194a Design Principles of Chemical Permeation Enhancers for Transdermal Drug Delivery

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Human skin is an attractive portal for administration of systemic therapeutics. This route, referred to as the transdermal drug delivery route, provides increased patient compliance, sustained delivery over extended time periods and avoids hepatic first pass metabolism. The success of this route, however, is extremely limited due to low skin permeability. Stratum corneum, the most superficial component of skin and 15 microns in thickness, is entirely responsible for this transport barrier. In the last two decades a significant emphasis in using the transdermal route has been centered on the understanding of the constitutional aspects of this enormously complex interface. This knowledge is critical to the design of vehicles or formulations of excepients that alter this membrane to facilitate the movement of active therapeutics. We report a comprehensive study of the effect of 100 chemical permeation enhancers (CPEs) on the stratum corneum. These compounds were chosen from ten different classes of chemicals that include: 1. anionic surfactants, 2. cationic surfactants, 3. zwitterionic surfactants, 4. non-ionic surfactants, 5. fatty acids, 6. fatty esters, 7. sodium salts of fatty acids, 8. alkyl amines, 9. azone like molecules and 10. others. We study the effect of these chemicals on the building blocks of the stratum corneum, namely the lipid bilayers and the keratin containing corneocytes. These effects are mapped using Fourier Transform Infrared Spectroscopy (FTIR). Based on the organizational effects introduced by these chemicals in the skin we hypothesize the pertinent mechanisms by which such chemicals or groups of chemicals alter the stratum corneum. All studied CPEs fall in two categories: ones that extract lipids from the bilayers, called extractors and ones that partition into the bilayers causing decrease in the bilayer order, called fluidizers. The extent of extraction or fluidization correlated well with the ability of the CPEs in increasing transport across the skin. The irritation associated with the CPEs correlated well with protein denaturation in the corneocyte pockets. We then identify the pertinent molecular forces that are responsible for bilayer disruption and protein denaturation. Quantitative structure activity correlations (QSARs) based on understanding of molecular forces were used to screen, in silico, newly designed CPEs. Several new fluidizers were discovered that fluidize the lipid bilayers to facilitate molecular transport without causing skin irritation. This study should contribute significantly to the understanding of chemicals used to alter the skin membrane and will aid in design of safe and potent penetration enhancers in future.