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Research Paper

Ionic liquids as potential enhancers for transdermal drug delivery

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ABSTRACT

The aim of this study was to verify the effect of several cyclic onium based ionic liquids (ILs), including mono- and dicationic derivatives of 1,4-diazabicyclo[2.2.2]octane (DABCO), a dialkyl morpholinium salt and a Brønsted acidic IL, as enhancers of the in vitro transdermal permeation and skin retention of diltiazem through and into hairless rat skin. The drug was used as both the hydrochloride salt (DZHCl) and the free base (DZB) to highlight the relationship between the enhancement effect and the physico-chemical characteristics of the active agent. Permeation tests were carried out using Gummer-type diffusion cells and excised rat skin with a 0.005 M aqueous solution of diltiazem hydrochloride or diltiazem free base with and without the addition of 1% w/w ionic liquids. At the end of the permeation experiments with diltiazem hydrochloride, a suitable extraction procedure allowed for the determination of the drug content retained in the skin. Depending on the ionic liquid structure, a significant enhancement in diltiazem hydrochloride levels in the receiving phase was observed, and the transdermal permeation of the diltiazem free base was markedly increased by treatment with all of the ionic liquids. *N*-dodecyldabco bromide was the best enhancer for both salified and free base drug forms, even though it showed a certain toxicity. On the other hand, *N*-methyl-*N*-decylmorpholinium bromide showed a good balance between enhancer activity and cytotoxicity.

1. INTRODUCTION

Transdermal drug delivery systems have been accepted as potential non-invasive routes of drug administration, with the advantages of avoiding first-pass metabolism, sustained therapeutic action and better patient compliance. However, their prevalent use is restricted because of the excellent impervious nature of skin. The outermost layer of the epidermis, the stratum corneum (SC), provides an outstanding barrier to the absorption of chemicals, related to the unique hierarchical structure made up of multiple lipid bilayers and embedded corneocytes. Many approaches have been used to perturb the skin barrier and enhance drug transdermal delivery, including physical disruption (thermal, magnetic, pressure, laser or mechanical modulation, hydration, iontophoresis, phonophoresis, microneedles, skin abrasion and puncture), chemical disruption (permeation or penetration enhancers and prodrug design) and combinations of these methods (Biradar and Sanghavi, 2014; Moghadam et al., 2013). In particular, chemical permeation enhancers act by increasing drug cutaneous permeation through the following: 1) the alteration of SC structure and fluidity; 2) the enhancement of the solubility characteristics of the skin for the drug to be delivered (increase in the partition coefficient of the drug into the skin as well as drug diffusivity in the SC); 3) the creation of disorder among the alkyl chains of SC lipids; and 4) the localized separation of lipid domains to create hydrophilic pores and/or establish a drug reservoir in the SC itself.

Another current trend is the development of structured vehicles acting as carriers through the skin, such as liposomes, niosomes, transfersomes, microemulsions, and solid lipid nanoparticles (Carafa et al., 2009; Bseiso et al., 2015).

In the past decade, to facilitate the passage of molecules through the SC, transdermal permeation enhancers have been extensively studied, and more than 360 chemicals have been demonstrated to enhance skin permeability, including terpenes,

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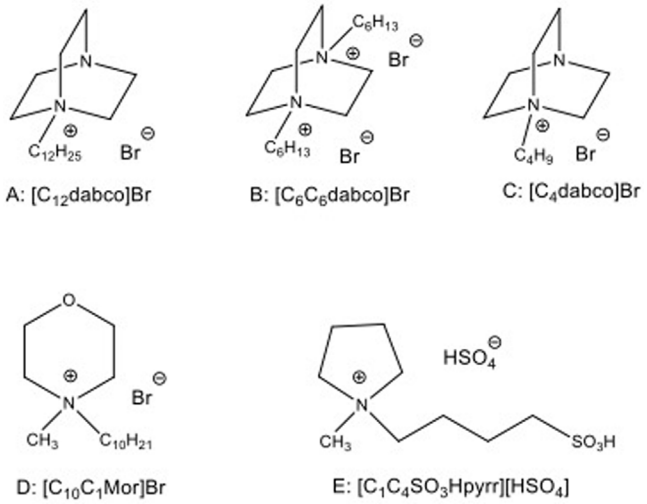
sulphoxides, pyrrolidones, fatty acid and alcohol, surfactants, urea, etc. (Chen et al., 2014). However, despite these findings, only a few products are currently used in the market because of incompatibilities in the formulation or local irritation. Therefore, the exploration of chemicals to safely improve the skin permeability remains an intensive research area.

Here, we report the use of ionic liquids (ILs) as enhancers of drug delivery into and across the skin. Briefly, ionic liquids are organic salts, generally composed of a large and asymmetric organic cation and an organic or inorganic anion, that are liquid at or near room temperature. They have some peculiar properties, such as a negligible vapour pressure, the ability to dissolve organic, inorganic and polymeric materials and a high thermal stability. Due to these properties, ionic liquids have largely been successfully used as "green" alternatives to volatile organic solvents for a wide range of applications. As designer solvents, they can be synthesized for particular applications or with specific chemical and physical properties by simply changing the anion/cation combination or introducing specific functional groups on the cation or anion.

