Biol. Pharm. Bull. 25(1), 134-136 (2002)

In Vitro Skin Permeation of Morphine Hydrochloride during the Finite Application of Penetration-Enhancing System Containing Water, Ethanol and *l*-Menthol

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The effect of composition of applied solutions, containing water, ethanol (EtOH) and *l*-menthol (LM) as penetration enhancers, on the *in vitro* permeation of morphine hydrochloride (MPH) through excised hairless rat skin were examined in finite application experiments. Three of the five different applied solutions contained almost saturated LM and two contained levels of LM below the limit of solubility. Despite similar pseudo steady-state fluxes (maximum fluxes observed) of MPH from the solutions, lag time for the permeation of MPH from the saturated systems was shorter than that from the unsaturated systems. Lag times for the permeation of EtOH and LM from the saturated systems were also shorter than those from the unsaturated systems. Thermodynamic activity of LM is important for the enhancing effect against MPH permeation. At the beginning for the permeation experiment, the activity of LM in the unsaturated systems was lower than that in the saturated solutions. As the skin permeability of EtOH was higher than that of other components, the content of EtOH in the applied solution gradually decreased with time, while the activity of LM increased eventually showing a sufficient enhancing effect. Solvent drag effect was not important for the permeation of MPH, since penetration rate of MPH was independent of the time course of that of EtOH. The amount of LM migrating into skin appeared to be the most important parameter for the penetration-enhancing effect of the mixed system in the in vitro permeation of MPH through excised hairless rat skin.