

Enhancement of Skin Penetration of Nonsteroidal Anti-Inflammatory Drugs from Extemporaneously Compounded Topical-Gel Formulations

Abstract

Ketoprofen and ibuprofen topical gels were compounded with decylmethyl sulfoxide and the terpenes d-limonene, (-)-menthone, terpinen-4-ol, and α -terpineol as penetration enhancers. Transdermal penetration profiles for both ketoprofen and ibuprofen were determined using full-thickness human skin, modified Franz diffusion cells and an isotonic (pH 7.4) phosphate buffer solution. Human skin was used in these experiments to approximate the therapeutic use of these gels. Ibuprofen was found to have superior transdermal kinetics when compared to ketoprofen. Ibuprofen is a smaller and more lipophilic molecule than ketoprofen, which gives it better penetration properties. All enhancers tested significantly increased the penetration (except (-)-menthone) and skin retention (except terpinen-4-ol) of ketoprofen. None of the enhancers tested significantly increased the penetration or retention of ibuprofen. Despite the lack of enhancer activity, ibuprofen still demonstrated higher skin penetration and retention than enhanced delivery of ketoprofen. The results of these studies suggest that the addition of penetration enhancers can significantly increase the amount of ketoprofen penetration, while enhancers demonstrated no significant increase (and can actually decrease) the amount of ibuprofen penetrating into and through the skin.

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The main barrier to drug penetration through the skin is its topmost layer, the stratum corneum. The stratum corneum consists of protein-filled cells surrounded by lipid lamellar sheets in a brick and mortar wall-like configuration. Several methods have been employed to decrease the barrier function of the skin. One popular approach has been the use of transdermal penetration enhancers. These agents are chemical compounds that reversibly alter the barrier function of the skin and allow an increased rate of percutaneous permeation of coadministered drugs. Many effective enhancers have not yet been adopted commercially due to concerns regarding their systemic and localized toxicity. The use of natural products as enhancers may avoid some of these problems.

Terpenes are constituents of essential oils that are the volatile and fragrant substances found mainly in flowers, fruits and the leaves of plants. They consist of highly lipophilic isoprene (C₅H₈) units. These compounds have previously been used as flavorings, perfumes and medicines and the Food and Drug Administration (FDA) has given them the Generally Recognized as Safe designation. Recently these compounds have been shown to be effective enhancers for a number of hydrophilic and lipophilic drugs, including diclofenac sodium, ketoprofen and indomethacin.

The objectives of this study were: (1) to determine the transdermal penetration properties of ketoprofen and ibuprofen from topical-gel formulations, (2) to determine the enhancement activity of decyl methyl sulfoxide on transdermal penetration of those drugs, and (3) to determine the transdermal penetration of ketoprofen and ibuprofen from a series of terpene-enhanced formulations. Terpenes were chosen from the chemical classes of hydrocarbons (d-limonene and (-)-menthone) and alcohols (α -terpineol and terpinen-4-ol)

Introduction

Ketoprofen and ibuprofen, both nonsteroidal anti-inflammatory drugs, have been administered orally for the acute and long-term management of pain and inflammation. However, their short elimination half-lives and other adverse effects, such as abdominal pain and ulceration of the gastrointestinal (GI) tract, restrict the oral use of these drugs. To overcome these disadvantages, ketoprofen and ibuprofen have been administered topically to treat a variety of conditions, including arthritis, burns, ankle sprains and other soft-tissue injuries.

Transdermal drug delivery possesses several advantages over more traditional methods. These include: (1) avoidance of first-pass metabolism and variable rates of adsorption inherent with oral administration; (2) continuous, noninvasive infusion of drugs having short half-lives; (3) avoidance of the risks and the inconvenience associated with parenteral treatment; and (4) elimination of the GI irritation resulting from pharmaceutically active and inactive ingredients. Unfortunately, only a few drugs possess the physicochemical properties necessary for delivery in quantities required for successful systemic therapy.

Materials and Methods

Materials

Full-thickness human skin was obtained from patients undergoing voluntary abdominal-reduction surgeries at University Hospital, Albuquerque; NM. Skin samples were anonymous except for the age, race and gender of the donor. Ketoprofen (Aldrich, Milwaukee, WI); ibuprofen (Aldrich); hydroxypropylcellulose (Aldrich); 70% unscented isopropyl alcohol (Spectrum Chemical); propylene glycol (JT Baker, Phillipsburg, NJ); decylmethyl sulfoxide (Aldrich); d-limonene, menthone, terpinen-4-ol, and α -terpineol (Sigma, Milwaukee, WI); acetonitrile (JT Baker); methanol (JT Baker); 36% w/w formaldehyde (JT Baker); polyoxyethylene 20 cetyl ether (Aldrich); and sodium phosphate monobasic (JT Baker) were used as received.

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