We aim to provide a nonbiased overview of the currently available *in vitro* models with the potential to be used in the topical formulation development. The models most widely used in the skin irritancy and toxicity studies are not prioritized, and the focus is formulation optimization.

48.2 THE SKIN AS A BARRIER

The anatomy and physiology of the skin, particularly the barrier properties of the skin, have been summarized in various extensive reviews (Bouwstra et al., 2003; Bouwstra and Ponec, 2006; Groen et al., 2011; Hadgraft, 2001; Jepps et al., 2013; Mathes et al., 2014; Van Gele at al., 2011). In brief, the SC is considered the main contributor to the skin barrier properties (Baroni et al., 2012; Menon et al., 2012), while the role of the full epidermis should not be neglected (Andrews et al., 2013). Drug/active substance transport through the skin usually occurs through the epidermal penetration pathway or through skin appendages (Bolzinger et al., 2012; Schaefer et al., 2008). The mode of transport is predominantly by passive diffusion; therefore, the nonviable skin models mimic this process only to a limited extent.

Metabolism that occurs particularly in the living parts of the epidermis is rather difficult to mimic by any *in vitro* modeling. In addition, the residence time of a molecule in the dermis is rather short (Souto, 2005). Moreover, the dermis includes permeable capillaries driving the molecule to the microcirculation upon exiting the epidermis. Considering the drugs/active substances of interest for (trans)dermal therapy, the lipophilicity of the molecule plays a crucial role. A very lipophilic molecule able to overcome the SC barrier will be "stopped" by the aqueous interface beneath the horny layer.

In dermatopharmacokinetics, the permeation of drugs through the skin is often presented as an infinite sink (Lam and Gambari, 2014). The final potential of the drug (penetrant) can be increased (transdermal therapy) or limited (dermal therapy) by the right choice of a carrier/vehicle. Therefore, the penetrant's partitioning into skin, diffusivity through the skin, and exposure at the skin surface determine the permeability of a penetrant. However, by tailoring the vehicle features, it is possible to overcome the penetrant's limitations and optimize the therapy (Chittenden, et al., 2014).

48.3 UTILIZING THE CARRIER/VEHICLE TO TAILOR SKIN PENETRATION

Carriers/vehicles for active substances/drugs can be utilized to control the effectiveness and acceptability of skin formulations. By choosing the right carrier, we can control the (trans)dermal delivery. To be specific, we used the term percutaneous/dermal absorption to describe the passage of various compounds across the skin. The penetration was defined as the entry of a substance into a particular skin layer, whereas the permeation represents the penetration from one layer into another (Bolzinger et al., 2012). Although most of the studies have been focused on the permeation of drugs, it is important to follow the potential unwanted penetration of the cosmetics, as well as occupational exposure. By understanding the interplay between the vehicle, skin, and drug, it is possible to control the drug release, its penetration through the SC, permeation through the skin layers, potential drug deposition inside the skin, or the absorption into systemic circulation (Daniels and Knie, 2007). Many vehicles can affect the physical state and permeability of the skin through the hydration effect or an alteration of the skin temperature. Occlusive and lipophilic vehicles such as paraffin, fats, and oils reduce water loss and increase the skin moisture content, thus promoting the drug penetration. The water-in-oil (W/O) emulsions are less occlusive than the lipid materials, but more occlusive than the oil-in-water (O/W) emulsions. On the contrary, hydrogels comprising a high water content may improve the hydration level of the skin. Stahl et al. (2011) studied the permeability of ibuprofen from various vehicles and reported a rapid increase of ibuprofen permeability from the gel formulation within the first four hours, followed by a deposition of the drug inside the