

skin was applied to optimize a microemulsion formulation proposed for the treatment of skin fungal infections (Butani et al., 2014). A microemulsion comprising 5% isopropyl myristate and 35% mixture (3:1, Tween 80:propylene glycol) exhibited twofold higher drug permeation of amphotericin B into the skin as compared to a plain drug solution. Rabbit skin can also be used as an animal skin model. The full-thickness skin from the inner side of albino rabbit ear was used to compare ketotifen skin permeability from the two types of vesicles: deformable liposomes and ethosomes (Elsayed et al., 2006).

Although not commonly used, shed snake skin can also serve as an alternative skin model; the snakes molt periodically, and a single animal can provide repeated sheds, thus eliminating interindividual variability seen in other animal models. Moreover, removal is injury-free and no chemical or heat pretreatment is required (Itoh et al., 1990). Moreover, since it is not a living tissue, storage at room temperature for relatively long periods of time is feasible (Haigh and Smith, 1994). However, the lack of hair follicles could influence drug permeability (Godin and Touitou, 2007). Therefore, this model is not appropriate for investigating dermal absorption of drugs that penetrate the skin via the follicular route. When the shed snake membrane was compared with hairless mouse and human as models to evaluate the permeability of 5-fluorouracil in formulations comprising different penetrating enhancers, it became evident that human skin cannot be replaced by snake skin (Rigg and Barry, 1990). Ngawhirunpat et al. (2008) confirmed that the skin metabolisms in snake and shed snake skin were significantly different from human skin.

#### 48.7 EX VIVO HUMAN SKIN MODELS

Human skin is the most relevant model for evaluating the effect of formulation components on (trans)dermal drug delivery. Human skin can originate from various sources, mostly from plastic surgery (Godin and Touitou, 2007). However, the use of human skin is very restricted by the ethical permissions and laboratory facilities, and only a limited number of laboratories have access to human skin. In addition, human skin permeability varies greatly between the specimens taken from the same or different anatomical sites of the same donor (27% variance *in vivo* and 43% *in vitro*, respectively). Even greater variations (45% *in vivo* and 66% *in vitro*, respectively) are reported between the specimens from different subjects or different age groups (Haigh and Smith, 1994). These variations are contributed to differences in the lipid composition, skin thickness, or hydration, which are affected by body site, sex, race, age, and disease (Barbero and Frasch, 2009). The metabolism and biotransformation of chemicals applied to the skin after excision of the tissue from the donor can also affect model suitability (Haigh and Smith, 1994).

Various topical formulations have been evaluated on *ex vivo* human skin, and selected relevant studies are discussed here in more detail. For example, Zhao et al. (2009) evaluated nanoparticles incorporated in hydrofluoroalkane foam for enhanced dermal delivery of tocopherol acetate using full-thickness human skin. Optimization of a gel vehicle for dermal delivery of epicatechin has been performed on full-thickness human cadaver skin obtained from the back region of Caucasian subjects. Ultrez 10 gel was confirmed to promote the penetration and retention of epicatechin in the upper layers of human cadaver viable skin (Suppasrivassuth et al., 2006). Typically, skin was used to compare two or more nanocarriers or vehicles. For example, Dubey et al. (2007) compared the penetration potential of methotrexate-containing ethosomes with the conventional liposomes using dermatomed (500  $\mu\text{m}$  thickness) human cadaver skin and concluded that ethosomes enhanced the transdermal flux of the drug and decreased the lag time across the skin. In another study, full-thickness breast skin obtained after cosmetic surgery was used for the estimation of celecoxib skin delivery by ethosomes conventional liposomes and deformable liposomes. An increased skin accumulation of the drug has been determined for ethosomes and deformable liposomes (Bragagni et al., 2012). The full-thickness human abdominal skin was utilized to optimize temoporfin-loaded