



Effect of 1,4-cyclohexanediol on percutaneous absorption and penetration of azelaic acid

Nan Li^a, Qian Su^a, Fengping Tan^{a,**}, Jerry Zhang^{a,b,*}

^a Tianjin Key Laboratory of Drug Delivery & High-Efficiency, Department of Pharmaceutics, College of Pharmaceutical Science and Technology, Tianjin University, Tianjin, PR China

^b Zymedis Pharmaceuticals, Inc., Lake Bluff, IL, USA

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ABSTRACT

The objective of this study is to investigate the effect of 1,4-cyclohexanediol as a retardant on the percutaneous absorption and penetration of azelaic acid. Hairless rat skin was mounted on Franz diffusion cells and treated with topical formulations containing solubilized azelaic acid with and without 1,4-cyclohexanediol. The skin was separated into stratum corneum and the deeper skin layers. The azelaic acid collected in receptor medium and each layer at the end of each time point was extracted and quantified. A significant decrease in flux across the skin suggests a penetration retardation effect of 1,4-cyclohexanediol (42.50 $\mu\text{g}/\text{cm}^2/\text{h}$ in the presence of vs. 76.25 $\mu\text{g}/\text{cm}^2/\text{h}$ in the absence of) at active loading level of 1.13 mg/cm^2 . The penetration retardation effect was also observed at higher active loading level (2.82 mg/cm^2). Furthermore, presence of 1,4-cyclohexanediol in the topical formulation did not reduce the skin and epidermal retention of azelaic acid, suggesting its potential use in the development of superior topical formation for reducing potential systematic side effect while maintaining therapeutic efficiency.

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1. Introduction

Rosacea is a chronic condition characterized by recurrent episodes of facial flushing, erythema, papules, pustules, and telangiectasia in a symmetrical, facial distribution (Esther et al., 2007). A number of compounds have been investigated for control and treatment of rosacea, including, for example, metronidazole and azelaic acid. Azelaic acid (1,7-heptanedicarboxylic acid, AZA) is a saturated, straight-chained C_9 -dicarboxylic acid (Dermer et al., 1989) that has been reported to be the active pharmaceutical ingredient in a number of prescription drugs for the treatment of rosacea and acne.

Treatment of dermatological disorders relies on the ability of active agents to effectively penetrate the stratum corneum (SC) from applied formulations and reached the deeper skin layers such as epidermis and dermis (Cross and Roberts, 2000). At mean time, due to the local nature of dermatological disorders and potential systematic side effect of the applied active agents, ideal topical formulations would impart maximal skin retention and minimal skin penetration. For personal care applications, for example,

sunscreens and bug repellents, minimizing potential systematic toxicity effect of applied chemicals is just as important as providing protection benefits.

Research in the area of permeation enhancement or retardation yields valuable insights into the structure–activity relationships of permeation enhancers as well as retardants. A number of studies have been carried out to minimize the systemic penetration by using chemical penetration retardants (Asbill and Michniak, 2000). It has been reported that the existence of certain compounds N-0915 of a similar structure to Azone which acted as drug retardants rather than enhancers. The mechanism of N-0915 may be expected to condense the skin lipids making them less permeable (Hadgraft et al., 1996). For example, phospholipids as penetration retardants apparently reduced the skin absorption of flurbiprofen (Fang et al., 2003). Oxazolidinones have the ability to retain the applied drugs in the skin layers, resulting in low systemic permeation (Rajadhyaksha and Pfister, 1996; Seth, 1999). The structures of oxazolidinones, e.g., 4-decyloxazolidin-2-one, are closely related to sphingosine and ceramide lipids, which are found naturally in the upper skin layers, which may explain skin retention effect of oxazolidinones. S,S-dimethyl-N-(benzenesulfonyl) iminosulfurane, S,S-dimethyl-N-(2-methoxycarbonylbenzenesulfonyl) iminosulfurane, and S,S-dimethyl-N-(4-chlorobenzenesulfonyl) iminosulfurane decreased the permeation of hydrocortisone significantly ($P < 0.05$) (Kim et al., 1999). Ideally, a penetration retardant should be chemically and pharmacologically inert, nontoxic, non-irritant, and non-allergenic.

* Corresponding author at: Zymedis Pharmaceuticals, Inc., 11 N. Skokie Hwy, Suite G-16, Lake Bluff, IL 60044, USA. Tel.: +1 847 604 8474; fax: +1 847 604 8856.

** Co-corresponding author at: Department of Pharmaceutics, College of Pharmaceutical Science and Technology, Tianjin University, Tianjin, PR China.

E-mail addresses: tanfengping@163.com (F. Tan), jerryzhang@zymedis.com (J. Zhang).

Table 1
Formulations containing solubilized azelaic acid.

Formulation	Ingredient (g/100 g)			
	Azelaic acid	Niacinamide	1,2-Hexanediol	1,4-Cyclohexanediol
F1	10.0	4.0	25.0	–
F2	10.0	4.0	25.0	1.0

It should have a rapid and reversible onset of action, be potent in low concentrations, compatible with the formulation ingredients and cosmetically acceptable (Chattaraj and Walker, 1995).