Recently, ionic liquids have gained interest for use in several pharmaceutical applications, although the unknown toxicity profile of many ionic liquids has for a long time hindered their employment in this context, where the tightly regulated active pharmaceutical ingredient manufacturing practices often discourage the use of new solvents, additives and procedures (Smiglak et al., 2014). Ionic liquids have thus been employed for the solubilization of poorly soluble drugs (Jaitely et al., 2008; Mizuuchi et al., 2008; Moniruzzaman et al., 2010a) and to synthesize active pharmaceutical ingredients with modified solubility, increased thermal stability and enhanced efficacy compared to their starting materials (Bica et al., 2010; Hough and Rogers, 2007; Hough et al., 2007). Furthermore, ionic liquids exhibiting antimicrobial activity have been proposed as active pharmaceutical ingredients or formulation preservatives (Pernak et al., 2003). However, because of their physico-chemical and biological properties, they can also be used as additives in formulations for topical drug delivery. Only a few studies have been published regarding the use of ionic liquids in such a specific field, and many of the studies are related to the use of ionic liquids as oil or water substitutes or, more simply, as additives in microemulsions (Moniruzzaman et al., 2010b). Nonetheless, recently, Zakrewsky et al. (2014) have studied the influence of several ionic liquids (including imidazolium, phosphonium, pyrrolidinium and choline based salts, often having long chains on anions) on the transdermal delivery of mannitol and cefadroxil (model drugs), emphasizing some of the beneficial properties, such as enhancer effects, solubilizing abilities, irritating effects and antibacterial activity.

In the present study, we focused our attention on several cyclic onium based ionic liquids, including the mono- and dicationic derivatives of 1,4-diazabicyclo[2.2.2]octane (DABCO), a dialkyl morpholinium salt and a Brønsted acidic ionic liquid. In particular, we have evaluated the influence of the following ionic liquids on drug penetration: *N*-dodecyldabco bromide, A, [C_{12}dabco]Br; *N,N*-dihexyldabco bromide, B, [C_6C_6dabco]Br; *N*-butyldabco bromide, C, [C_4dabco]Br; *N*-methyl-*N*-decylmorpholinium bromide, D, [C_1C_{10}mor]Br; (*N*-methyl-*N*-(4-butylsulfonic acid) pyrrolidinium hydrogensulfate, E, [$C_1C_4SO_3$Hpyrr][HSO_4].



These compounds have been selected based on their surfactant properties derived from the presence of a sufficiently long alkyl chain on the cation, the generally low environmental impact of onium salts and the diffuse use of the DABCO base on pharma applications (Pashirova et al., 2015).

The purpose of this study was, therefore, to verify the effect of these ionic liquids as enhancers of the in vitro transdermal permeation and skin retention of diltiazem, a drug used as a model, through and into hairless rat skin. The drug was used as both the hydrochloride salt and the free base to highlight the relationship between the enhancement effect and the physico-chemical characteristics of the active agent (partition coefficient, water solubility, etc.). The choice of this drug was rational; diltiazem, a calcium channel blocker, is widely used in the management of angina pectoris and hypertension. Because of its short biological half-life (3.5 h), low oral bioavailability (40%), and hepatic metabolism leading to high-frequency drug dosing, the continuous delivery of the drug is required. Therefore, the development of a transdermal drug delivery system containing diltiazem with appropriate enhancers should be of great interest (Limpongsa and Umprayn, 2008).

2. Materials and Methods

Diltiazem hydrochloride (DZHCl) and sodium dodecyl sulfate were supplied by Sigma-Aldrich, Milan, Italy. Diltiazem free base (DZB) was obtained by treating an aqueous solution of diltiazem hydrochloride with an alkalinized (NaOH) solution, adjusted to a pH 9.5. The precipitate was collected, washed and dried under a vacuum. A white amorphous powder of the diltiazem free base was obtained.

DABCO, *N*-methylmorpholine and *N*-methylpyrrolidine were purchased from Sigma-Aldrich and used without further purification, as well as bromobutane, bromohexane, bromodecane, bromododecane and 1,4-butane sultone. DABCO and morpholinium-based bromides were synthesized by the Menschutkin reaction of 1,4-diazabicyclo[2.2.2]octane with the appropriate alkyl bromide, as previously reported (Chiappe et al., 2009; Pretti et al., 2011). The SO_3H-functional Brønsted acidic IL was prepared by stirring methylpyrrolidine with an equimolar amount of 1,4-butane sultone, under solventless conditions, following a previously reported protocol (Wu et al., 2007).

All other chemicals and solvents were analytical grade.