EO inhibition condition (pH 7.15), lysozyme had the lowest net charge (7.7), but the skin had more negatively charged binding sites, which was significant for EO inhibition (Dubey and Kalia 2014). If an increase in the total current does not produce sufficient delivery to elicit the desired effect, the molecule simply might not be a good candidate for iontophoresis, as skin binding might be too important an effect in limiting drug electrotransport (Dubey and Kalia 2014).

46.2.4.2 Increasing Total Current and Current Density

The total current (and hence the charge passed) can be increased by extending the application time or augmenting current density.

Even though it might seem logical to expect the same permeation under conditions of equivalent charge, in which lower current densities are compensated by longer application times, experiments have demonstrated current density may affect the drug distribution profile (Santer et al. 2018). A recent ocular iontophoresis study using the entire eye globe *ex vivo* demonstrated at constant charge (30 mA·min/cm^2; 1.44 C), but with different application times and current densities (20 min at 1.5 mA/cm^2 and 5 min at 6 mA/cm^2), the total delivery for both conditions was statistically equivalent, but not the drug distribution in the ocular compartments, i.e., the longer treatment time of 20 minutes enabled increased drug deposition in the deep ocular tissues (Santer et al. 2018). Extrapolating these results to cutaneous drug delivery, one might assume higher current densities could be useful for epidermal targeting, avoiding systemic distribution in short-time delivery of active cosmetic ingredients. Even though there might be a linear relationship between deposited amounts and increases in current density, the total drug transported may not be directly proportional to the total current. This was observed in the delivery of conotoxin CnIIIC, cited earlier (del Rio-Sancho et al. 2017). Even though this peptide binds in the skin, generating more complex interpretations of transport mechanisms, regression analysis confirmed deposition increased linearly with the current density ($r^2 = 0.99$). Still, the total amount of peptide deposited was not directly proportional to total current, as ~30 μg/cm^2 was deposited after 15 minutes of 0.5 mA/cm^2 (0.45C), while only ~22 μg/cm^2 were deposited after 30 minutes of 0.3mA/cm^2 (0.54C) (del Rio-Sancho et al. 2017). Indeed, the equations presented to describe iontophoretic transport mechanisms relate to drug flux in steady-state conditions; these may be achieved faster under higher current densities; hence, total delivered amounts or drug distribution may vary in conditions of the same total charge (Coulombs) but different current densities and application times.

In cases where there is a linear correlation between flux and current density, increasing current density may be sufficient to increase drug delivery, attaining a complete control over input kinetics and enabling therapy individualization (Abla et al. 2005; Kalaria et al. 2012, 2014, 2018; Patel et al. 2009). Nevertheless, the tissue resistance to current flow, given by Ohm's law, limits the maximal current density applied:

$$I = \frac{V}{R} \tag{46.15}$$

where V is the potential difference measured across the tissue in volts, and R is the resistance of the tissue in Ohms. Hence, the higher the aqueous content of a tissue, the lower the resistance and the higher the tolerability towards current application, explaining why I_D of 6 mA.cm^{-2} is tolerable for the sclera (Santer et al. 2018), but not for the skin, in which the value of 0.5 mA.cm^{-2} has been considered the higher safe current density to be applied. Above this value, unwanted cutaneous effects can occur, ranging from tickling sensations to erythema and discomfort (Ledger 1992). Still, when flux increase by only altering electronic parameters is not sufficient to achieve therapeutic levels, chemical modification of the molecule may be a promising alternative.

46.2.4.3 Pro-Drug Synthesis

The pro-drug strategy has been widely used to increase drug lipophilicity (improving K_m) rendering satisfactory cutaneous passive permeation. Monoester and diester derivatives of corticosteroid