J. Control. Release, **62**, 201-208 (1999)

# Simultaneous transport and metabolism of ethyl nicotinate in hairless rat skin after its topical application: the effect of enzyme distribution in skin

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*In vitro* permeation study of ethyl nicotinate (EN) was carried out using excised hairless rat skin, and simultaneous skin transport and metabolism of the drug were kinetically followed. Fairly good steady-state fluxes of EN and its metabolite nicotinic acid (NA) through the skin were obtained after a short lag time for all the concentrations of EN applied. These steady-state fluxes were not proportional to the initial donor concentration of EN: EN and NA curves were concave and convex, respectively, which suggests that metabolic saturation from EN to NA takes place in the viable skin at higher EN application. Further permeation studies of EN or NA were then carried out on full-thickness skin or stripped skin with an esterase inhibitor to measure their permeation parameters, such as partition coefficient of EN from the donor solution to the stratum corneum and diffusion coefficients of EN and NA in the stratum corneum and the viable epidermis and dermis. Separately, enzymatic parameters (Michaelis constant *Km* and maximum metabolism rate *Vmax*) were obtained from the production rate of NA from different concentrations of EN in the skin homogenate. The obtained permeation and enzymatic parameters were then introduced to differential equations showing Fick's second law of diffusion in the stratum corneum and the law with Michaelis-Menten metabolism in the viable epidermis and dermis. The calculated steady-state fluxes of EN and NA by the equations were very close to the obtained data. We then measured the esterase distribution in skin microphotographically using fluorescein-5-isothiocyanate diacetate. A

higher enzyme concentration was observed in the epidermal cells and near hair follicles than in the dermis. Simulation studies using the even and the partial enzyme distribution models suggested that no significant difference between the models was observed in the skin permeations of EN and NA, whereas concentration-distance profiles of EN to NA were very different. This finding suggests that the total amount of enzyme in skin which converts EN to NA is a determinant of the metabolic rate of EN in skin. The present approach is a useful tool for analyzing simultaneous transport and metabolism of many drugs, especially those showing Michaelis-Menten type-metabolic saturation in skin.