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Investigating the potential of essential oils as penetration enhancer for transdermal losartan delivery: Effectiveness and mechanism of action

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ABSTRACT

The effect of tea tree oil (TTO), cumin oil (CO), rose oil (RO) and aloe vera oil (AVO) on the skin permeation of losartan potassium (LP) was investigated. *In vitro* skin permeation studies were carried out using rat skin. The mechanism of skin permeation enhancement of LP by essential oils treatment was evaluated by FTIR, DSC, activation energy measurement and histopathological examination. Both concurrent ethanol/enhancer treatment and neat enhancer pretreatment of rat SC with all the oils produced significance increase in the LP flux over the control. The effectiveness of the oils as the penetration enhancers was found to be in the following descending order: AVO > RO > CO > TTO. However, only AVO was the only enhancer to provide target flux required to deliver the therapeutic transdermal dose of LP. FTIR and DSC spectra of the enhancer treated SC indicated that TTO, CO, RO and AVO increased the LP permeation by extraction of SC lipids. The results of thermodynamic studies and histopathological examination of AVO treated SC suggested additional mechanisms for AVO facilitated permeation i.e. transient reduction in barrier resistance of SC and intracellular transport by dekeratinization of corneocytes which may be attributed to the presence of triglycerides as constituents of AVO. It is feasible to deliver therapeutically effective dose of LP via transdermal route using AVO as penetration enhancer.

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1. Introduction

Hypertension is the most common cardiovascular disease worldwide; hypertension is cited as the leading cause of non-communicable disease mortality worldwide. It is a progressive disorder, which if not effectively managed results in a greatly increased probability of coronary thrombosis, strokes and renal failure. Moreover, it requires long-term treatment that may result in poor patient compliance with conventional dosage forms due to greater frequency of drug administration [1]. These findings suggest that despite the availability of a plethora of therapeutically effective antihypertensive molecules, inadequate patient welfare is observed; this arguably presents an opportunity to deliver antihypertensive agents through a different route. Skin is a complex organ that serves to protect the living organisms from chemical, physical, and biological intrusion. In an average adult it covers an area of about 1.73 m^2 and receives one third of circulating blood through the body at any given time. Thus, it presents an excellent opportunity for systemic delivery of active pharmaceutical ingredients [2].

Transdermal delivery of drugs promises many advantages over oral or intravenous administration, though human skin provides an effective barrier to the permeation of most drugs in the form of stratum corneum (SC) [3,4]. Success of the transdermal route depends on the ability of drugs to breach this barrier and permeate the skin at a rate sufficient to attain effective plasma concentration. There are many approaches were employed to enhance the skin permeation rate of active moieties. However, the most convenient and widely implemented approach is the use of chemical penetration enhancers [5,6] such as DMSO, DMF, azone, ionic surfactants, but their use are also associated with unpleasant and toxic side effects. In recent years there has been a search for natural compounds as permeation enhancers to improve drug permeation that also exhibit low toxicity while maintaining their enhancing activity.

The natural absorption promoters documented so far include essential oils, terpenes, terpenoids, fatty acid esters, fatty acid glycols, and herbal extracts. The essential oils are nontoxic, non-allergic, and compatible with drug and excipients have received much attention of researchers and found one of the promising groups of candidates to be employed as clinically acceptable penetration enhancers. Essential oils present a large range of chemically acceptable and relatively safe penetration enhancers to aid percutaneous drug delivery and are considered as GRAS (generally regarded as safe) compounds for medicinal use. They have been reported to use for permeation enhancement of both hydrophilic and lipophilic drugs. They cause no skin toxicity or if any, only mild irritation [7].

Very recently, Patil and Saraogi, reviewed the details of different natural products including essential oils as potential permeation enhancer for transdermal delivery of various actives [8]. Antecedently, the feasibility of natural oils viz. corn (maize) oil, groundnut oil and jojoba oil as penetration enhancer was reported for enhanced transdermal olanzapine delivery [9]. The author claimed that the magnitude of flux enhancement factor with corn oil, groundnut oil and jojoba oil was 7.06, 5.31 and 1.9 respectively at 5 mg/ml concentration in solvent system. Amongst the oil used, corn oil containing unsaturated fatty acids was found to be promising natural permeation enhancer for transdermal delivery of olanzapine with greatest cumulative amount of drug permeated (1010.68 $\mu g/cm^2/h$) up to 24 h and caused no skin irritation. In this quest, the present work was carried out to monitor the effect of commonly used essential oils namely, tea tree oil (TTO), cumin oil (CO), rose oil (RO) and aloe vera oil (AVO) on skin permeation of losartan potassium (LP) and to elucidate the mechanism of skin permeation enhancement.

The interactions of penetration enhancers with SC lipids and proteins (mechanism of permeation) can be elucidated with instrumental methods such as Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). FTIR provides the information about the molecular and conformational changes of lipids and proteins, whereas the DSC provides the information about their thermotropic behavior [10]. FTIR and DSC techniques were used to investigate the mechanism of LP permeation in presence of test enhancers.

Briefly, LP (Biopharmaceutics classification system class 3 drug) is an orally active angiotensin II receptor antagonist indicated for the treatment of hypertension. The normal daily dose of LP is 50 mg and in case of severity 100 mg dose is given. The drug possesses extensive hepatic first pass metabolism (67%) and short biological half-life (2 h) [11,12]. Therefore, LP bypass hepatic first pass metabolism, hence its dose can be reduced in transdermal formulation significantly. All these properties, such as extensive hepatic first pass metabolism (67%), short biological half-life (2 h), low dose (25–50 mg), low oral bioavailability (33%), log P = 4.5, and low molecular weight (461.01 Da), make it suitable for transdermal drug delivery system [13–16]. In the present study, TTO, CO, and RO were selected as essential oils and these were compared with AVO as penetration enhancers to promote the percutaneous absorption of LP.

2. Materials and methods

2.1. Materials

LP was received as gratis sample from Ranbaxy Research Laboratories Ltd, Gurgaon, India. All the investigated oils namely tea tree oil (TTO), cumin oil (CO), rose oil (RO) and aloe vera oil (AVO) were purchased from authentic source (Sigma–Aldrich Chemicals Private Limited New Delhi, India). Sodium chloride, Sodium Hydroxide, ethanol, Potassium sulfate, Sodium azide and Sodium bromide were purchased from S.D. Fine chemicals, India. Potassium dihydrogen orthophosphate were purchased from Merck India Ltd. India. High-performance liquid chromatography (HPLC) grade acetonitrile and methanol were purchased from Spectrochem Pvt Ltd, Mumbai, India. All other chemicals used were of reagent grade. All materials were used as received. Double distilled water was used for all experiments.

2.2. Animals

Wistar rats (200–250 g) were supplied by Central Animal House of Hamdard University and inhabited under standard

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