and it is crucial for drug PK processes. ISF and plasma together contain all extracellular fluids of the body, with ISF being the much larger of these two extracellular compartments. ISF is considered a plasma ultra-filtrate, and one may expect that it contains various dissolved substances in similar concentrations as in plasma. However, ISF contains 50% to 80% less protein than plasma [3, 6, 7], and it contains slightly more anions than plasma, which is attributed to the net-negative charge of plasma proteins that attracts positively charged ions (Donnan effect) [8]. Small, water-soluble molecules circulate relatively freely between the two compartments, and their concentrations are similar in ISF and plasma [9, 10].

Nonetheless, sampling of dermal ISF is challenging, and the limited accessibility of dermal PK data contributes to the underrepresentation of topical drugs on the market.

Data on the dermal PK is also a prerequisite for the development of more cost-effective generic drug products, which requires proof of bioequivalence (BE) of the prospective generic drug relative to the respective reference-listed drug. For topical generic drugs acting in the skin, systemic PK data derived from blood samples are of limited value, because the measured drug concentrations are mostly below the lower limit of quantification of the analytical method used. Clinical endpoint studies are often performed to show BE of the generic and the respective reference-listed drug, because methods to assess effective drug concentrations directly in the skin are very limited. However, such clinical endpoint studies are expensive and have a high risk of failure, as the therapeutic effect of the drug is highly variable [11–13]. The lack of dermal PK data and the urgent need to access PK data of topical drugs directly in the skin promote the development of techniques capable of directly monitoring percutaneous drug penetration.

57.2 OVERVIEW OF DERMAL SAMPLING TECHNIQUES

Techniques to monitor percutaneous drug penetration and to assess dermal PK data by extracting and analyzing dermal ISF samples include a range of models and may be applied ex vivo and in vivo. Ex vivo dermal sampling can be performed with skin explants from humans or animals. In vivo assessment of percutaneous drug penetration can be performed in preclinical (animal studies) or in clinical studies with human participants. Although drug absorption into animal skin can predict the drug absorption kinetics in human skin to a certain degree, human studies are the gold standard against which all methods for measuring percutaneous absorption should be judged [14, 15].

The applied sampling techniques to gain dermal ISF deliver either snapshots of the drug concentration in the targeted skin layers or provide time-resolved data delivering PK profiles of the respective topical drug in the skin. Also, the collected dermal sample fluids differ regarding their composition, i.e. protein content, unbound drug content, contamination with intracellular fluid or with drug from the stratum corneum depot of the skin, etc., depending on the applied technique.

Dermal ISF can be collected using wicks or capsules implanted into tissue [16–18]. Further, access to dermal ISF is provided by tissue centrifugation, skin biopsies, and suction blisters. In addition to these rather invasive sampling techniques, minimally invasive continuous dermal ISF sampling can be performed with microdialysis (MD) [39] and open flow microperfusion (OFM) [43].

Skin biopsies and suction blister are well established in vivo sampling techniques to assess dermal drug concentration. Skin biopsies involve surgical removal of a piece of the skin for analysis and represent a commonly applied diagnostic procedure in dermatology practice [19]. However, the relevance of biopsies as tools in topical PK studies is limited due to several reasons: Their invasiveness prevents repeated sampling and thus excludes monitoring of PK concentration–time profiles. The concentrations derived from biopsy samples may not reflect the concentrations at the drug target site in the skin due to sample contamination with the drug from the stratum corneum depot of the skin or due to metabolic activity. Data reliability is highly dependent on the quality and standardization of the biopsy procedure, and the lack of standardized procedures when taking biopsy samples presents a major hurdle for reliable data collection.