

dorsal skin of hairless mice producing melanin in response to light exposure. It has been shown that iontophoresis provided an accumulation of nanoparticles in the epidermal layer, as well as that this combination decreased UV-induced melanin spots and melanin content in the skin. Thus, Shiota et al. (2017) confirmed that melanin production was prevented by the application of redox nanoparticles in combination with iontophoresis.

Some authors reported that there has been no advantage when a drug, flufenamic acid was encapsulated into PLGA nanoparticles and applied with iontophoresis. The permeation of flufenamic acid through the skin from PLGA nanoparticles was not enhanced compared to free drug formulation, either in passive or iontophoretic delivery regimens (Malinovskaja-Gomez et al., 2016).

In addition, also layer-by-layer polymer coated gold nanoparticles (AuNP) were investigated as carriers for the iontophoretic delivery of drugs. The authors (Labala et al., 2015) showed that AuNP combined with iontophoresis are able to deliver imatinib mesylate into the skin for the treatment of melanoma. Skin penetration studies performed *in vitro* in excised porcine ear skin showed that iontophoresis enhanced the skin penetration of imatinib mesylate from nanoparticles by 6.2-fold compared to passive application. Tape stripping studies revealed that iontophoresis provided a 7.8- and 4.9-fold greater imatinib mesylate amount in the SC and viable skin, respectively, compared to iontophoresis of free imatinib mesylate. Furthermore, AuNP loaded with imatinib mesylate significantly decreased B16F10 cell viability compared to free imatinib mesylate. The obtained results confirmed the potential of AuNPs to be used in combination with iontophoresis for the percutaneous penetration enhancement of drugs. Dohnert et al. (2012) evaluated the therapeutic effects of GNPs and diclofenac diethylammonium used together with iontophoresis on the inflammatory parameters in rats challenged with traumatic tendinitis. The results confirmed the efficacy of drug administration used with nanoparticles and iontophoresis in treating tendinitis in an animal model.

AuNPs applied together with iontophoresis could be used in physiotherapy, i.e. they were investigated for their effects in the skeletal muscle of wistar rats exposed to a traumatic muscle injury. Iontophoresis with AuNPs showed significant differences in inflammation and oxidative stress parameters, preserved morphology in the histopathological evaluation, as well as an improvement in the locomotor response and pain symptoms of treated rats. Thus this approach accelerated the inflammatory response of the injured limb and would be promising method in physiotherapy (da Rocha et al., 2020).

Bernardi et al. (2016) investigated an interesting approach for TCI using OVA as a model antigen, which included a vaccine formulation composed of OVA-loaded liposomes and silver nanoparticles (NPAg). These OVA-liposomes associated with NPAg and applied together with iontophoresis increased OVA penetration *in vitro* into the viable epidermis by 92-fold in comparison to passive delivery. As to *in vivo* studies, TCI with a suitable combination of liposome, nanoparticles and iontophoresis induced indeed the production of antibodies and differentiation of immune-competent, thereby confirming the ability of this approach to be used for TCI (Bernardi et al., 2016).

#### 64.1.4 COMBINED USE OF NANOPARTICLES AND ELECTROPORATION

Electroporation is a physical technique used to enhance drug penetration into/through the skin. Usually electroporation requires application of high-voltage electric pulses of very short duration (microsecond-millisecond). This protocol is able to reversibly enhance cell or tissue permeability for bioactive molecules such as drugs, dyes, vitamins, peptides, proteins, DNA, RNA etc. (Medi et al. 2017). It holds promise for the percutaneous penetration enhancement of macromolecules, such as peptides and gene-based drugs, enabling their transdermal delivery (Dujardin and Pr at 2004; Medi et al. 2017). Electroporation is an efficient penetration enhancing method depending on itself and the properties of drugs, i.e. the cumulative drug permeation increases with increasing drug solubility, decreasing oil–water partition coefficient (logP) and dissociation constant (pKa) (Chen et al., 2020). Nowadays, there are novel electroporation protocols which allow at low voltages sufficient delivery of DNA and siRNA into mouse skin (Huang et al., 2020). For more detail on electroporation, the reader should refer to [Chapter 45](#) of this book and to references (Medi et al., 2017; Angamuthu and Murthy, 2017).