of calcein and bovine albumin serum (Chen et al., 2010). It has also been shown that the combination of ultrasonic waves and iontophoresis improved the efficiency of hyaluronic acid MNs by shortening the reaction duration, and that this combination strategy could be used for delivery of macromolecules (Bok et al. 2020). In addition to physical methods, MN technology has been used in combination with nanocarriers also, especially nanoparticles for vaccine and gene delivery, as well as delivery of large molecules (Lawson et al., 2007; Combadiere and Mahe, 2008; Manolova et al., 2008; Pamornpathomkul et al. 2017a, Tort et al. 2020).

In an attempt to prove that microconduits created by MNs can act as channels for nanoparticles to penetrate through the SC and epidermis, a lot of studies were performed which will be discussed in following sections. For more details on the mechanism of drug delivery by MNs, MN evaluation in humans and the fabrication of MNs, the reader should refer to the comprehensive references (Kalluri et al. 2017; McAlister et al. 2017, Singh et al. 2017).

The combination of MNs and nanoparticles has been used to date mostly to achieve dermal delivery of low-molecular-weight drugs (Donnelly et al., 2010) and for transcutaneous immunization (Bal et al., 2010; Kumar et al., 2011; Siddhapura et al., 2016; Ali et al., 2017; Pamornpathomkul et al., 2017a).

When using nanoparticles together with MNs, one should differ between the two-step and the one-step delivery strategy. The two-step drug delivery with MNs requires MN puncture followed by drug application. The one-step delivery strategy uses MNs manufactured from biocompatible polymers which contain the drug alone or incorporated in nanoparticles. This strategy combines the advantages of nanoparticles and polymeric MNs showing synergistic effects. Also the nanoparticles are directly deposited across the skin by MN tips which encapsulate nanoparticles.

Donnelly et al. (2010) investigated different possibilities to enhance percutaneous delivery of highly lipophilic photosensitizers used in topical photodynamic therapy (PDT). The authors showed that after insertion of water soluble polymeric MNs containing PLGA nanoparticles (150 nm in diameter) loaded with the hydrophobic model dye, Nile red, into porcine skin, high tissue concentrations of Nile red were observed at 1125 mm depth, but not in the receiver compartment indicating that only intradermal delivery was achieved (without the risk of systemic delivery). As to the application of Nile red-loaded nanoparticles without MNs pretreatment, amounts of Nile red found in the skin were low, i.e. no Nile red was detectable below 1.0 mm. This was expected as it is generally accepted that nanoparticles do not penetrate the intact skin, but accumulate at the skin surface, hair follicles and sweat glands. MNs delivered significantly higher Nile red amounts into the skin (3.59%) compared to the control patch without MNs (0.13%). These results, i.e. high percutaneous drug penetration without delivering the drug into the receiver compartment were very important for topical PDT, indicating that transdermal (systemic) delivery using this system would be very limited, and the prolonged photosensitivity would be overcome. This strategy has also been used in the study by Zaric et al. (2013).

Park et al. (2006) investigated one-step delivery strategy by using biodegradable polymer MNs composed of PLGA, containing drugs. Calcein or bovine serum albumin were directly incorporated into the MN matrix or were first encapsulated into carboxymethylcellulose (CMC) microparticles (mean diameter 9.6 μm) and poly-L-lactide (PLA) microparticles (1–30 μm), which were further incorporated into the PLGA MN matrix. Depending on the encapsulation method, the sustained drug release could be controlled, ranging from hours to months.

This one-step delivery strategy using polymeric MNs with encapsulated nanoparticles has been frequently applied in the past years. Thus, nanoparticles-encapsulated polymeric MNs have nowadays been used for transdermal delivery of various therapeutic cargos, particularly for diabetes therapy, infectious disease therapy, cancer therapy, dermatological disease therapy etc. (Chen et al. 2020).

This strategy has been shown to be effective in the treatment of keloids. 5-fluorouracil (5-FU)-loaded carboxymethyl chitosan (CMC) nanoparticles were prepared and coated on stainless steel solid MNs. 5-FU-loaded CMC nanoparticles showed a significant inhibitory effect on the human keloid fibroblast i.e. up to 16%. The intercellular uptake of the 5-FU-loaded CMC nanoparticles was observed in both controls and keloid fibroblasts (by using a confocal microscope) and nanoparticles