In this study, 1,4-cyclohexanediol as a penetration retardant was investigated. Its effect on percutaneous absorption and penetration of azelaic acid from topical formulations was studied in an *in vitro* skin model.

2. Materials and methods

2.1. Materials

Azelaic acid was purchased from ALFA AESAR (Ward Hill, MA, USA) and 1,4-cyclohexanediol was purchased from Sigma–Aldrich (St. Louis, MO, USA). 1,2-Hexanediol was purchased from Sabina Corporation (Piscataway, NJ, USA). Klucel® MF was obtained from Hercules, Inc. (Wilmington, DE, USA). All other reagents are of analytical grade.

2.2. Methods

2.2.1. Preparation of azelaic acid formulations

Azelaic acid formulation containing 1,4-cyclohexanediol was prepared as follows: 1,4-cyclohexanediol and niacinamide were dissolved in a solution of 1,2-hexanediol in water. Azelaic acid was dispersed in the above solution with a stirrer and the mixture was heated to 45 °C. The pH was adjusted to 4.9 ± 0.1 with triethanolamine. The stirring at 45 °C was continued until azelaic acid was dissolved. The solution was allowed to cool to room temperature. Klucel® MF (0.75%) was added to the cooled solution while stirring until the solution was gelled. The azelaic acid formulation without 1,4-cyclohexanediol was prepared similarly. The role of 1,2-hexanediol in the formulations is twofold: one is to enhance solubilization of azelaic acid in aqueous solution; the other is to serve as a moisturizing agent. Niacinamide is present in the formulations to provide anti-inflammation benefits. The final formulations are listed in Table 1.

2.3. Animals

Male hairless rats (30–40 days old) were purchased from Radiation Medicine Institute for Laboratory Animal Research, Chinese Academy of Medical Sciences, Tianjin, China. The abdominal skin was surgically removed from the animal, and subcutaneous fat was carefully cleaned. The skin samples were stored at –20 °C until use.

2.4. *In vitro* percutaneous absorption and penetration studies

The skin sample was mounted to Franz diffusion cells (diffusion area 1.77 cm²) with SC side facing the donor chamber. The receptor chamber (16 ml) was filled with normal saline, which was continuously stirred with a magnetic stirrer setting at 500 r.p.m. The skin sample was equilibrated with normal saline for 1 h at 32 ± 0.1 °C. Finite doses (20 and 50 mg of the formulations, which correspond to 2 and 5 mg azelaic acid, respectively) were applied to the skin surface. Each experiment was run in six replicates. At the end of each time interval (8, 12, 16, 20, and 24 h), the skin surface was

wiped with cotton ball soaked with phosphate buffered saline (pH 8.0). The tape-stripping method was used to remove the SC layer. The first strip was combined with the soaked cotton ball. The combination was digested with 1.0 M NaOH, neutralized to pH 5.0 using glacial acetic acid, filtered, and ready for HPLC analysis (Howes et al., 1996). Repeated tape-stripping (average 10 strips) was continued until SC layer was disappeared. All the strips were collected, combined, and digested in 10 ml 1.0 M NaOH. The mixture was then neutralized to pH 5.0 using glacial acetic acid, filtered, and ready for analysis. AZA retained within the epidermis/dermis layer was collected by methanol extraction. After tape-stripping, the remaining skin was minced, vortexed with 1 ml methanol and centrifuged, the supernatant was removed. The extraction step was repeated three times. The supernatants were combined, filtered and ready for analysis. The flux of AZA through the skin into the receptor fluid was determined from slopes of plots of concentration in the receptor phase vs. time and expressed as µg/cm²/h.

2.5. HPLC analytical methods

HPLC analysis was carried out with an Agilent 1100 HPLC system. A 250 mm × 4.6 mm stainless steel C₁₈ column (5 µm, Thermo, USA) was used. The mobile phase was a mixture of ammonium acetate/acetic acid buffered solution (pH 5.0, 10 mmol/L) and methanol at 60:40 (v/v) (Mansour and Ibrahiern, 2002). The flow rate was 1 ml/min. The ultraviolet detector was set at a wavelength of 210 nm and the temperature of the column was maintained at 30 °C.

2.6. Statistical analyses and data presentation

Statistical analyses were performed using Excel software. Paired two-tailed Student's *t*-test was performed to calculate the statistical significance. Values were given as mean ± SD.

Enhancement ratio (ER) for flux was calculated by using the following formula (Goodman and Barry, 1988):

$$ER = \frac{\text{flux for formulation containing retardant}}{\text{flux for control formulation}}$$

3. Results and discussion

In this study, 1,4-cyclohexanediol as a potential penetration retardant was investigated in an *in vitro* skin model of hairless mouse. Hairless mouse skin tends to be thinner and has few layers in the SC. Therefore, the hairless mouse skin is more permeable than human skin (Catz and Friend, 1990; Fang et al., 2003). The hairless mouse skin is, perhaps, not a good membrane for screening skin penetration enhancers. However, it is quite suitable for studying the permeation retardation effect, precisely due to its lower permeation barrier. It is reasonable to assume that if a permeation retardation effect were observed in the more permeable mouse skin, it would have been more likely that a similar effect would be observed in the less permeable human skin.

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