applied as a noninvasive and efficient percutaneous penetration enhancement method for biological macromolecular drugs. For more details on iontophoresis, its mechanism of action and drugs which were delivered intradermally via iontophoresis, the reader should refer to Chapter 46 in this book and to references (Guy et al. 2000; Grice et al. 2011; Gratieri and Kalia 2017a,b). It can be used to enhance dermal and transdermal drug delivery and noninvasive skin sampling applications, while it has mostly been used for the treatment of palmoplantar hyperhidrosis and the diagnosis of cystic fibrosis (Kalia et al., 2004; Delgado-Charro, 2009, 2011; Del Río-Sancho et al., 2017; Merino et al. 2017). Due to the popularity and high therapeutic effectiveness of nanocarriers, espicially nanoparticles, iontophoresis has also been used in combination with nanoparticles in order to synergistically enhace the drug penetration into/through the skin (Dragicevic and Maibach, 2018; Helmy, 2021).

Huber et al. (2015) investigated the effect of iontophoresis on the skin distribution and antitumor effect of doxorubicin-loaded cationic SLN (DOX-SLN). The encapsulation of DOX increased the distribution of DOX in the SC *in vitro*. The combined use of SLN and iontophoresis increased the *in vitro* skin penetration of DOX and led to the formation of drug reservoirs in the hair follicles. Iontophoresis of cationic DOX-SLN increased the DOX penetration into the viable epidermis by approximately 50-fold, while it increased the skin penetration of DOX from the solution only by approximately fourfold. As to the antitumor effect investigated *in vivo* in squamous cell carcinoma induced in nude BALB/c mice, iontophoresis combined with DOX-SLN was highly effective in inhibiting tumor cell survival and tumor growth, indicating a synergistic effect of iontophoresis and DOX-SLN in the treatment of skin cancer (Huber et al. 2015). These results are in accordance with the results of Taveira et al. (2014), who found that iontophoresis of DOX-SLNs increased DOX delivery to the viable epidermis (56% of DOX), compared to passive DOX-SLN delivery, where most of DOX remained in the SC (43% of DOX) and only a small amount penetrated into the viable epidermis (26% of DOX). Further, DOX-SLNs increased DOX cytotoxicity against melanoma cells by 50%.

Charoenputtakun et al. (2015) investigated iontophoretic delivery of hydrophilic and lipophilic drugs through the skin, when applied as encapsulated lipid nanoparticles. Iontophoresis did not enhance the delivery of the lipophilic all-trans-retinoic acid across human epidermal membrane from SLN and NLC compared to passive delivery. In contrast, iontophoresis significantly enhanced the amounts of the hydrophilic drug salicylate delivered across human epidermal membrane (HEM) from salicylate-loaded lipid nanoparticles and salicylate solution compared to those obtained during passive delivery. In addition, the amounts of salicylate delivered from lipid nanoparticles during iontophoretic delivery were significantly larger than those delivered from the solution (Charoenputtakun et al., 2015). As for the amounts of salicylate extracted from HEM after 5 hours of iontophoretic delivery, they were significantly larger than those achieved after 24 hours of passive delivery, and amounts of salicylate delivered from lipid nanoparticles (SLN and NLC) during iontophoresis into the HEM were significantly larger than those delivered from salicylate solution during iontophoresis. Thus, the combined use of iontophoresis and lipid nanoparticles (SLN and NLC) provided significantly higher permeation of hydrophilic SA into and across HEM than iontophoresis applied with plain salicylate (without lipid nanoparticles). The different effect of iontophoresis on the permeation of salicylate and all-trans-retinoic acid could be explained by the different iontophoresis effect on hydrophilic and lipophilic drugs. Similarly, iontophoresis significantly enhanced the amount of acyclovir permeated from SLN compared to passive acyclovir delivery from SLN and suspension applied with and without iontophoresis. These results suggest that lipid nanoparticles combined with iontophoresis represent a promising penetration enhancement method to improve skin delivery of hydrophilic drugs.

Tomoda et al. (2011, 2012a) applied negatively charged PLGA nanoparticles loaded with indomethacin onto rat skin *in vitro* and *in vivo* with or without iontophoresis. When iontophoresis was applied together with indomethacin-loaded nanoparticles *in vivo* in rats, a significantly higher amount of indomethacin was delivered into the systemic circulation, i.e. plasma concentration increased after 60 minutes and continued to increase in next 5 hours (at 6 hours, approx. 200 ng/ml), compared to indomethacin-loaded nanoparticles and indomethacin solution (at 6 hours less than approx. 20 ng/ml). Thus, the combined use of iontophoresis and nanoparticles can be used for an efficient