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The effect of urea and taurine as hydrophilic penetration enhancers on *stratum corneum* lipid models

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Abstract:
To optimize transdermal application of drugs, the barrier function of the skin, especially the *stratum corneum* (SC), needs to be reduced reversibly. For this purpose, penetration enhancers like urea or taurine are applied. Until now, it is unclear if this penetration enhancement is caused by an interaction with the SC lipid matrix or related to effects within the corneocytes. Therefore, the effects of both hydrophilic enhancers on SC models with different dimensionality, ranging from monolayers to multilayers, have been investigated in this study. Many sophisticated methods were applied to ascertain the mode of action of both substances on a molecular scale. The experiments reveal that there is no specific interaction when 10 % urea or 5 % taurine solutions are added to the SC model systems. No additional water uptake in the head group region and no decrease of the lipid chain packing density have been observed. Consequently, we suppose that the penetration enhancing effect of both substances might be based on the introduction of large amounts of water into the corneocytes, caused by the enormous water binding capacity of urea and a resulting osmotic pressure in case of taurine.

Keywords:
stratum corneum lipids; model membrane; transdermal drug delivery; penetration enhancer; mode of action

1 Introduction

The *stratum corneum* (SC) is the outermost layer of the human skin and mainly responsible for the strong barrier function against physical, microbiological and chemical influences. This barrier function is based on the structure of the SC, composed of corneocytes which are embedded in a lipid matrix, according to the "brick and mortar" model [1]. Here, the dead corneocytes represent the bricks, whereas the highly ordered multilamellar lipid matrix is described as mortar containing ceramides (CER), free fatty acids (FFA) and cholesterol (CHOL) in a nearly equimolar ratio [2-7]. Both, extremely hydrophilic and lipophilic drugs are not able to overcome the SC, resulting in a very low bioavailability. However, from a pharmaceutical point of view, the transdermal drug application has many advantages, since it enables a reduction of side effects, a circumvention of the first pass effect and the possibility for a controlled release [8]. Consequently, to achieve reasonable bioavailability, hydrophilic or lipophilic penetration enhancers, which reduce the skin barrier function by a reversible decrease of the SC lipid order, are used. Hydrophilic penetration enhancers are thought to interact with the lipid head group region by loosening the hydrogen bonds. As a result, the distance between the molecules in one layer as well as between adjacent bilayers increases, facilitating the penetration potential for hydrophilic drugs [9]. The change in the packing density in one layer may also influence the lipid chain region, causing a penetration enhancement for lipophilic drugs [10, 11]. However, these mechanisms are not completely understood on a molecular scale.

Urea and taurine, for example, are such hydrophilic penetration enhancers. As one of the most abundant endogenous free amino acids in mammals, taurine exhibits a variety of functions [12]. Specifically, in the skin, taurine stimulates the synthesis of SC lipids, prevents surfactant induced transepidermal water loss [13] and acts as osmoregulator in human keratinocytes [14]. To realize this osmoregulation function, in keratinocytes, a special taurine transporter (TAUT) is expressed, which is mainly localized in the *stratum granulosum* and to some extend in the *stratum spinosum* [15]. Thus, the highest concentrations of taurine are also found in these skin layers, as well as in the dermis [16, 17]. However, penetration studies of a taurine formulation into excised human skin showed significant higher taurine amounts in all skin layers, compared to the natural taurine concentration [16]. This additional taurine amount in the SC could either be located in the corneocytes or in the lipid matrix between the lipid head groups. Since in the corneocytes, there is no special taurine carrier expressed anymore, the small and hydrophilic taurine molecule might be able to interact with the lipid head groups in the SC lipid matrix and hence, act as a penetration enhancer. The penetration enhancing potential of taurine has already been used in oral mucosal drug delivery systems [18], but until now, has not been investigated with respect to the SC. However, many patents indicate the penetration enhancing function of taurine and its hydratizing effect on the skin [19-21].

As opposed to taurine, urea has been investigated extensively in terms of its effect on the SC. A study with human volunteers revealed an important regulatory function of urea in the epidermal permeability barrier [22]. In addition, there are several studies, proving the penetration enhancing effect of urea for different drugs to treat skin diseases like psoriasis and neurodermatitis, summarized in [23]. In this regard, different ways of interaction are postulated. The penetration enhancing potential of urea in the SC is thought to be predominantly related to its high water binding capacity combined with the keratolytic properties and the formation of hydrophilic diffusion channels within the barrier [24]. The ability of urea to bind large amounts of water, has been proved in several studies [25, 26]. Confocal Raman microspectroscopy studies showed, that within the SC, this excess of water causes lens shaped water inclusions, which are larger than fully hydrated corneocytes and have spectral properties similar to bulk water [27]. Beyond that, due to the presence of large amounts of water, the hydrophilic head group regions of the lipid matrix, especially the water layer between adjacent bilayers, might be affected as well [28]. Performing DSC studies on human SC, Barry *et al.* stated an increased