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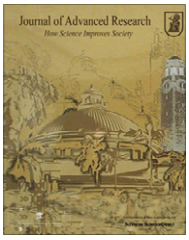

ORIGINAL ARTICLE

In vitro transdermal permeation of fenoterol hydrobromide

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KEYWORDS

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Abstract The aim of this study was to determine if transdermal penetration of fenoterol, a β-agonist drug, could be enhanced and controlled by formulation modification and formulation of transdermal patches. Pre-formulation studies were performed to determine the feasibility of a transdermal dosage form of fenoterol. Penetration of fenoterol was determined using the hairless guinea pig skin with unjacketed Franz diffusion cell. Transdermal patches were formulated using drug in-adhesive technique. Several enhancers were investigated for fenoterol skin penetration. Transcutol–oleic acid co-solvent gives the highest drug flux among all tested liquid formulations. Pretreatment of the skin with oleic acid 2 h before patch application significantly increases drug diffusion. *Cis*-oleic acid gives best results compared to oleic acid. Azone derivative (1-dodecyl-2-pyrrolidinone) gives the highest drug diffusion amongst all tested enhancers. Results of this study show the feasibility of using fenoterol formulated in transdermal delivery system in the treatment of chronic asthma to improve patient compliance, bioavailability and reduce the inter-subject variability.

Introduction

The transdermal route of administration has been recognized as one of the highly potential routes. It has the advantages of obviating drug metabolism or chemical degradation in the gastrointestinal tract as well as the hepatic first-pass effect [1,2]. Transdermal delivery has the potential for highly prolonged and controlled drug delivery. In many cases, delivery can be interrupted when it is desired [3].

On the other hand, the main limitation of transdermal delivery of drugs is that the skin layers provide a great resistance to the penetrant molecules. To overcome these limitations, different strategies have been developed to minimize the skin's barrier function, such as employing appropriate components, skin enhancer [4] or applying electricity or ultrasound [5] to facilitate the penetration of drugs.

Fenoterol is a selective β_2-adrenoreceptor agonist with effect on smooth and skeletal muscles, which include bronchodilation, relaxation of the uterus. It is structurally related to orciprenaline and terbutaline but is more selective

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than the parent drug for β_2-receptors. It has a longer duration of action than isoprenaline and has a less side effect on the heart rate [6]. A transdermal dosage form (TDD) of fenoterol may be quite useful in the treatment of chronic asthma and the reversible element of airway obstruction commonly found in chronic obstruction airways disease (COAD).

The development of a transdermal dosage form for fenoterol can be based on its pharmacokinetic properties, i.e. the short half-life and incomplete absorption from the gastrointestinal tract due to its first pass metabolism. Only 14% and 9% of fenoterol were absorbed after nasal and pulmonary administration, respectively [7].

A 2.5 mg oral dose provides bronchodilatation for about 6 h which may not be sufficient to prevent nocturnal wheezing. A sustained release fenoterol microsphere was formulated by Lin et al. [8].

In the light above, the objective of this paper was to develop a transdermal formulation for the delivery of fenoterol.

Experimental

Materials

Fenoterol, *cis*-oleic acid and dimethyl sulphoxide (DMSO) were purchased from Sigma (St. Louis, Mo, USA). Transcutol® (Gattefoss, St. Priest, France). Propylene glycol was obtained from Fisher scientific (Fair Lawn, NJ, USA). Polyethylene glycol 300 NF was provided by Union Carbide Chemicals (Danbury, CT, USA). (R)-(+)-limonene, (R)-(−)-carvone, cineole, α-pinene and 1-dodecyl-2-pyrrolidinone were purchased from Aldrich chemical company (Milwaukee, WI, USA). Duro-Tak® 87-2074 was purchased from National Starch and Chemical Company (Bridgewater, NJ, USA). Scotchpak® polyester multilam film 1006 with 2.84 mm thickness and Scotchpak® 1022 release liner with 3 mm thickness from 3 M (St. Paul, MN, USA).

