

Abstract

Ondřej Kučera

Charles University in Prague, Faculty of Pharmacy in Hradec Králové

Synthesis and study of 6-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)hexanoic acid derivatives as transdermal permeation enhancers

Transdermal permeation enhancers are used to increase absorption of drugs through skin or, more importantly, through the stratum corneum, which is the uppermost layer of the skin. Mechanism of action of enhancers is not fully understood. In general the most active enhancers consist of hydrophilic and hydrophobic parts. In this work, we prepared and studied fluorescent permeation enhancers. Fluorescent dye NBD (7-nitrobenzo[c][1,2,5]oxadiazol) is fairly hydrophilic, so we used it as a hydrophilic head of potential enhancers based on dodecyl 6-(dimethylamino)hexanoate (DDAK). Such fluorescent enhancers could help us understand more about the mechanism of action. It enables determination of this enhancer and imaging of its penetration pathways in the skin.

We synthesized three esters of 6-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)-hexanoic acid (NBD-acid) with ester-linked C8-C12 alkyls. 6-Aminocaproic acid reacted with 4-chloro-NBD and then with a series of alcohols to give us different lengths of alkyl chains. We applied these enhancers to human skin in Franz diffusion cells using two model drugs, theophylline and hydrocortisone, in two different media. We measured the concentrations of the drugs and also the enhancers beneath the skin in time to yield the flux values as well as concentrations in the skin after the test.

We found that the drug permeation was two to six times higher (depending on drug and donor medium) in the presence of 1% ester enhancers in comparison with control (only drug without the NBD-enhancer) and 1% NBD-acid. Significant enhancer concentrations were found in epidermis and dermis and we also observed, considering the amount of NBD-acid in skin samples treated with NBD esters, significant ester hydrolysis in the skin.