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Effect of lactic acid and iontophoresis on drug permeation across rabbit ear skin

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Abstract

The aim of this paper was to explore the efficacy of lactic acid as permeation enhancer for drug molecules across the skin. Three model permeants were chosen: acetaminophen (non-ionized), buspirone hydrochloride (cationic drug) and ibuprofen lysine (anionic drug). We also explored the association of lactic acid and iontophoresis as a means of enhancing drug delivery. Permeation experiments were performed in vitro, using rabbit ear skin as barrier. The results obtained indicate that lactic acid has some effects on model drug permeation across the skin. The effect was more evident with the anionic drug ibuprofen. Cathodal intophoresis increased ibuprofen transport, but when lactic acid was associated with cathodal iontophoresis, a concentration-dependent reduction of ibuprofen iontophoretic flux was observed, probably for the competition by the co-ion. The application of electric current (anodal iontophoresis) to a solution of acetaminophen produced an increase in its transport, due to the presence of an electroosmotic contribution; however, the effect of the association of anodal iontophoresis and lactic acid produced no further enhancement.

Keywords: Transdermal; Permeation enhancer; Iontophoresis; Permeability; Skin

1. Introduction

Drug penetration enhancement across the skin is a key issue for the development of a transdermal drug delivery system, because the excellent barrier properties of the skin can reduce the applicability of this administration route. Several approaches have been attempted, such as the use of chemical enhancers and of physical techniques. The use of chemical penetration enhancers has been recently reviewed by Williams and Barry (2004). The authors underline the difficulty to select rationally a penetration enhancer for a specific permeant.

Among physical techniques, iontophoresis, i.e. the application of an external electric field to enhance drug transport across the skin, although efficient primarily

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for ionized molecules, can also be useful for non-ionized molecules (Naik et al., 2000). In fact, one of the transport mechanisms, electroosmosis, is a convective solvent flow, which transports all solutes present, regardless of their charge (Pikal, 1992; Delgado-Charro and Guy, 1994).

A combined approach can also be used. Ethanol (Srinivasan et al., 1990), fatty acids (Oh et al., 1998; Valjakka-Kostla et al., 2000; Nicoli et al., 2001; Wang et al., 2003; Smyth et al., 2002), benzalkonium chloride (Costa et al., 1997; Fang et al., 1998), therpenes (Bhatia and Singh, 1998b) and Azone® (Meidan et al., 2003) have been successfully associated with iontophoresis. The use of iontophoresis together with a chemical enhancer can also produce a synergic effect. The main drawback is that skin irritation can be increased as well. Additionally, due to the different individual response to the enhancer, the overall variability of the effect can be augmented.

Lactic acid belongs to the class of α-hydroxy acids, widely used in cosmetic products as exfoliants, moisturizers and emollients. The specific action of α-hydroxy acids on the skin is not completely known. It has been suggested that α-hydroxy acids can reduce stratum corneum corneocyte cohesion by interference with ionic bonding (Kraeling and Bronaugh, 1999). Given this mechanism of action, lactic acid could be effective in increasing the permeation of drugs across the skin. Kraeling and Bronaugh (1997) showed that the permeability of the skin to tritiated water was increased by a factor of 2 after treatment with glycolic acid. Nakamura et al. (1996) used a combination of lactic acid, ethanol and isopropyl myristate to enhance the permeation across the skin of ketotifen fumarate, although the effect of each enhancer was not determined individually.

We explore in this paper the efficacy of lactic acid as permeation enhancer for drug molecules across the skin. Three model permeants were chosen: acetaminophen (non-ionized), buspirone hydrochloride (cationic drug) and ibuprofen lysine (anionic drug). We also explored the association of lactic acid and iontophoresis as a means of enhancing drug delivery. Rabbit ear skin was used as barrier, since it has been shown to be a reasonable model for human skin in vitro (Hirvonen et al., 1991; Nicoli et al., 2003; Blanco et al., 2003; Artusi et al., 2004).

2. Materials and methods

2.1. Materials

Ibuprofen lysine was a gift from Lisapharma S.p.A. (Erba, I). For HPLC solvent preparation, distilled water and HPLC grade acetonitrile were employed. L-Lactic acid 85 % w/v was used. Acetaminophen and buspirone were obtained from ACEF (Fiorenzuola D'Arda, I) and Sigma (Sigma Chemical, St. Louis, MO, USA), respectively.

2.2. Drug analysis

2.2.1. Acetaminophen

Acetaminophen analysis was performed by HPLC (Perkin-Elmer, Norwalk, USA), using a Waters C18 Novapack® 150 mm × 3.9 mm column (Millipore Corporation, Milford, MA) and a mobile phase composed of 10 mM sodium acetate (pH 4):acetonitrile 60:40 (v:v), at 1 ml/min. UV detection at 254 nm was employed.

2.2.2. Buspirone

Buspirone analysis was performed by HPLC (Perkin-Elmer, Norwalk, USA), using a Waters C18 Novapack® 150 mm × 3.9 mm column (Millipore Corporation, Milford, MA) and a mobile phase composed of phosphate buffer (pH 7.5):acetonitrile 60:40 (v:v), at 1 ml/min. The column was thermostated at 25 °C. The UV detector was set at 235 nm.

2.2.3. Ibuprofen

The quantitative determination of ibuprofen permeating across the skin was performed by HPLC analytical assay according to Santi et al. (2003), using a Shimadsu instrument (isocratic pump LC-10AS, UV–vis detector SPD-10A, integrator C-R6A Chromatopac, Shimadsu, Kyoto, J) and a Waters C18 Novapack® 150 mm × 3.9 mm column (Millipore Corporation, Milford, MA, USA). The mobile phase consisted of acetonitrile (50% in volume) and 100 mM dipotassium phosphate brought to pH 5 with phosphoric acid, pumped at 1 ml/min. The UV detector was set at 225 nm.

2.3. Skin sample preparation

Rabbit skin was excised post-sacrifice from the inner part of rabbit ears (6 months old) obtained from a local