

of permeability relative to those in human skin or hairless rat skin can be expected. To improve the model and permit testing of a wider spectra of drugs, the PDMS and PEG 6000 copolymer-impregnated membrane has been developed. The improved model has so far only been tested using the drugs in the aqueous solutions (Miki et al., 2015); whether the model can be used to assist in formulation development remains to be confirmed.

48.4.3 LIPID-BASED MODEL MEMBRANES

48.4.3.1 PAMPA

The skin–PAMPA model comprising synthetic ceramides, cholesterol, stearic acid, and silicon oil, was introduced as an improvement of the original pure solvent-based PAMPA membrane, described earlier (Sinko et al., 2009, 2012). Although the ceramides are structurally different from ceramides, their comparable molecular mass and hydrogen acceptor/donor capacity enable them to act as the lipid constituents in the PAMPA sandwich membrane, together with cholesterol, stearic acid, and silicone oil (Sinko et al., 2009, 2012).

The permeability data obtained for a selection of the model drugs tested on the skin–PAMPA model were correlated with the human skin penetration data obtained from the different skin databases. The skin–PAMPA model was shown to exhibit rather poor correlation with the epidermis, but good correlation with the full-thickness skin (Sinko et al., 2012). The skin–PAMPA model has been further evaluated and compared to mammalian skin and *in silico* models (Alonso et al., 2019; Luo et al., 2016; Zhang et al., 2019). The skin–PAMPA model has shown to be much more permeable compared to human skin, however, the permeability values determined on skin–PAMPA overall show a good linear correlation with data obtained using both pig ear and mammalian skin (Luo et al., 2016; Zhang et al., 2019).

Compatibility between the PAMPA barrier and lipophilic solvents/penetration enhancers, as well as topical formulations containing nonionic emulsifiers, has been confirmed (Balázs et al., 2016; Köllmer et al., 2019). Furthermore, the effect of drug permeation in the presence of penetration enhancers evaluated in the skin–PAMPA model correlated well with the permeability data obtained in human skin (Balázs et al., 2016). The model has also shown to be able to discriminate between different formulations, as well as rank them according to permeation of the selected drug comparably to what was observed in human skin (Karadzovska et al., 2013; Luo et al., 2016; Tsinman and Sinko, 2013). In the study by Tsinman and Sinko (2013), a modified version of the skin–PAMPA model was applied to evaluate different ibuprofen-containing skin formulations: silicone-based gel, silicone and acrylic copolymer, and one commercially available formulation. In the simple penetration experiments, the modified skin–PAMPA models were able to distinguish between the different formulations, and the ranking of the tested formulations according to the flux was in an agreement with the penetration through human epidermis.

Moreover, the skin–PAMPA model has been further proposed as a useful tool to evaluate and classify transdermal patches by modifying the setup so that the traditional donor compartment was replaced by the patch to be tested (Vizserálek et al., 2015)

48.4.3.2 Phospholipid Vesicle–Based Permeation Assay

The PVPA was originally introduced as a liposome-based barrier model for estimation of intestinal permeability, with the potential to perform in a medium- to high-throughput screening format (Flaten, et al. 2006b, 2009). The PVPA consists of a tight layer of liposomes on a filter support, thus mimicking the cells of biological barriers (Figure 48.1) (Flaten, et al. 2006a,b). By changing the lipid composition of the liposomes, the PVPA barriers could be modified to mimic the other biological barriers, including the skin (Berben et al., 2018; Engesland et al., 2013; Naderkhani et al., 2014). The first PVPA models mimicking the SC barrier of the skin were introduced by Engesland et al. (2013); thereafter several modified versions have been described (Engesland et al., 2013, 2016; Ma et al. 2017; Palac et al., 2014; Shakel et al., 2019; Zhang et al., 2016). All proposed PVPA models