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Research paper

Effect of chemical penetration enhancer on transdermal iontophoretic delivery of diclofenac sodium under constant voltage

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ABSTRACT

The study aimed to enhance the transdermal permeation of diclofenac sodium using combined strategy of constant voltage iontophoresis (CVI) and chemical penetration enhancers (CPE). Four hydrogels of diclofenac sodium were formulated with the key CPE and hydroxyethyl cellulose (HEC) as a viscosity imparting agent. In vitro permeation studies of the hydrogels indicated CVI significantly increased (ANOVA, $P < 0.05$) the steady state flux of diclofenac sodium through the porcine skin in the order geraniol (F1) > l-menthol (F2) > thymol (F3) > SLS-urea (F4) compared to the Fc (Passive control) under the applied voltage. F1 was identified as the lead formulation as an overall increase in steady state flux of 5.157 fold compared to Fc was observed at 1.5V. Pharmacokinetic studies in rats indicated that CVI at 1.5V following application of the lead formulation increased the Cmax and AUC0-8h by ~3.5 folds compared to passive treatment. The higher systemic levels of diclofenac are likely to enhance the drug concentration in synovial fluid which is the site of action in most musculoskeletal disorders. The results of the study indicate that CVI can effectively deliver therapeutic amounts of diclofenac sodium transdermally to relieve chronic deep-seated muscular pain in several rheumatic disorders.

1. Introduction

People worldwide are known to suffer from the pain and disability due to rheumatic musculoskeletal disorders. Musculoskeletal disorders contribute to 3.4% and 1.7% of the total global disease burden in the developed and developing countries [1]. However, the burden of the disease in the developing countries is about 2.5 times higher than that in the developed countries. The currently available therapeutic option to treat musculoskeletal disorders involves oral or parenteral administration of steroidal or non steroidal anti-inflammatory drugs (NSAID's). NSAID's provide symptomatic relief from pain, allow quicker recovery and return to normal activity [2]. Diclofenac sodium is a NSAID used in the management of pain associated with various musculoskeletal disorders [3]. The drug is known to relieve the pain by interfering with the prostaglandin synthesis by inhibiting both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes [4]. However, diclofenac is known to undergo extensive first pass metabolism limiting the oral bioavailability to 50–60%. Therefore, the drug demands frequent oral administration at a dose of 150 mg a day in three divided doses [3]. Due to the non-selective COX inhibition and the frequent dosing, oral diclofenac has been associated with severe gastrointestinal side effects including gastrointestinal perforations, ulcers and bleeding that can often limit its long-term use. Dyspepsia owing to the gastrointestinal side effects is the major cause of discontinuation of oral therapy in sensitive patients. Though topical therapy is known to overcome the gastrointestinal adverse effects of oral NSAID's the penetration of therapeutic amounts of drug into underlying inflamed tissues such as muscle, tendon sheath, synovium and synovial fluids of superficial joints has been a big challenge [5]. Therefore, the currently available topical products are only used as an adjunct in moderate to serve conditions. Considering the limitations of topical products, transdermal patches of diclofenac have been developed and marketed at present. The passive transdermal patches are designed to deliver diclofenac to systemic circulation and exert the effect at sites distant from the site of application. These patches are known to obviate the first pass metabolism frequently encountered with oral diclofenac and thereby reduce the dose by improving the bioavailability. Moreover, transdermal patches result in significantly lower systemic exposure thus reducing the

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dose-dependent side effects associated with oral administration. Thus, passive transdermal patches often result in improved patient compliance and adherence, which could be an added advantage in patients who cannot take oral diclofenac. Despite the innumerable advantages, the conventional transdermal patches are likely to be less efficacious owing to the poor permeation of the diclofenac sodium through the stratum corneum that acts as a major barrier for the transport of ionic permeants. The poor permeation of diclofenac sodium can be attributed to the fact that the drug from these patches can only passively diffuse across the stratum corneum to reach the blood stream and the underlying muscles. Considering the limitations of passive transdermal patches, the current work aims to assess the feasibility of constant voltage iontophoresis (CVI) to enhance the transdermal permeation of diclofenac sodium. Iontophoresis is an electrically mediated technique that facilitates the transport of ions through the stratum corneum under the applied voltage or current by electrorepulsion and electroosmosis. Electrorepulsion enhances the permeation of the charged ions through the skin using an electrode bearing a similar charge while electroosmosis involves the bulk transport of the solvent along with the ions. Iontophoresis has been found to be more effective compared to passive diffusion to deliver charged therapeutic agents to subdermal tissues [5]. CVI has been used in the past to assist the transdermal delivery of salmon calcitonin [6], Azidothymidine [7], Leuprolide diacetate [8] and iron pyrophosphate [9]. However, most of the reports involved mechanistic studies that were less focused to investigate the synergistic action of the chemical penetration enhancers and CVI. Considering the limited work undertaken in the proposed area, an effort has been made to elucidate the synergistic effect of CVI and chemical enhancers on the transdermal permeation of diclofenac sodium in order to enable a more patient compliant home drug therapy. The combination strategy is likely to reduce the side effects associated with high concentrations of enhancers or by high current densities. By virtue of the higher efficacy, the combination strategy allows milder and more patient compliant transdermal administration of diclofenac in a tailored manner.

