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Analysis of skin disposition of flurbiprofen after topical application in hairless rats

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Cutaneous disposition of topically applied flurbiprofen (FP) was evaluated using a new *in situ* experimental model in hairless rats. A disc-shaped agar gel (3.85 cm in diameter and 0.5 cm in thickness) was subcutaneously implanted in the abdominal region of rats as a drug receptor, and a drug donor cell was subsequently placed above this agar gel. No significant pharmacokinetic modification of FP was observed as a result of this experimental procedure. A bolus injection and a constant intravenous infusion of FP were applied to the rats, followed by an analysis of FP levels in plasma and agar gels. Using these results, the clearance rate of FP from the systemic circulation to the agar gel could be calculated. FP (1% gel formulation, 1.0 g/3.14 cm^2) was then topically applied to the skin of these rats. From these experiments, the amount of FP that migrated from the formulation to the systemic circulation and the amount of FP that migrated directly to the agar gel across the skin, over 10 h, were separately evaluated to be 235.4 and 2.0 μg, respectively. Thus, most of FP was absorbed into the systemic circulation. The effect of endogeneous vasoactive compounds and penetration enhancers on the FP disposition within skin was also determined. Epinephrine and bradykinin were used as vasoactive compounds that were entrapped in agar gel, and an isopropyl myristate system (IPM system) and a *l*-menthol-ethanol-glycerin-water system (MEGW system) were used as enhancers in the formulation. Epinephrine enhanced the direct delivery of

FP into the agar gel to more than ten times its former level, in spite of the fact that it had no effect on systemic delivery. Bradykinin strengthened systemic delivery slightly, without changing the quantity of FP in the gel. IPM increased only the systemic delivery of FP, as was the case with bradykinin, whereas the MEGW system markedly increased both the blood concentration and the quantity of FP in the gel (13 and 200 times, respectively). This technique has proven to be an effective tool for the quantitative evaluation of cutaneous disposition of a topically applied drug.