# ABSTRACT

Acyclic nucleoside phosphonates (ANP) are broad-spectrum antivirals highly effective against herpes-, retro- and hepadnaviruses. They also exhibit cytostatic, antiparasitic, immunomodulatory activities. Their transdermal delivery offers an attractive and advantageous route of administration, but is limited due to the polar character of their phosphonate moiety.

The aim of this work was to study the possibility of both transdermal and dermal application of a series of 2,6-diaminopurine derivatives including (*R*)-PMPDAP and (*S*)-PMPDAP, (*S*)-HPMPDAP, (*S*)-8-azaHPMPDAP, cyclic (*S*)-HPMPDAP and lysolipid prodrugs, i.e., hexadecyloxypropyl (HDP) esters of (*R*)-HDP-PMPDAP and (*S*)-HDP-HPMPDAP. Ability of ANP to penetrate trough the skin by themselves is generally very low. For this reason the influence of permeation enhancer dodecylester of 6-(dimethylamino)hexanoic acid (DDAK) through and into human skin was investigated. The evaluation was performed *in vitro* by using Franz diffusion cells and human skin.

The results of this work confirm that ANP (60 mM in 60 % propylene glycol) delivery through the skin is very low (flux 0.53-1.40 nmol/cm$^2$/h), except for the lysolipid prodrugs (*R*)-HDP-PMPDAP and (*S*)-HDP-HPMPDAP), which were not detected in the acceptor phase at all. 1 % DDAK enhanced transdermal flux of ANP through skin approximately 16-31 times. However, it did not have any influence on the flux of the lysolipid prodrugs (*R*)-HDP-PMPDAP and (*S*)-HDP-HPMPDAP. There was no statistically significant difference between (*R*)-PMPDAP and (*S*)-PMPDAP isomers.

Concerning the topical aplication, maximal skin concentrations reached mM values in the stratum corneum. Epidermal and dermal concentrations reached values of ten up to hundred μM. Also in the case of topical administration, DDAK increased the concentration of drugs in epidermis up to 5.5 times. HDP esters reached relatively high concentrations both in epidermis and dermis.

By a combination of highly effective antiviral compounds with synthetic permeation enhancer DDAK, desirable drug concentrations in the systemic circulation can be successfully obtained by transdermal delivery. On the other hand, usage of lysolipid prodrugs can be advantageous for the topical administration of antivirals, because it leads to their skin accumulation without systemic absorption.