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Original Research Article

Temperature influencing permeation pattern of alfuzosin: An investigation using DoE

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ABSTRACT

Background and objective: There has been relatively little investigation of the effect of temperature on skin permeation compared to other methods of penetration enhancement. A principal physicochemical factor which controls the passive diffusion of a solute from a vehicle into the skin arises from the skin temperature. The aim of this ex vivo study was to probe into the effect of heat on transdermal absorption of alfuzosin hydrochloride from ethyl cellulose-polyvinyl pyrrolidone (EC-PVP) based transdermal systems.

Materials and methods: Principles of design of experiment (DoE) were used to systematically study the influence of temperature on transdermal permeation of alfuzosin. Ex vivo transdermal permeation studies were carried out at varied donor compartment temperatures. Permeation data analysis was carried out and activation energy for transdermal permeation was estimated.

Results: Temperature found to enhance ex vivo permeation parameters of alfuzosin hydrochloride from its transdermal systems. It was also noted that chemical permeation enhancers potentiate permeation enhancing effect of temperature. The permeation flux values approximately doubled after exposure to 45 °C. The activation energy for transdermal permeation was found lower for the runs with chemical permeation enhancers indicating existence of a lower energy barrier in the presence of chemical permeation enhancers.

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Conclusion: The method reported here is a simple and useful tool for studying the effect of heat on percutaneous absorption. Such temperature dependent enhancement of flux can be more pronounced at skin surface temperatures >45 °C.

1. Introduction

The use of heat as a means of enhancing percutaneous absorption has been documented historically [1], but it has never been fully exploited as a means of aiding drug delivery across the skin. Thus, there has been relatively little investigation of the effect of temperature on skin permeation compared to other methods of penetration enhancement. It is essential that the effect of temperature on penetrant and also the cellular components (keratin, ceramides, etc.) and functions of the skin be well defined in order to understand the mechanism of enhancement. In addition, the FDA has produced an article describing the possibility of toxicity due to the percutaneous absorption of topically applied material as a result of the increased temperature and exposure to UV radiation associated with the sun [2]. A principal physicochemical factor which controls the passive diffusion of a solute from a vehicle into the skin arises from the skin temperature. It is an established fact that skin temperature rise increases penetration of solute [3,4]. Additionally, temperature enhanced permeabilities of the solutes were associated with the gel to liquid-crystalline transition of lipid hydrocarbon chains [5] and increasing temperatures of the stratum corneum (SC) resulted in increased fluidity (rotational disorder) of the intercellular lipids [6,7]. Phase behavior studies of SC have shown that arrangement and state of lipid bilayer is changing with temperature. Lipid bilayer of SC can exist in crystalline gel, liquid-/crystalline state or mesomorphic form depending upon the temperature.

In a recent study reported by Petersen et al. [8], controlled heat application (43 °C) caused significant cutaneous hyperaemia (up to ninefold increase in skin perfusion) with an increase in nicotine uptake (up to 13-folds). In another study, the transdermal permeation was found to increase exponentially when the donor environment temperature was varied from 2 to 47 °C [9].

Use of heat energy to enhance transdermal delivery of drugs has been adopted by few pharmaceutical companies. The controlled heat-aided drug delivery patch (CHADD) developed by Zars Inc. (Salt Lake City, Utah) consists of a patch containing a series of holes at the top surface regulating the entry of oxygen into the patch. This works on generation of heat chemically in a powder filled pouch by an oxidative process regulated by the rate of flow of oxygen through the holes into the patch. The CHADD technology was used in the delivery of a local anesthetic system (lidocaine and tetracaine) from a patch (S-Caine®) and found to enhance the depth and duration of the anesthetic action in human volunteers when the results obtained in active and placebo groups were compared [10]. Zars Inc. together with Johnson and Johnson, recently developed Titragesia™ (a combination of CHADD disks and Duragesic Patches, the latter contains fentanyl for treatment of acute pain).

Consequently, increasing the temperature of the skin and its environment may well provide the potential for overcoming the barrier properties of the SC, and thus, warrants a systematic investigation.

The absolute bioavailability of alfuzosin is about 49% under fed conditions, while the corresponding value under fasting conditions is approximately 25% [11]. This shows that food has a significant impact on the oral absorption of alfuzosin. This originates the need for an alternative route of administration, which can bypass the hepatic first-pass metabolism. Transdermal route is an alternative choice of route of administration for such drugs. Various physicochemical parameters like molecular weight, log *P* value and aqueous solubility of alfuzosin hydrochloride are 425.92, 1.51 at a pH of 7.4 and >10%, respectively [12]. These favorable parameters make it an ideal drug candidate for transdermal delivery.

The aim of this ex vivo study was to probe into the effect of heat on transdermal absorption of alfuzosin hydrochloride from EC-PVP based transdermal systems. Temperatures used in this study were in the range 30–50 °C range so as to minimize the thermal damage to the skin [9,13].

2. Materials and methods

2.1. Materials

Alfuzosin hydrochloride was obtained as a gift sample from Cipla Ltd. (Mumbai, India). Ethyl cellulose (EC; ethoxy content 47.5%–49%, viscosity 14 cps in 5% (w/w) solution in 80:20 toluene/ethanol at 25 °C) was purchased from BDH Chemicals Ltd., Poole, England. Polyvinylpyrrolidone (PVP; *K* value: 26–35) and polyvinylalcohol (PVA) were purchased from HiMedia Laboratories Pvt. Ltd., Mumbai, India and S.D. Fine-Chem. Ltd., Boisar, India, respectively. Di-n-butylphthalate was purchased from Central Drug House (P) Ltd., Mumbai, India.

2.2. Experimental design

A D-optimal response surface design was used to study the influence of temperature on ex vivo human cadaver skin permeation of alfuzosin hydrochloride. One numeric factor (X_1) and one categoric factor (X_2) were evaluated. The categoric factor was evaluated at two levels and the numeric factor was evaluated at five levels. The levels of categoric factor indicate either absence (Level 1) or presence (Level 2) of chemical permeation enhancers. Temperature was taken as the numeric factor and was studied at 30, 35, 40, 45 and 50 °C.