Abstract

Permeation enhancers are compounds that promote drug flux into systemic circulation or adjacent tissues. This doctoral thesis follows our previous results and aims at studying two different groups of potential permeation enhancers: dicarboxylic acid derivatives and analogues of Transkarbam 12. The main purpose of my work was to study the structure-activity relationships in these permeation enhancers and to contribute to the elucidatation of their mechanism of action.

The first part of my work was focused on derivatives of dicarboxylic acids. Series of enhancers based on maleic, fumaric, succinic, tartaric and *meso*-tartaric acids were prepared. The enhancing activity of these compounds was investigated *in vitro* in Franz diffusion cells using theophylline as a model drug and porcine skin. The single-chain amphiphiles were markedly more effective than the double-chain ones. The most active enhancer, monododecyl maleate, that is a *cis*- derivative, was a more potent enhancer than its respective *trans*- isomer. Furthermore, the activity of similar succinates, i.e. compounds having a single bond, strongly depended on the donor vehicle. No difference between diastereoisomeric tartaric and *meso*-tartaric acid derivatives was found.

The second part of my work dealt with Transkarbam 12, an ammonium carbamate formed by the reaction of dodecyl 6-aminohexanoate with carbon dioxide, which is a highly active, broad-spectrum, nontoxic, and nonirritant transdermal permeation enhancer. First, a series of Transkarbam 12 isomers was prepared. It was found that their activity highly depends on the position of the ester group. Furthermore, we hypothesized that trankarbams probably act by a dual mechanism: a part of their activity is associated with the carbamic acid salt and/or its decomposition in the acidic stratum corneum releasing carbon dioxide. Surprisingly, the ammonium esters thereby released are active enhancers as well and contribute to the overall activity of trankarbams. Furthermore, pH-dependent effects of Transkarbam 12 were described, which were in agreement with the above hypothesis. The effects of this enhancer on the permeation of two different drugs and on the skin electrical impedance suggested that Transkarbam 12 influences more drug penetration pathways through the stratum corneum. These findings will be used in a more rational design of novel transdermal permeation enhancers.