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Interaction of phloretin and 6-ketocholestanol with DPPC-liposomes as phospholipid model membranes

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Abstract

Phloretin and 6-ketocholestanol are penetration enhancers for percutaneous delivery of certain topically applied drugs. In the present study some physicochemical experiments have been performed to elucidate the mechanism of action of phloretin and 6-ketocholestanol. The penetration enhancing effect of phloretin and 6-ketocholestanol is believed to be due to their increase of the fluidity of the intercellular lipid bilayers of the stratum corneum. Phospholipid vesicles were chosen as a simple model to represent these bilayers. The effect of phloretin and 6-ketocholestanol on phase transition temperature and enthalpy was studied using differential scanning calorimetry. Beside of that the size of liposomes was monitored when the amount of penetration enhancer in the liposome preparation was changed. Addition of increasing amounts of phloretin and 6-ketocholestanol to the bilayer resulted in lowering of phase transition temperatures and increasing the enthalpy. Additionally the size of the liposomes was increased when penetration enhancer was added. The results suggest that phloretin as well as 6-ketocholestanol would interact with stratum corneum lipids in a similar manner, both reduce the diffusional resistance of the stratum corneum to drugs with balanced hydrophilic–lipophilic characteristics.

Keywords: Phloretin; 6-ketocholestanol; DPPC; Liposomes; DSC

1. Introduction

In the last years, the role of the stratum corneum in the barrier function of the skin has been thoroughly investigated (Moore et al., 1988; Wertz and Downing, 1989; Barry, 2001; Hadgraft, 2001). Two major routes of drug penetration through the human stratum

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corneum have been proposed: the transcellular and the intercellular pathways (Michaels et al., 1975; Elias, 1983; Barry, 1987). For most drugs, the major barrier effect of the stratum corneum has been attributed to the intercellular lipids, mainly to their nature and to their ordered multilayers (Madison et al., 1987; Williams and Elias, 1987; Wertz and Downing, 1989). Consequently, in order to extend the variety of drugs that might be administered via the skin and also to increase the local activity of topically applied drugs, considerable attention has been focused on the mechanism of action of skin penetration enhancers (Stoughton, 1982; Aungst et al., 1986; Barry, 1987; Beastall et al., 1988; Walters, 1989).

Most of the penetration enhancers have been proved to interact in some way with the stratum corneum lipid structure, generally by increasing the fluidity of the intercellular lipid bilayers (Barry, 1988). In recent studies two new penetration enhancers have been proposed. It could be shown that 6-ketocholestanol enhanced the flux of bacitracin, sodium fluorescein and 5-ALA (Cladera et al., 2003; Auner et al., 2003a, 2003b, 2004a) and it could be demonstrated that phloretin enhanced the permeation of lidocaine and progesterone (Auner and Valenta, 2004b; Valenta et al., 2001).

The aim of the present study was, to show interactions of phloretin and 6-ketocholestanol with multilamellar vesicles (MLV or liposomes) of dipalmitoylphosphatidylcholine (DPPC), concerning the phase transition temperature as well as the enthalpy. Since thermodynamic parameters for the gel-to-liquid crystalline phase transition of liposomes are best obtained by DSC, the effect of phloretin and 6-ketocholestanol on the thermodynamic properties of MLV was investigated using this technique. Besides that additional size measurements of liposomes was performed. The stability of the vesicles was checked employing a microreaction calorimeter.

2. Materials and methods

2.1. Materials

1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) was purchased from Lipoid (Switzerland).

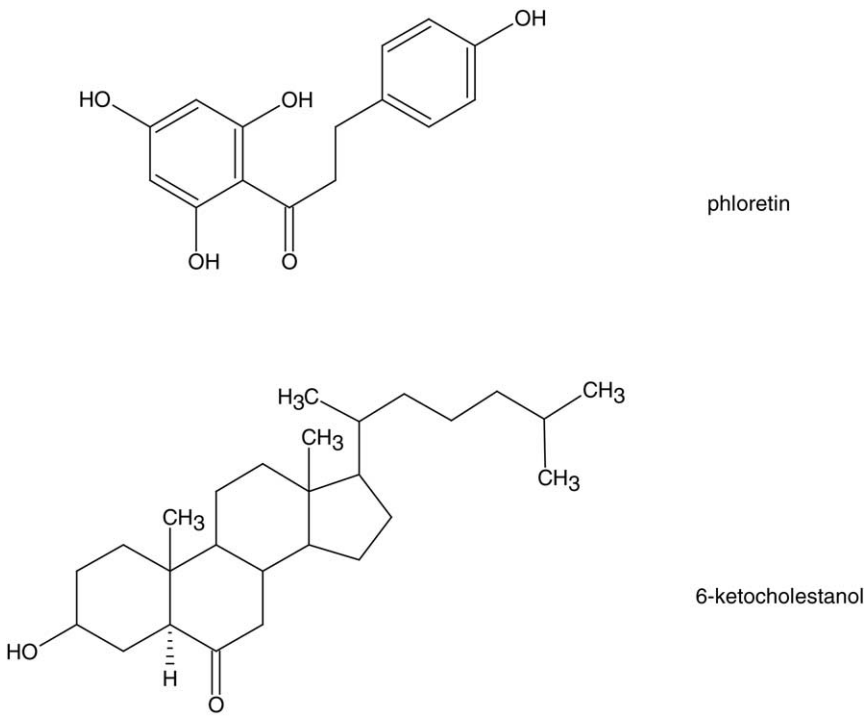

Fig. 1. Chemical structure of phloretin and 6-ketocholestanol.