physical penetration enhancement methods such as ultrasound (Oberli et al., 2014; Azagury et al, 2014), electroporation (Engelke et al., 2015; Berkó et al., 2016; Ita, 2016; Mohammad et al., 2016), iontophoresis (Patel et al., 2016; Del Río-Sancho et al., 2017) and microneedles (Arya et al., 2017; Dul et al., 2017; Ripolin et al., 2017).

For a comprehensive review of different nanocarriers used to enhance percutaneous drug penetration, the reader should refer to Dragicevic and Maibach (2016). For a review of physical methods, the reader should refer to Dragicevic and Maibach (2017), and for a detailed review on the combined use of different kinds of nanocarriers with physical methods, the reader should refer to Dragicevic and Maibach (2018).

64.1.1 Nanoparticles – Classification and Their Percutaneous Penetration

For the treatment of skin diseases, it is important to create drug reservoirs in the skin with sustained drug release. Therefore, it is believed that nanoparticles would be a good choice to provide the skin with the drug for a prolonged time, maintaining the required drug concentration in the skin. Further, this would allow dose reduction due to formation of depots with sustained drug release.

As to their composition, nanoparticles can be lipid-based (Pardeike et al., 2009; Mitri et al., 2011; Puglia and Bonina, 2012; Suter et al., 2016; Jain et al., 2017) and polymer-based (Zaric et al., 2013, 2015; Abrego et al., 2016; Parra et al., 2016). First-generation lipid-based nanoparticles are the SLNs produced from solid lipids only, either glycerides or waxes or mixtures of both (Figure 64.1). In order to improve on the drawbacks of the first-generation nanoparticles, second-generation nanoparticles were developed and named as nanostructured lipid nanocarriers (NLC) (Figure 64.1). These new nanoparticles are obtained by blending solid lipids with longer chain fatty acids and oils with shorter chain fatty acids (for details see Müller et al., 2016).

Polymer-based nanoparticles (Zaric et al. 2013, 2015, Abrego et al. 2016, Parra et al. 2016) have also been extensively used for skin delivery of numerous drugs/actives. Depending on the preparation technique, polymeric nanoparticles can be nanospheres (matrix-type nanoparticles) or nanocapsules (reservoir-type nanoparticles) (Figure 64.2). Besides non-biodegradable polymers, various biodegradable polymers (synthetic and natural) have also attracted attention and, hence, are now used for the production of nanoparticles. Polylactides and polyglycolides are commonly used biodegradable polyester polymers. However, other polymers are also used, such as hyaluronic acid, chitosan, etc. (for details see Abdel-Mottaleb and Lamprecht, 2016).

Numerous studies showed that nanoparticles enhanced the drug penetration and drug accumulation in the skin due to the sustained drug release. As to the penetration of the carrier, i.e. the nanoparticles, into the skin, they were not found inside the skin (Alvarez-Roman et al., 2004a, 2004b; Luengo et al., 2006). This was not encouraging as for the treatment of skin diseases, it is crucial to have drug reservoirs inside the skin and not only on the skin surface. Authors reported that nanoparticles are unable to penetrate into the intact skin, thus mostly remaining at the skin surface,

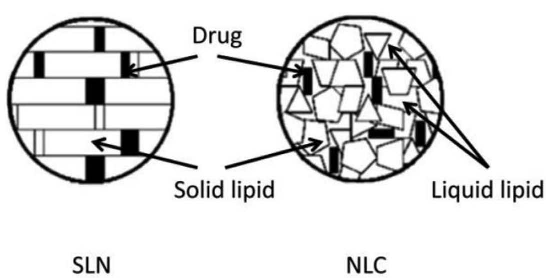

FIGURE 64.1 Schematic representation of lipid-based nanoparticles. Solid lipid nanoparticle (SLN) with an almost perfect solid lipid matrix and nanostructured lipid carrier (NLC) with an imperfect lipid matrix consisting of solid and liquid lipids. (Adapted from Abla et al., 2016.)