SUMMARY

One of the subjects studied in the Department of Inorganic and Organic Chemistry of the Faculty of Pharmacy focuses on the synthesis and biological evaluation of potential transdermal permeation enhancers. Over the past few years, series of esters of 6-aminohexanoic acid of high enhancing activity and their analogues have been prepared. Presently, the structure-activity relationships are being studied. This work contributes to this problem by searching for the mechanism of action of one of the most active compounds, transkarbam 12 (T12).

Transdermal permeation enhancers facilitate drug absorption through the skin. Generally, their mechanisms of action include the disturbance of highly ordered structure of stratum corneum, promotion of drug solubility in the vehicle or enhancing the partitioning of drug from the vehicle into stratum corneum. Nevertheless, the exact mechanism is usually unclear.

T12 is a carbamic acid salt derived from two molecules of 6-aminohexanoic acid dodecyl ester. In slightly acidic environment (as in stratum corneum, its target place) it decomposes easily releasing a molecule of CO_2 and free amino ester. To find out whether this ability contributes to its high activity, a series of T12 analogues with CO_2 covalently bound in the polar head was prepared (esters of carbonic, carbamic and oxalic acid). Their enhancing activities were negligible when compared to that of T12.

Another series of T12 analogues with symmetrical terminal methyl or ethyl branching was synthesized with the purpose to improve the enhancing activity. But the introduction of methyl branching didn't change the activity, furthermore, ethyl branching increased it slightly. Thus we hypothesize that terminal branching probably decreased the ability of enhancer to incorporate into the stratum corneum lipids.

The ability of T12 to release CO_2 in slightly acidic environment was studied by two different methods. The IR spectroscopy of the mixture of T12 with palmitic acid or with lipids extracted from stratum corneum (they contain ca 10 % of fatty acids) enabled us to describe the proposed interaction leading to T12 decomposition and CO_2 release. Thermogravimetric analysis of similar mixture proved that slightly acidic environment leads to faster T12 decomposition in comparison with the decomposition caused only by elevated temperature.

The theory about specific mechanism of action of T12 was supported also by the fact that this enhancer didn't influence the model drug solubility neither its partitioning into stratum corneum.

Finally, we can conclude that the mechanism of action of T12 arises from the exceptional structure of its polar head formed by carbamic acid salt and from the ability of such structure to decompose in slightly acidic environment releasing a molecule of CO_2. The decomposition very probably leads to the conformational changes in T12 molecule. Such changes together with the released CO_2 disturb the highly ordered lipid structure in stratum corneum and thus facilitate the drug absorption through the skin. The mechanism of action of such type hasn't been described before.