Chem. Pharm. Bull., **47**, 749-754 (1999)

Skin disposition of drugs after topical application in hairless rats

Go Yanagimoto (柳本 剛), Teruaki Hayashi (林 輝朗),
Tetsuya Hasegawa (長谷川 哲也), Toshinobu Seki (関 俊暢),
Kazuhiko Juni (從二 和彦), Kenji Sugibayashi (杉林 堅次)
and Yasunori Morimoto (森本 雍憲)

Drug fraction transported from a topical formulation on skin to subcutaneous tissues or muscles is dependent on the physicochemical properties of the entrapped drug. Cutaneous disposition of model drugs, antipyrine (ANP), lidocaine (LC) and piroxicam (PXC) as well as flurbiprofen (FP) was thus evaluated in hairless rats in which an agar gel disc was subcutaneously inserted into the abdominal region as a drug receptor and a drug donor cell was placed above it. Time courses of plasma level and agar gel amount were measured after topical application of 50% ANP, 3% LC, 1% PXC and 1% FP in hydroxypropylcellulose gel. Percutaneous absorption clearance of unionized form, *CL*ab* was proportional to true octanol/water distribution coefficient and the order of FP > PXC > LC > ANP, suggesting that skin permeation of the drug was determined mainly by its distribution from the formulation to the skin barrier. PXC, however, had a relatively low flux compared to the other three drugs, probably due to its high molecular weight and melting point. Migration clearance of unionized form from systemic circulation to the subcutaneous agar gel, *CL*g* was also influenced by the lipophilicity of drugs. On the other hand, fraction from the formulation to the systemic circulation was in the order of PXC > FP > ANP > LC. This fraction was much higher than the direct migration fraction from the formulation to the subcutaneous agar gel. Factors determining for these fractions are still unclear. A drug having a low lipophilicity and a low protein bind-

ing, however, had a tendency to have a great targeting ability to the subcutaneous agar gel. In addition, most of the drug in agar gel was contributed by the direct flow from formulation, not from the systemic circulation. The present *in situ* experimental method is a useful tool to evaluate skin disposition of drugs. Detailed understanding of the skin disposition of drugs from several formulations will enable the finding of a good drug and formulation candidates.