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Effect of *l*-Menthol-Ethanol-Water System on the Systemic Absorption of Flurbiprofen after Repeated Topical Application in Rabbits

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The effect of the *l*-menthol-ethanol-water system (MEW system), a skin penetration enhancer, on the systemic absorption of flurbiprofen (FP) after repeated topical applications was investigated. FP (1%) gel containing ethanol (25%) and *l*-menthol (3%) as penetration enhancers was applied to rabbit dorsal skin and the *in vivo* absorption rate of FP was compared with the *in vitro* penetration rate through excised skin. *In vivo* absorption rate of FP was initially high and decreased with time to a value approximately equal to the *in vitro* rate. The remaining FP in the gel 6 h after the application was 60% of the initial loading and the systemic bioavailability over the 6 h application was about 10%, suggesting that the rest (30%) had accumulated in the skin tissues. The gel was applied for 6 h on the same site or on a new site after the first 6 h-application to learn the effect of repeated applications on FP absorption. The maximum FP concentration after the second application on the virgin skin was slightly higher than that after the first application, as expected in a typical pharmacokinetic process. In contrast, the same site application induced remarkably lower plasma concentration and area under the curve (*AUC*). A drug-free gel was also utilized to evaluate the effects of the enhancer system. Pretreatment of the drug-free gel on the same site also decreased

the FP absorption, whereas post-treatment increased the plasma level of FP, in spite of the removal of the drug gel. These phenomena could be explained by ethanol in the MEW system acting a local irritant and a drug carrier.