Animal models

Male hairless Guinea pig 8–10-week-old of 400 g weight obtained from Charles River laboratories (MA, USA). The study protocol was reviewed and approved by the Institutional Animal care and use Committee IACUC (University of Rhode Island, Kingston, RI, USA).

High performance liquid chromatography

A water liquid chromatography (Waters associates, Milford, MA, USA) was equipped with an automated gradient sampler controller, model 717 plus auto sampler, model 515 HPLC pump, model 480 LC spectrophotometer and model 746 data module integrator. The column used was supelcosil LC-18-DB (5 μm, 4.6 × 250 mm) and the mobile phase consisted of 0.01 M potassium dihydrogen phosphate adjusted to pH 6.5 and methanol (30:70). The absorbance wavelength was set to 231 nm.

Determination of fenoterol saturated solubility in different solvents or co-solvents systems

The saturated solubility of fenoterol in a variety of solvents viz. water, transcutol, polyethylene glycol 300 (PEG 300), propylene glycol (PG), dimethyl sulfoxide (DMSO), dimethyl isosorbide (DMI), ethyl acetate and oleic acid was determined in triplicate at room temperature of 25 °C. In addition, fenoterol solubility was determined in co-solvents viz. 90% propylene glycol in isotonic phosphate buffer (pH 7.4), 10% PG in isotonic phosphate buffer (pH 7.4), dimethyl isosorbide/transcutol (1:1) ratio and oleic acid/transcutol (1:1) ratio. An excess amount of fenoterol was suspended in different media in tightly closed screw cap vials equilibrated in a rotating bottle for 24 h. Then, an aliquot of the suspensions was transferred to a 1-ml microcentrifuge filter, fitted with a 0.22 μm nylon filter (Corning Incorporated, Corning, NY, USA), and centrifuged. The filtrates were appropriately diluted with methanol before assaying by HPLC.

Preparation of different fenoterol liquid systems

Different fenoterol liquid systems were prepared by dissolving or suspending 40 mg/ml of fenoterol in different solvents such as polyethylene glycol 300, propylene glycol, transcutol, a mixture of 90% v/v and 10% v/v of propylene glycol in isotonic phosphate buffer of pH 7.4 or in co-solvent systems formed from transcutol/dimethyl isosorbide (1:1) and transcutol/oleic acid of the same ratio.

Physicochemical investigation of the interaction

DSC analysis was carried out on pure substances (fenoterol and Duro-Tak® adhesive) and their physical mixtures. Thermograms were performed using a Perkin Elmer DSC7 system equipped with a computerized data station. All samples (5 mg) were weighed and heated at scanning rate of 10 °C/min between 30 and 300 °C. The measurements were performed in triplicate.

Preparation of fenoterol patches with different drug concentration

Prototype patches were prepared by using a lab hand coater. The calculated amount of fenoterol was weighed and dispersed in oleic acid. The drug/oleic acid dispersion was then mixed with Duro-Tak® containing 28% total solids as a selected adhesive in a ratio of 1:9 inside a screw-cap bottle having a hole at the center of the cap. Samples with different drug concentrations 2%, 5%, 9% and 12% (w/w) were mixed with stirrer (Cole Parmer instrument Co., Chicago, IL) equipped with an appropriate size propeller at 100 rpm for 1 h. Following drug mixing the drug/adhesive solutions were casted using a lab-hand coater adjusted at clearance of 500 μm onto a Scotchpak® 1022 release liner (3M, St. Paul, MN), left overnight and then, cured at 65 °C for half an hour, then the laminate was covered with a heat seable Scotchpak® packing polyester film 1006 (3M, St. Paul, MN) and kept in the dark at room temperature until use. In all the above prepared patches 10% (v/v) oleic acid in Duro-Tak® adhesive was used.