The immunogenicity of the nanoparticles after administration of dissolving MNs (NP:HA weight ratio 1:4) was compared with that of hollow MN-delivered nanoparticles in mice. The study revealed that the immunization with free antigen in dissolving MNs resulted in equally strong immune responses compared to the delivery by hollow MNs. However, humoral and cellular immune responses evoked by nanoparticles-loaded dissolving MNs were inferior compared to those elicited by nanoparticles delivered through hollow MNs. However, the authors found that the critical formulation parameters are important for the further development of nanoparticle-loaded dissolving MNs, such as the NP:HA ratio used for the preparation of dissolving MNs, drying conditions during MN preparation, and others, which they can vary to obtain the formulation with desired characteristics (Mönkäre et al., 2018).

Niu et al. (2019) investigated the use of the hollow MNs for the intradermal delivery of polymeric nanoparticles in rats. The model antigen OVA and TLR agonists imiquimod and monophosphoryl lipid A were encapsulated in PLGA nanoparticles. Hollow MNs with encapsulated nanoparticles bearing antigens were used due to their advantages, such as the pharmacokinetic profile, characterized by an early burst transit through the draining lymph nodes and a relatively limited overall systemic exposure compared to subcutaneous or intravenous delivery. OVA-loaded nanoparticles demonstrated faster antibody affinity maturation kinetics compared to soluble OVA-based vaccine. Furthermore, antigen-loaded nanoparticles delivered via a hollow MN array elicited a significantly higher IgG2a antibody response and higher number of interferon (IFN)-γ secreting lymphocytes, both markers of Th1 response, in comparison to antigen-loaded nanoparticles delivered by intramuscular injection and soluble antigen delivered through hollow MN array. The authors confirmed that hollow MN-mediated intradermal delivery of polymeric nanoparticles represents a promising approach to improve the effectiveness of vaccine formulations (Niu et al., 2019).

Nanoparticles combined with MNs besides being used for TCI, are also used to enhance the penetration of various drugs through the skin. Poly (D, L-lactic acid) (PDLLA) nanoparticles loaded with ketoprofen and applied to the skin upon the application of silicon MN arrays enhanced ketoprofen flux and supplied the porcine skin with the drug over a prolonged (24 hour) period of time (Vučen et al. 2013). Nanoparticles provided a 2.4-fold higher amount of drug permeated through MN-treated skin compared to nanoparticles applied to intact skin. The flux of ketoprofen was also more than twofold higher for MN-treated skin compared to intact skin. Thus, the MN- pretreatment of skin significantly enhanced the ketoprofen skin permeation from nanoparticles compared to ketoprofen permeation from nanoparticles through intact skin. MNs were also used with gold nanoparticles and they enhanced the penetration of gold nanoparticles into the skin, leading to a 150% increase in optical coherence tomography (OCT) contrast agent levels, enabling improved early-stage detection of oral cancer *in vivo* (Kim et al. 2009).

64.1.3 Combined Use of Nanoparticles and Iontophoresis

Among electrical physical penetration enhancement methods, iontophoresis has been extensively studied (Takeuchi et al., 2017; Manjunatha et al., 2018; Ronnander et al., 2019). Iontophoresis is a noninvasive method which involves the application of a small electric current to drive ionic and polar drugs exhibiting poor skin permeation into/through the skin. Good candidates for iontophoresis are hydrophilic molecules with high water solubility and little affinity for lipids. Fukuta et al. (2020) investigated the influence of iontophoresis on the skin delivery of biological macromolecular drugs, such as antibodies and fusion protein drugs. The authors confirmed the intradermal delivery of biological macromolecular drugs (FITC-labeled IgG antibody) via iontophoresis as fluorescence was broadly observed in the skin, i.e. it extended from the epidermis to the dermis layer of hairless rats, while passive antibody diffusion was not observed. Antibodies were also delivered via iontophoresis into inflamed skin tissue in a psoriasis model, and upregulation of interleukin-6 mRNA levels (marker for progression of psoriasis) was significantly inhibited by iontophoresis of the anti-tumor necrosis factor-α drug etanercept, which also ameliorated epidermis hyperplasia (symptom of psoriasis). Thus, Fukuta et al. (2020) were the first to demonstrate that iontophoresis can be