drugs and vehicles are most similar in their various solubility parameters (HSP). They also showed that solvent uptake into the stratum corneum obeys the same rule. The uptake of formulations into the stratum corneum increases as R_a decreases, and the uptake is highest for formulations that are most similar to the stratum corneum in terms of solubility parameters [27]. Ezati [24] also showed that when the HSP of nanoemulsions are very close to that of human stratum corneum, the formulation will be taken up very well by the stratum corneum, but is then entrapped in this membrane due to high affinity (similarity in HSP values), resulting in decreased permeation.

To conclude, it is clear that solubility parameters can be used as an effective tool in formulation design for optimized dermal/transdermal drug delivery and enhancement. However, we are in the early stages of using this concept for skin drug delivery and formulation design, and further investigation is required to enable us to find truly predictive equations.

17.4 PERCUTANEOUS PERMEATION ENHANCEMENT APPROACHES

The stratum corneum is an effective barrier that limits skin permeation and consequently the extent to which the skin can be effectively used to deliver compounds for therapeutic outcomes in the skin, underlying tissues, or systemically. Many compounds do not possess the ideal physicochemical criteria to passively permeate the skin in therapeutic quantities, thus limiting the potential for topical and transdermal delivery. Many different approaches to enhance delivery into the skin have been investigated. "Passive" technologies involve the use of formulation design and excipients, chemical permeation enhancers, and various types of microtechnology- and nanotechnology-based delivery systems. Technologies using an external driving force ("active" or "physical" enhancement methods) have employed electrical (iontophoresis and electroporation), thermal (laser and radiofrequency thermal ablation), ultrasound, magnetic, heat, mechanical (microneedles), and velocity (jet injector) based energies. In this chapter the focus is on formulation-based approaches to enhance skin delivery. Other permeation enhancement methods have been reviewed elsewhere.

17.5 FORMULATION APPROACHES TO ENHANCE AND/OR TARGET SKIN DELIVERY

Formulation encompasses multiple processes that lead eventually to a successful product in the market. There are many considerations in the selection of a suitable topical formulation, including the physicochemical properties of the permeant, the stability and compatibility of the permeant and excipients, and the cosmetic acceptability of the product. Dosage form design, composition design, packaging design, and industrial scaleup are also essential parts of the formulation development process, but the focus of this chapter is on the use of the formulation to optimize skin delivery.

Based on the theoretical requirements described in previous sections, improved skin delivery of a solute can be achieved by increasing its concentration in the stratum corneum and its rate of transport in this barrier. Table 17.2 summarizes formulation-based approaches for percutaneous absorption enhancement and their possible effect on the amount of permeant retained in the stratum corneum (R_m) and/or the rate constant of permeant transfer in the stratum corneum (T_r) [28]. Formulation-based approaches to enhance percutaneous permeation are discussed in the following sections, including manipulation of permeant thermodynamic activity, chemical permeation enhancers, advanced formulations based on nanosystems and microsystems, and briefly transdermal patch design.

17.5.1 Permeant Concentration and Thermodynamic Activity

Fick's law illustrates that the flux through skin is dependent on the concentration, or more accurately, the thermodynamic activity of the permeant in the applied formulation vehicle. Maximal flux is achieved when a saturated solution is applied to the skin surface because at saturation