending on the pH of the topical formulation and the stratum corneum, resulting in poor skin delivery. There is the potential to mitigate this through ion pairs [7–9] and pH adjustment in the formulation [10, 11]. Ion pairing involves addition of an oppositely charged counter-ion to form a neutral pair, with increased lipophilicity and improved stratum corneum diffusivity. The ion pair can dissociate in the viable epidermis or deeper tissue to release the parent compound. The pH of the formulation can be used to alter the degree of ionization, as has been shown with a 50-times difference in the permeability coefficient of lidocaine with pH adjustment [11]. Again, one factor cannot be considered in isolation, as was illustrated by the increase in flux of diclofenac (pKa of 4.7) from pH 3 to 7 in the vehicle [12]. As the diclofenac ionization increased with pH, the permeability coefficient decreased, but was offset by the increased solubility of the ionized species in the vehicle.

17.3.1 HANSEN SOLUBILITY PARAMETERS (HSP) AS A TOOL FOR PREDICTING VEHICLE/DRUG UPTAKE AND ENHANCEMENT

The polarity of the permeant in relation to those of the formulation and membrane is an important parameter in drug permeation through biological barriers, including skin. Polarity is a relative