

soluble drugs such as estradiol [33], ibuprofen [34], and piroxicam [35, 36]. Approximate linear relationships between the degree of saturation (and consequent increase in permeant thermodynamic activity) and skin flux have been reported [33, 35]. In addition, these systems can be stabilized by the addition of antinucleating polymers, such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, and polyvinyl alcohol, which act to prevent nucleation and subsequent crystallization of the permeant. Pellet et al. [35] suggested that human skin may also provide antinucleant properties based on their determination of piroxicam in stratum corneum tape strips and viable skin layers following administration of solutions with up to four degrees of saturation. Despite the antinucleating polymers' inability to enter the skin, a linear relationship existed between the degree of saturation and the amount of piroxicam in the stratum corneum and the viable layers of the skin. This may occur as a result of the antinucleating ability of the intercellular lipids of the stratum corneum [35].

Alternative formulations apply the same principles but offer more stable systems. For example, a water-free microemulsion base saturated with bupranolol applied to rabbits with an occlusive patch was converted *in situ* to a microemulsion from the transepidermal water accumulated under the occlusive patch [37]. The decreasing bupranolol solubility with increasing water content resulted in supersaturation, with the pharmacodynamic effect of the bupranolol monitored over a 10-hour period. The effect vs. time curves were inversely correlated with the solubility vs. water content curves.

Marc Brown's group have further applied this principle to a quick drying spray that can be applied to the skin as a metered dose aerosol [38–40]. Buprenorphine dipropionate was formulated in hydrofluoroalkane propellant 134a, ethanol, and polyvinyl pyrrolidone. The drug was supersaturated on the skin surface as the ethanol evaporated. With a similar approach, the skin delivery of betamethasone valerate was increased by six times compared to a conventional cream.

17.5.1.2 Formulating for Efficacy (FFE)

Johann Wiechers introduced the concept of “formulating for efficacy” [41, 42], which was aimed at aiding the rational design of topical formulations for skin delivery, and cosmetic applications in particular. He developed FFE to combine two contradictory properties that are required by a formulation, namely, (1) the formulation has maximum solubility for the permeant in order to accommodate the required therapeutic dose and (2) the formulation should have the minimum solubility for the permeant so as to promote its release from the formulation and partitioning into the stratum corneum. A Relative Polarity Index (RPI) provides a measure of the polarity difference between the permeant and the vehicle. To achieve the first property, the composition of the formulation vehicle (solvent or emollient) is chosen that will provide a low RPI. However, as this has a similar polarity to the permeant, they are mutually soluble, and the escaping tendency of the permeant is low. Therefore, a second solvent or emollient is added to the formulation to adjust the formulation vehicle to the required solubility to solubilize the permeant only to the amount of the required therapeutic dose; then a second vehicle component (solvent or emollient with a large RPI) is added that will reduce the permeant solubility. In 2012, Wiechers published a practical application of the principles of FFE based on his investigation of the *in vitro* human epidermal permeation of four model permeants (testosterone, hydrocortisone, 5-fluorouracil, and ketoconazole) applied in five different formulations (a hydro-alcoholic gel, an o/w emulsion, a w/o emulsion, a microemulsion, and an oil) [43]. He showed that the maximum flux of each permeant was related to its size and polarity and that enhanced permeation fluxes can be achieved by appropriate choice of emollients/solvents in the formulation.

17.5.2 BARRIER MODULATION BY CHEMICAL PERMEATION ENHANCERS

The ability of formulation components to alter permeant flux has long been recognized, with extensive research devoted to understanding their mechanism of action and how they can be applied to enhance skin and target delivery. Barry's papers in the early 1990s [44, 45] brought together the