2. Materials and methods

2.1. Materials

Diclofenac sodium was purchased from Yarrow chemicals, Mumbai, India, Hydroxyethyl cellulose (Natrosol 250 M) was kindly donated by Ashland Chemicals Ltd, Mumbai, India. Geraniol, Levomenthol (*l*-menthol), thymol, delta-carrageenan and Parafilm® were purchased from Sigma–Aldrich, Bangalore, India. Sodium lauryl sulphate (SLS), urea, mono-sodium phosphate, di-sodium hydrogen orthophosphate, citric acid, sodium hydroxide, sodium chloride, polyethylene glycol-400 (PEG-400), orthophosphoric acid, hydrochloric acid, methanol, and n-hexane were bought from S.D. Fine Chemicals, Mumbai, India. Vitamin-E polyethylene glycol 1000 succinate (TPGS) was procured from VB Medicare Pvt. Ltd, Hosur, India while sodium hyaluronate (Naturmoist HA) was a generous sample of Naturganic Chemicals Pvt. Ltd, Bangalore, India. Deionised water having a resistivity of 18 MΩ-cm was used to prepare all the aqueous solutions and buffers.

2.1.1. Animals

The *in vivo* experimental protocol was approved by institutional animal ethical committee No-06/SAK/HNSK/01/2013, dated 31st August 2013. Male wistar rats were used for pharmacokinetic studies. The animals weighing around 200–250 g were housed in polypropylene cages (4–6 animals per cage) with adequate arrangement for water and feed. About one week time was allowed for acclimatization of animals before the studies were initiated. Prior to start of the experiments, animals were fasted overnight.

2.2. Partition coefficient

The partition coefficient of diclofenac sodium was determined in phosphate buffer saline (PBS) of pH 7.40 and n-octanol system following the method reported earlier [10]. About 20 mg of diclofenac sodium was dissolved in 10 ml of PBS to obtain aqueous solution having a concentration of 2 mg/ml. About 10 ml of n-octanol was added to equal volume of this aqueous solution in a separating funnel and was allowed to equilibrate for 24 h at room temperature with intermittent shaking. Following equilibration, the aqueous phase was separated from the organic phase by centrifugation at 2000 rpm for 10 min in a laboratory centrifuge (R4C, Remi instruments, Mumbai, India). The concentration of drug in aqueous phase was determined by suitably diluting and measuring the absorbance at 276 nm in a UV-Spectrophotometer (UV 1800, Shimadzu Corporation, Kyoto, Japan). The partition coefficient was determined using the Equation (1) after calculating the differential amount of diclofenac sodium that would have got distributed in the organic phase [11].

$$\log P = \log \frac{C_O}{C_{PBS}} \quad (1)$$

Where C_O = Concentration in organic phase and C_{PBS} = Concentration in PBS.

2.3. Preparation of skin

Porcine ears of freshly slaughtered pig were obtained from the local abattoir and the whole skin was carefully separated from the underlying cartilage using a stainless steel scalpel. The fat underlying the subcutaneous layer was carefully removed using a pair of scissors. Finally the full thickness skin was washed under the running tap water, stored in a refrigerator and used within 2 days [12]. The average thickness of the skin after clearing the subcutaneous layer was found to be approximately 0.50 mm.

2.4. Preparation of electrodes

Silver–silver chloride electrodes were used for all the iontophoresis trials taking into account their stability and reversibility [13]. Silver wires having a diameter of 0.8 mm were immersed in 0.1 M hydrochloric acid and the other ends were connected to the either terminals of direct current source from a single channel constant power supply (PSU 2510/Lab, digital display, current: 0–10 mA, voltage: 0–25 V, Ultra pure scientific, Mumbai, India). A grey layer of silver chloride was gradually deposited on the anode after 6 h. This silver electrode coated with silver chloride used as a cathode in all the iontophoresis trials.

2.5. Iontophoretic screening of potential chemical penetration enhancers

Penetration enhancers like 40% w/v of transcutol-P [14], 40% w/v of ethanol [15], 20% of PEG-400 [16], 20% w/v of TPGS [17], 5% w/v of SLS [18], 10% w/v of urea [19], 2% w/v of sodium hyaluronate [20], 5% w/v of terpenes such as geraniol, *l*-menthol and thymol [18] were screened to assess their ability to improve the iontophoretic transport of diclofenac across porcine ear skin used as a barrier.

A definite weighed amount of diclofenac sodium and appropriate amount of enhancer as indicated above was dissolved and diluted to volume with PBS, to obtain an aqueous solution having a drug concentration of 2 mg/ml. However, in solutions containing