mediastinitis revealed similar results obtained after intramuscular vancomycin administration and treatment by combined iontophoretic skin delivery of vancomycin encapsulated in ethosomes.

Another study tested a system combining iontophoresis and drug-loaded lipid vesicles for the controlled transdermal delivery of diclofenac sodium [58]. Four different types of lipid vesicles were prepared. The conventional vesicles comprised phophatidylecholine (PC) and cholesterol (Chol) (3:1). The pegylated liposomes contained PC and Chol (3:1) with 2.5% (mol/mol%) of DSPE-PEG2000. Transfersomes were made of PC with Tween 80 as the edge activator, and ethosomes were fabricated from PC and Chol in the presence of 20% ethanol. The pegylated liposomes were prepared to reduce the electro-negativity of the conventional one by shielding the negative charge of the vesicle so as to study the effect of the surface charge of the lipid nanocarriers on the diclofenac sodium transport under iontophoretic current. Using full-thickness porcine skin, passive and iontophoretic (direct current or pulsed current 0.5 mA/cm^2 for eight hours) models were tested. The results indicated that the use of drug-loaded vesicles led to decreased flux values with increased lag times compared to that from the aqueous solution, both under passive delivery. This was explained by the hydrophilic nature of the drug. Iontophoretic drug transport from the liposomes was significantly affected by the composition and the charge of the lipid bilayer of the vesicles and the current mode used. Ethosomes resulted in the highest iontophoretic flux under direct constant current. Conventional liposomes with the highest negative surface charge led to better transport efficiencies of the model drug due to the higher mobility of the drug carriers under iontophoretic current. Based on their findings, pulsed current treatment has no clear advantage over constant current treatment in combination with any type of lipid vesicles, opposite to what has been described earlier with polymeric nanocarriers by Malinovskaja-Gomez [59, 60].

37.2.2 Electroporation and Ultra-Deformable Liposomes

Enhanced transdermal penetration by electroporation is believed to depend on many mechanisms. These include increased permeability of the skin due to electrical breakdown, electrophoresis (repulsion force between the applied current and the entity of the same polarity), and/or—but less likely—from electro-osmosis. The mechanism of pore formation was reported to be due to a temperature rise within the SC intercellular lipids to above their phase transition temperature. The temperature rises in localized regions known as local transport regions (LTRs) [31, 61]. Additionally, the bulk of the SC is not homogenous, but exhibits defects, so it is likely that at least temporary aqueous pathways exist, e.g., in desmosomes or protein structures between adjacent corneocytes. The electric field can force electrolytes into such areas, expanding them so that SC resistance reduces markedly [62].

Few investigations are available on the combined use of liposomes and electroporation. For example, electroporation was achieved by application of electrical pulses (250 V, 20 ms, 10 pulses/min for five minutes), and its effect on the epidermal delivery of colchicine encapsulated in positively charged standard liposomes (DSPC: cholesterol;1:0.5 molar ratio) was investigated [63]. The total charge and cumulative amount of colchicine delivered over 24 hours were less than that after iontophoresis (0.5 mA/cm^2) for six hours. Interestingly, the authors proposed that intact vesicles could penetrate through such a potentially modified skin structure.

The investigation of vesicular transdermal delivery under electroporation has been extended to the highly deformable liposomes, which comprised PC with sodium cholate (86:14 w/w) [64]. The study employed human epidermal membrane and applied five pulses (100 V, 100 ms, and one-minute spacing) to negatively charged vesicles containing estradiol. Saturated aqueous solution of estradiol was used as the control. Electroporation resulted in significant increase in skin permeation and deposition of estradiol over eight hours from control solution (about sixteenfold relative to passive diffusion). Contrary to this, the permeation parameters were not enhanced after delivering the ultra-deformable liposomes under electroporation compared to simple occluded passive delivery from the same vesicles. Such low penetration was unexpected for ultra-deformable liposomes, as it