〈シンポジウム〉
「香粧品と経皮吸収－現在と将来」

皮膚における物質移行動態とその評価，予測

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Evaluation and Prediction of Skin Permeation Behavior of Substances

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Abstract

The ability to predict quantitatively the absorption of substances through the skin has implications in the pharmaceutical, chemical, cosmetic industries. Because all compounds are believed to permeate the skin by a passive diffusion mechanism, it is possible to apply Fick's diffusion laws to establish a mathematical model. In addition, it is necessary to consider the fundamental anatomy and physiology of the skin and relate this to the possible rate-limiting steps in the permeation process. We developed a diffusion model, where the skin is composed of two layers, *i.e.*, stratum corneum and viable layer, and the stratum corneum has parallel polar and nonpolar pathways. A numerical computation algorithm, called Fast Inversion of Laplace Transform (FILT), allows such a complicated model analysis to be conducted. In an *in vitro* skin diffusion experiment, skin permeation of drugs increased with their lipophilicity. When the skin was pretreated with an penetration enhancer, 1-geranylazacycloheptan-2-one (GACH), a bell-shaped relationship between the enhancer's effect and drug lipophilicity was observed. The skin diffusion model analysis revealed that GACH increases drug partitioning into the nonpolar pathway by letting the pathway more hydrophilic. Based on the mechanism, skin permeation of drugs and its enhancement were totally described. A prodrug/enhancer combination approach was examined. Since the diffusion model analysis revealed that GACH would be effective for drugs with intermediate lipophilicity (octanol/water partition coefficient ($PC_{oct/w}$) of～0.5), synergism in penetration enhancement by prodrug/enhancer combination would be expected by synthesizing a prodrug having the optimal $PC_{oct/w}$. In fact, GACH enhanced skin permeation of acyclovir butyrate ($PC_{oct/w}$: 0.40) much more greatly than that of native acyclovir ($PC_{oct/w}$: 0.012). Moreover, skin permeation of various acyclovir prodrugs in the presence/absence of the enhancer could be predicted by our diffusion model. The diffusion model analysis is also useful to estimate drug concentration profiles in skin. We proposed a method of estimating drug concentration in skin *in vivo*. *In vivo* absorption profile of drug was obtained by deconvoluting its urinary excretion profile after topical application with that after intraveous injection. Penetration parameters were obtained from the absorption profile using a diffusion model, and used for calculation of concentration profile in skin. This approach was applied to the analysis of topically applied acyclovir in ointment. The analysis revealed that acyclovir concentration in the skin is fairly high, although urinary excretion (or absorption) of acyclovir was low. In conclusion, a diffusion model based on the fundamental anatomy and physiology of the skin can totally describe percutaneous absorption of substances. It would be a useful tool to predict the absorption of substances based on their physicochemical properties.

Key words: percutaneous absorption, penetration enhancers, diffusion model, rational design.