additional benefits. A charge can effectively be imparted to neutral drugs by encapsulating them in charged liposomes, thus enhancing their iontophoretic delivery. Charging the vesicles can be achieved using stearylamine which is commonly used to induce positive charges, with dicetyl phosphate to create negatively charged vesicles [16]. An early report of the combined use of iontophoresis and traditional liposomes in skin delivery was for enkephalin entrapped in positive or negative vesicles [38]. Iontophoresis increased liposomal enkephalin penetration compared to the control solution. During transport, the enkephalin solution underwent degradation, with a minimal amount being degraded after liposomal encapsulation. This reflects the potential protective effect of the vesicles for the encapsulated drug.

Iontophoretic delivery of neutral colchicine encapsulated in positively charged liposomes was able to augment the drug flux by four to five times compared to free colchicine [39]. The effect of different liposomal formulations on the iontophoretic transport of enoxacin through rat skin has been investigated *in vitro* [40]. The iontophoretic penetration of enoxacin depended on vesicular composition, with better flux being recorded by decreasing the fatty acid chain length of the phospholipid. This was attributed to the decrease in the phase transition temperature of the lipid.

The effects of zwitterionic lipids (phosphatidylcholine [PC] and distearoyl phosphatidylcholine DSPC]), cationic lipid (stearylamine), and the penetration enhancer Azone on the iontophoretic transdermal flux of neutral mannitol through human skin were examined [41]. The skin was pretreated with the placebo lipid suspensions or Azone solution, all containing 32% ethanol, prior to iontophoresis.

For the lipid suspensions, only PC increased mannitol flux compared to control (without pretreatment). Interestingly, the authors recorded an increase in mannitol flux after the combination of PC with electric current, with the recorded increase being comparable to Azone, suggesting a synergistic effect between PC and the electric current.

The combined use of iontophoresis and ultra-deformable (ultra-flexible or elastic) liposomes has been studied. Offering the potential to stabilize therapeutic agents undergoing iontophoresis, surfactant-based elastic vesicles (composed of octaoxyethylene laurate ester, sucrose laurate ester, and cholesterol sulfate) were used to deliver apomorphine through human skin *in vitro* [42].

Negatively charged Transfersomes were prepared using sodium cholate as the edge activator (PC: sodium cholate; 86:14% w/w). Using human epidermal membranes, cathodic iontophoresis (0.2 to 0.8 mA/cm^2 constant current) increased the delivery of estradiol compared to the control (saturated estradiol aqueous solution), even though the vesicles were delivered against electro-osmotic flow [43]. The steroid flux increased linearly with the applied current, confirming the ability of iontophoresis to provide programmed drug delivery. The fifteenfold enhancement in estradiol flux from liposomes under iontophoresis (0.8 mA/cm^2) was attributed to the synergistic effect of both electric current and phospholipid monomers released from the lipid vesicles under electric field. Both processes modulated the intercellular lipid lamellae of the SC, increasing membrane permeability. It was also suggested that under such conditions of a permeabilized skin structure, intact vesicles might penetrate someway down the SC because of their flexibility. Importantly, iontophoresis induced tritium exchange of the ^{3}H-labeled estradiol with water and had to be allowed for so as not to falsely elevate the flux data. Tritium exchange increased with increasing current density and time of application. Interestingly, the liposomal structure shielded the drug against the effect, producing a protective action [43].

To estimate the role of vesicle deformability on the enhanced drug penetration from ultra-deformable vesicles, iontophoresis (six hours of 0.8 mA/cm^2) of estradiol from the same ultra-deformable vesicles (containing sodium cholate as the edge activator) was compared with that from traditional liposomes (i.e., without edge activator).

The prototype nonrigid pure PC and membrane-stabilized (PC: cholesterol; 1:1 molar ratio) formulations were used. All preparations improved skin delivery of estradiol in terms of flux and skin deposition compared with the control solution, with ultra-deformable liposomes being the most effective. Nevertheless, there was no strong evidence that such higher results were due to any special