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International Journal of Pharmaceutics 297 (2005) 204–212
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Skin permeation enhancement by sucrose esters: A pH-dependent phenomenon

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Received 11 March 2005; received in revised form 29 March 2005; accepted 30 March 2005

Abstract

The purpose of the present study was to evaluate the effect of sucrose esters (particularly, sucrose laureate and sucrose oleate in Transcutol®) on the percutaneous penetration of a charged molecule as a function of ionization. We have investigated the influence of these sucrose esters on the in vitro diffusion profiles of lidocaine hydrochloride, a weak ionizable base ($pK_a = 7.9$), at different pH values, using porcine ear skin as the barrier membrane. As expected, lidocaine flux in the absence of an enhancer, increased from pH 5 to 9 with a corrresponding increase in the level of the unionized base. However, when skin was pretreated with 2% laureate in Transcutol (2% L-TC), drug permeation was higher at pH 5.0 and 7.0 than at 9.0. A different trend was observed in experiments with 2% oleate in Transcutol (2% O-TC), where skin flux was maximal at a more basic pH, when the degree of ionization is low. The results suggest that sucrose laureate enhances the penetration of the ionized form of the drug (12-fold greater flux relative to control), whereas sucrose oleate is more effective in promoting permeation of the unionized species. The structural properties of the sucrose esters as well as the degree of ionization of the drug are important characteristics affecting the transdermal flux of lidocaine.

Keywords: Lidocaine hydrochloride; Sucrose esters; Enhancer; Percutaneous absorption

1. Introduction

In the last few decades, a variety of chemicals with skin permeation enhancing properties have been investigated for use in topical and transdermal systems (Walters, 1989; Walters and Hadgraft, 1993; Hsieh, 1994; Ganem-Quintanar et al., 1998a). Although these compounds have been the subject of numerous studies (Suhonen et al., 1999), the relationship between enhancer structure and the effect induced in the membrane have yet to be fully understood.

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doi:10.1016/j.ijpharm.2005.03.020

Among known permeation enhancers, non-ionic surfactants have clearly been shown to influence the percutaneous absorption rate of many drugs (Sarpotdar and Zatz, 1986; Walters et al., 1988; Bialik et al., 1993; Thevenin et al., 1996). These compounds commonly act by altering the ordered structure of the intercellular region of the stratum corneum (Suhonen et al., 1999; Andega et al., 2001; Moser et al., 2001; Williams and Barry, 2004). However, differences in functional groups, hydrocarbon chain length and degree and position of unsaturation, can all influence the efficacy of these enhancers. For example, it is generally accepted that saturated C_{18} fatty acid compounds (e.g., stearic acid) are ineffective as absorption enhancers. Nevertheless, numerous reports agree on the disrupting effect of oleic acid, a monounsaturated C_{18} fatty acid, particularly on the stratum corneum lipid domain (Green et al., 1988; Potts et al., 1991; Aungst, 1995; Naik et al., 1995).

Moreover, the enhancing efficacy of a surfactant is not only dependent on its structure, but also on the physicochemical properties of the drug, the nature of the vehicle and whether the enhancer is used alone or in combination. Numerous drugs are weak organic electrolytes, the ionization of which depends on the delivery medium pH. Consideration of this pH, as well as of the drug dissociation constant (pK_a), allow some degree of absorption to be predicted. Katayama et al. (2001), demonstrated that the penetration enhancement of acidic drugs by 1-menthol–ethanol systems varied depending on the pH. In this case, the pH-dependency of the skin permeation enhancement was affected by the lipophilicity and the pK_a of the permeant. In addition, the nature of the vehicle may also play an important role in the surfactant–skin interaction. Recent studies have shown that diethylene glycol monoethyl ether (Transcutol®), a powerful solubilizing agent, increased significantly the percutaneous penetration of several drugs, particularly if used in combination with suitable surfactants (Watkinson et al., 1991; Touitou et al., 1994; Ganem-Quintanar et al., 1997). The presence of a cosolvent promotes the absorption of the surfactant into the skin, favouring its interaction with the stratum corneum (SC) lipids. Furthermore, it has also been reported that the addition of a cosolvent may lead to a change in the solubility of a solute, altering its thermodynamic activity and consequently the skin/vehicle partition coefficient (Mura et al., 2000).

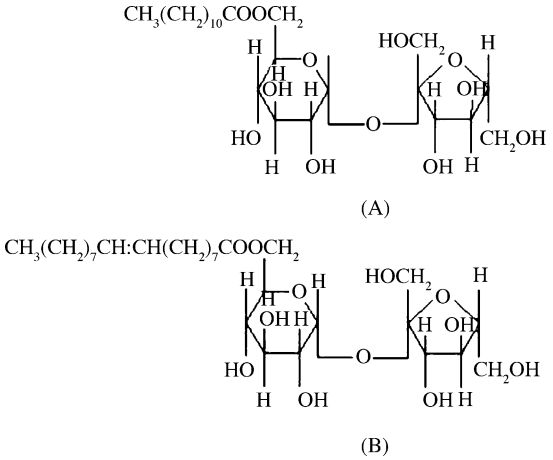

Fig. 1. Chemical structure of (A) sucrose laureate and (B) sucrose oleate.

Among non-ionic surfactants, sucrose fatty acid esters (SE) have been shown to temporarily alter membrane barrier properties. Previous studies (Ganem-Quintanar et al., 1998b) have shown that pretreatment with sucrose laureate enhances lidocaine permeation through porcine buccal mucosa. Although these compounds show many advantages as penetration enhancers (e.g., biodegradability and lack of toxicity), very few studies examining their mode of action have been reported. Ayala-Bravo et al. (2003), in an in vivo human study using infrared spectroscopy, demonstrated that sucrose oleate and sucrose laureate (Fig. 1) act on the SC lipids by fluidizing and extracting intercellular lipids. Furthermore, the authors found that SE were effective when combined with Transcutol, and importantly, that they lost their effectiveness above the critical micellar concentration. The present work investigates the effect of sucrose esters (laureate and oleate) in combination with Transcutol, on the permeation of lidocaine (a weak base) as a function of vehicle pH.

2. Materials and methods

Lidocaine hydrochloride was purchased from J.T. Baker (Phillipsburg, USA). Sucrose laureate (Ryoto Sugar Ester® L-1695) and sucrose oleate (Ryoto Sugar Ester® O-1570) were generously donated by Mitsubishi-Kasei Food Corporation (Tokio, Japan); butanol and glacial acetic acid were obtained from Merck