observed. However, the maximum dimensions of microchannels created in the skin are restricted by the desire for limited invasiveness, pain and safety concerns.

Gomaa et al. (2014) used two dyes, Rh B (hydrophilic model drug) and FITC (hydrophobic model drug), encapsulated in PLGA nanoparticles to gain information on the mechanism of their transdermal drug delivery across MN-treated full-thickness porcine skin. They found that their permeation through MN-treated skin was affected by physicochemical characteristics of nanoparticles and the encapsulated dyes. Dye flux was enhanced by smaller particle size, hydrophilicity, and negative zeta potential of nanoparticles. Reduction in particle size of Rh B nanoparticles from 422.3 to 155.2 nm resulted in significant increase of Rh B permeation, i.e. it led to a fivefold increase in total amount permeated per unit area at 48 hours. The authors explained this finding by faster release of the encapsulated Rh B from smaller nanoparticles with larger surface-to-volume ratio. Further, they suggest deeper and more extensive influx of smaller nanoparticles through MN-created channels leading to enhanced transdermal delivery of Rh B released at the deeper deposition sites of nanoparticles (Gomaa et al., 2014). As for nanoparticle's hydrophilicity, increasing PLGA copolymer hydrophilicity by reducing the lactide-to-glycolide ratio significantly enhanced permeation of Rh B from PLGA 50:50 nanoparticles compared to PLGA 75:25 and 100:0 nanoparticles. This was explained by greater compatibility of the more hydrophilic nanoparticles with the aqueous environment of microchannels, leading to deeper penetration. Regarding the surface charge, negatively charged nanoparticles larger in size (–4.5 mV, 367.0 nm,) allowed significantly greater ($P < 0.05$) permeation of FITC compared to smaller positively charged nanoparticles (122.0 nm, 57 mV), i.e. 2.7-fold and 2.9-fold increases in Q_{48} and flux, respectively, could be observed. The authors suggested that as porcine skin bears a net negative charge at physiological pH, repulsion of negatively charged nanoparticles may reduce adsorption at its surface, inducing influx of nanoparticles deeper into the microchannels and enhancing flux of released FITC.

As to the effect of dye-related variables on skin permeation, drug solubility at physiological pH and potential interaction with skin proteins proved to outweigh molecular weight as determinants of skin permeation. The effect of dye solubility was examined by comparing two encapsulated dyes of different solubility (solubility of 0.99 versus 0.09 g/L for Rh B and FITC, respectively), while other variables were kept constant. Statistically significant 33.2-fold and 35.8-fold differences in Q_{48} and flux values, respectively, were observed for Rh B compared to FITC. CLSM confirmed significantly higher skin permeability of nanoencapsulated Rh B (190 μm) compared to FITC (130 μm). Higher solubility was reported to increase drug flux across MN-treated skin, since the dermis does not represent a distinct barrier to hydrophilic drugs once the SC is bypassed (Gomaa et al., 2014). According to the authors, significantly lower flux of FITC can be ascribed to poor solubility due to the hydrophobic isothiocyanate substituent which probably resulted in slower release from nanoparticles and saturation of the microenvironment, resulting in reduced concentration gradient and molecular diffusion.

As to the effect of the percentage of initial drug loading on skin permeation of nanoencapsulated Rh B and FITC, permeation of Rh B increased significantly ($P < 0.05$) with the increase in dye loading. In contrast, increasing percentage of initial FITC loading led to reduced skin permeation. This was explained by the fact that increasing the initial FITC loading from 5% to 20% w/w was associated with increase in particle size and PDI (higher heterogeinity), and decrease in zeta potential. Gomaa et al. (2014) proposed a mechanism for percutaneous penetration of nanoparticles, particularly of smaller size, deep into MN-created channels, generating reservoirs of the drug. According to the authors, molecular diffusion of the released dye across viable skin layers proceeds at a rate determined by its molecular characteristics. It was confirmed that only the free dye released from nanoparticles permeated skin layers to the receiver compartment.

64.1.2.2 Influence of MN Characteristics and Application Variables on Drug Diffusion

Gomaa et al. (2012) investigated the effect of MN application, MN characteristics and application variables on the transdermal delivery of a hydrophilic small/medium-sized model drug (Rh B)