

## Abstract

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### Synthesis and evaluation of transdermal permeation enhancers based on terpenes

Transdermal drug delivery has many advantages over the conventional routes of administration. It could make a treatment of some diseases more acceptable for patients. Other advantage is a possibility of easy interruption of treatment in case of problems. And profit comes also from the fact that the drug doesn't pass through the gastro-intestinal tract, so it avoids the first-pass effect and doesn't irritate this tract, too.

But majority of drugs cannot cross the skin in sufficient amounts. To enable permeation of more drugs through the human skin, substances called transdermal permeation enhancers are used among others, some natural terpenes and amino acid derivatives such as dodecylester of 6-(dimethylamino)hexanoic acid (DDAK) are potent permeation enhancers (1) (2).

The purpose of my work was to combine these potent enhancers and prepare esters of 6-(dimethylamino)hexanoic acid with selected terpenes (menthol, citronellol, linalool, farnesol and borneol) and determine their permeation-enhancing activity *in vitro* using two model drugs (theophylline and hydrocortisone), human skin and Franz diffusion cell.

DDAK was able to increase skin flux of theophylline and hydrocortisone 23 and 37 times, respectively; their concentration in the skin was up to 5 times higher. In case of theophylline, citronellyl ester and farnesol reached similar activities but none of the newly prepared enhancers was better than DDAK. On the other hand, when using more lipophilic hydrocortisone as a model drug, bornyl and citronellyl esters were better enhancers than DDAK, reaching enhancement ratio values of 70 and 66, respectively.

In conclusion, we identified new highly potent permeation enhancers using a combination of amino acid derivatives and terpenic alcohols. In particular, citronellyl 6-(dimethylamino)hexanoate is a promising enhancer that warrants further study.

1. Williams A. C, and Barry B. W., Penetration enhancers. *Adv. Drug Deliv. Rev.* 2004, 56, 5, 603-618
2. Novotný J., Kovaříková P., Novotný M., Janůšová B., Hrabálek A., Vávrová K.. Dimethylamino acid esters as biodegradable and reversible transdermal permeation enhancers: Effects of linking chain length, chirality and polyfluorination. *Pharm. Res.* 2009, 26, 4, 811-821