large body of research in the area and efficiently described the mechanisms of chemical permeation enhancement, and, together with Williams, their excellent 2004 review [46] remains one of the most highly cited. Dragicevic and Maibach provided a book series devoted to percutaneous permeation enhancers, with their 2015 volume focused entirely on chemical methods [47].

Chemical permeation enhancers can act by a number of mechanisms. The primary mechanisms are those that act by altering stratum corneum lipids and/or proteins and/or affect permeant partitioning behavior, described as the lipid–protein-partitioning theory of skin permeation enhancement [44].

Interaction (disordering/fluidizing) the stratum corneum intercellular lipids: Chemical permeation enhancers disrupt the highly ordered packing arrangements of the intercellular lipids to facilitate permeant diffusion through the primary skin permeation route. The intercellular lipid lamellae are organized into (1) highly ordered, densely packed orthorhombic phase (crystalline; low permeability); (2) ordered, less densely packed hexagonal phase (gel-like; more permeable); and (3) a disordered, liquid phase (highly permeable) [48], as described in Chapter 1. In healthy skin, the orthorhombic phase predominates, and clearly any disruption of this ordered structure will alter percutaneous absorption. Chemical permeation enhancers with lipid chains (e.g., oleic acid, lauric acid, stearic acid, Azone) can insert into the intercellular lipids, with the enhancement efficiency related to the lipid chain length and number of *cis*-double bonds, reflecting the ability to disorder the intercellular lipid structure. Other permeation enhancers that interact with the lipid domains, such as DMSO and terpenes, distort the ordered intercellular lipid packing by associating with the polar head groups of the lipids. Water and surfactants have the potential to cause phase separation within the lipid domains, and solvents such as acetone can cause lipid extraction.

Interaction with the corneocytes: Keratolytic agents, such as urea, act on the corneocytes, possibly reducing the diffusional pathway, or by an indirect influence on the intercellular lipids, or by splitting the desmosomes that act as molecular rivets between the corneocytes. Urea is also a humectant, increasing hydration within the stratum corneum Other agents that have a direct action on keratin within the corneocytes (e.g., DMSO and surfactants) also act on the lipid bilayers, demonstrating the mixed mechanisms that exist.

Altering partitioning between the formulation vehicle and the stratum corneum: Increasing partitioning from the applied formulation vehicle to the skin can be achieved by altering the permeant (e.g., prodrug) or the vehicle to increase the thermodynamic activity of the permeant (e.g., solubility, supersaturation). Administration of a solvent that permeates into the skin can increase the permeant solubility within the stratum corneum, creating a "sink" for partitioning and a reservoir of permeant in the stratum corneum. Ethanol, pyrrolidone, and propylene glycol act in this way, potentially also enhancing the permeation of other enhancers in the formulation to further increase permeant flux. Many semisolid topical formulations contain vegetable oils that are composed of enhancers such as oleic acid, lauric acid, and stearic acid (e.g., olive oil, arachis oil, coconut oil) that when used in conjunction with water, propylene glycol, or Transcutol, can provide synergistic enhancement that leads to high loading of a permeant within the stratum corneum and the potential for sustained or prolonged skin delivery.

17.5.3 Hydration

Stratum corneum hydration was first demonstrated to be a major determinant in percutaneous absorption in the 1950s and 1960s by some of the pioneer scientists in percutaneous absorption (including Irvin Blank, Howard Maibach and Robert Scheuplein) [49–52]. Under normal conditions, water makes up 15% to 20% of the dry weight of stratum corneum, but when exposed to occlusion, soaking, or very high humidity, the water content can increase up to 400% of its dry weight [53]. Indeed, water is the safest and most widely chemical permeation enhancer in topical formulations and is likely to be a primary contributor to the effectiveness of highly occlusive products such as ointments and patches through increased drug diffusivity in the stratum corneum.