esters are routinely used to mask hydroxyl groups and so facilitate partition into the intercellular lipid matrix in the stratum corneum (e.g., triamcinolone acetonide and betamethasone dipropionate).

Conversely, the pro-drug strategy to further enhance iontophoretic delivery aims at improving a drug's ability to efficiently transport the electric current (improving t_d) and effectively migrate towards the skin (Figure 46.2). Hence, besides increasing hydrophilicity and aqueous solubility, imparting a charge to the molecule is extremely beneficial.

A cationic pro-drug of ketoprofen, the ester ketoprofen choline chloride, has been synthesized following this rationale showing five times higher flux after anodal iontophoresis than cathodal iontophoresis of ketoprofen across human epidermis skin (Lobo and Yan 2018). Also, a series of amino acid ester pro-drugs of acyclovir, an antiviral for the treatment of herpes simplex virus infections, were produced (ACV-X, where ACV = acyclovir and X = Arg, Gly, Ile, Phe, Trp, and Val) (Chen et al. 2016a). ACV has poor oil/water solubility, which limits its partitioning into the highly lipidic intercellular space in the keratinized stratum corneum. Exactly as described, the amino acid moieties are intended to improve the molecule hydrophilicity and consequently molecule t_d.

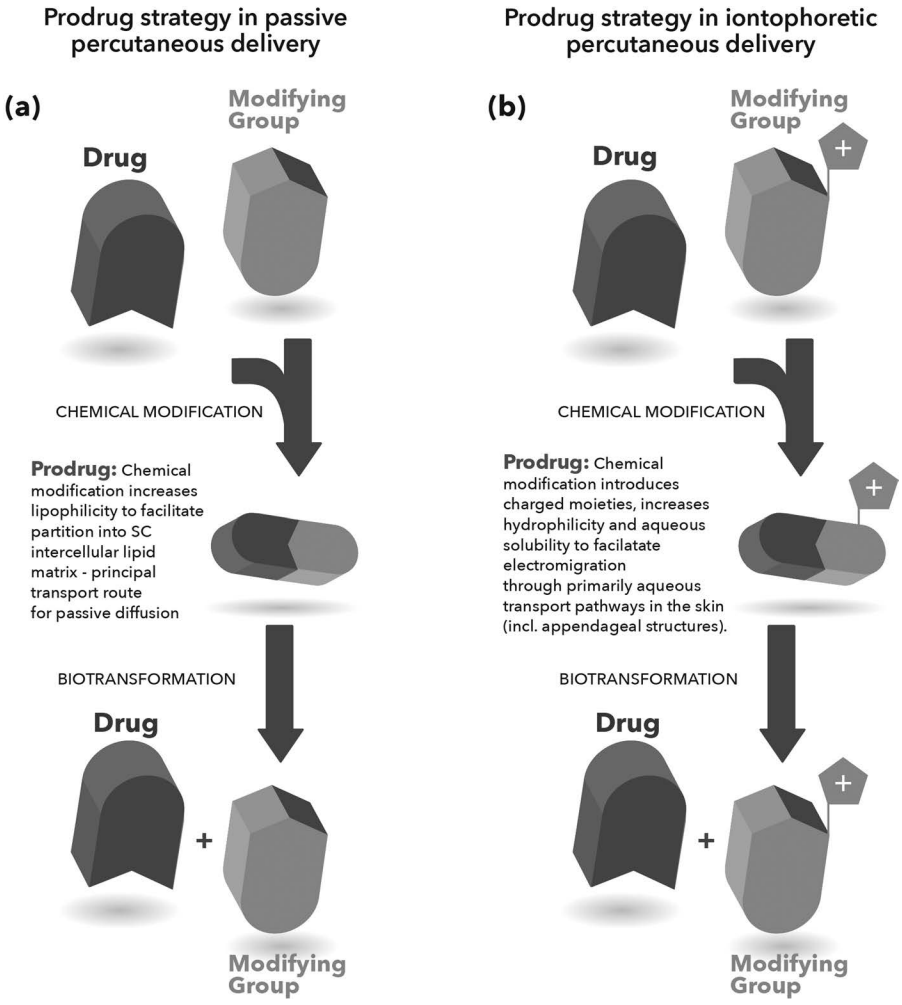

FIGURE 46.2 Schematic representations illustrating the different rationale for using pro-drugs to improve (a) passive and (b) iontophoretic transport into and across the skin. (Adapted and reproduced with permission from Chen et al. 2016a.)