Advances in the Science of (Trans)-Dermal Drug Delivery

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The application of medicines to the skin surface serves the purpose of delivering the active ingredient into the skin (dermal delivery) or through the skin and into the systemic blood circulation (transdermal delivery). Drugs are typically applied in sufficient quantity to form a depot on the skin surface from which prolonged delivery may be achieved over a time period of several hours up to a few days. Systems for (trans)-dermal delivery include liquid formulations of rather high viscosity (semi-solids) and patches. The transport of the active ingredient from the delivery system into the tissue takes place by diffusion. In this process, the keratinized top layer of the epidermis (stratum corneum) has to be overcome which represents a formidable permeation barrier due to its unique biophysical structure. The overall drug delivery rate is controlled by the rate of release from the delivery system and/or the rate of permeation through the stratum corneum.

Cutaneous semi-solid formulations are multicomponent systems comprising two or more phases whose occurrence and structure varies depending on the percentile composition of the formulation. It is shown that release of the active ingredient is governed by its distribution between the phases of the formulation which depends on the respective physicochemical properties. When patches are employed, delivery rate is frequently regulated by polymeric membranes. The permeability of a membrane depends on its chemical structure and the solvent it entraps. It is demonstrated that imbibition into the pores of the membrane of fluid contained in the drug vehicle modulates the permeation rate across the membrane in a fashion dependent on the fluid's viscosity. These methodologies provide the possibility to design delivery systems with a predictable drug release rate.

Components of drug formulations may interact with the stratum corneum in a way that alters its permeability characteristics, thereby enhancing transport across the skin. Such permeation enhancers are used deliberately in order to achieve transport rates that are sufficiently high to guarantee the delivery of therapeutic doses of the drug. Delivery may further be hampered by enzymatic degradation of the drug in the epidermis. The enzymatic activity of the skin extents over a wide range of reactions and may also be influenced by formulation components that enter the skin.

Drug delivery through the epidermis can be further enhanced and modulated on a real time scale by the application of an electric field to the skin, a process termed iontophoresis. The achieved permeation enhancement is a function of the electric charge of the permeant, its lipophilicity/hydrophilicity balance, the inherent electric charge of the skin giving rise to electroosmotic phenomena, the difference in the behavior of the permeant between the micro-environment of the tissue and the bulk, the interaction of the permeant with the skin on the grounds of electrostatic and molecular interaction processes, and the effect of the electric field on tissue characteristics. Iontophoresis is modeled based on the Nernst-Planck and the Poisson-Boltzmann equations following appropriate adaptation. This can be shown to afford a basic understanding of the process allowing reasonable predictions about its outcome.

The therapeutic effect of drug delivered dermally depends on its free concentration reached at the site of pharmacological activity in the tissue. Knowledge of this concentration is required for assessing the bioavailability of the formulation but its estimation with sufficient accuracy and spatial resolution represents a significant challenge. A methodology is presented relying on biophysical modeling and experimental transport parameters for distinct tissue layers for estimating the drug concentration at the target site. Based on this, pharmacological effect/concentration relationships are established for dermatological diseases using different drugs, demonstrating the validity of the approach.

References

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