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Original article

Effect of neat and binary vehicle systems on the solubility and cutaneous delivery of piperine

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ABSTRACT

Vitiligo is a skin disease characterized by depigmentation disorders due to lack of melanin production. Piperine, an alkaloid extracted from black piper, is active in melanocytes proliferation. To achieve this, the drug has to reach the melanocytes which exist in the deep layer of the epidermis. Higher drug concentration can be obtained after application of optimized formulation to skin. Accordingly, the aim of this work is to investigate the effect of vehicles on skin penetration of piperine as the first step in development of optimized formulation. The tested vehicles include ethanol (Eth), propylene glycol (PG), polyethylene glycol 400 (PEG), and oleic acid (OA) and their combinations. Water was used as the control and skin permeation was monitored using rabbit ear model skin. The highest piperine solubility (48.6 mg/ml) and flux (40.8 μg/cm^2 h) was achieved by Eth and the lowest piperine flux (1.17 μg/cm^2 h) was reported for PEG. PG and OA showed piperine flux values comparable to that of the control. Among different combination systems, Eth-OA (75:25) binary system had the highest piperine flux (59.3 μg/cm^2 h) followed by Eth-OA (50:50) (32.3 μg/cm^2 h) and PG-OA (90:10) (22.7 μg/cm^2 h). The study thus introduced a vehicle system as the first step in the development of topical formulation of piperine.

1. Introduction

Vitiligo is one of the most common acquired skin pigmentation disorders, affecting 0.5–2% of the population worldwide regardless of age, gender, color or ethnic origin (Ongenae et al., 2004; Roy, 2017). The disease is characterized by the development of milky white patches, usually with a typical symmetrical distribution pattern (Ongenae et al., 2004). The disease results from reduction or disappearance of melanin. Many authors have confirmed the disappearance of melanocytes (active or inactive) from the epidermis of vitiliginous macules (Nordlund and Ortonne, 2006).

Majority of studies on treatment of vitiligo have focused on symptomatic treatment strategies with the aid of phototherapy in order to stabilize the disease and repigment the achromic patches (Ongenae et al., 2004). These strategies comprise photochemotherapy, phototherapy with ultraviolet radiation (broadband and narrowband), corticosteroids, immunomodulators, vitamin D3 analogues, and surgical intervention (Falabella and Barona, 2008; Kostovic and Pasic, 2005). Unfortunately, these standard treatment strategies have been reported to achieve limited success (Nordlund and Ortonne, 2006). Accordingly, treatment regimen that focuses on repopulation of macules with melanocytes has been considered as an effective way to treat vitiligo. Many clinical and experimental trials have examined the use of natural products for vitiligo. Lin et al. (1999) studied the effect of black pepper extract on the proliferation of mouse melanocytes. This extract was shown to stimulate growth activity in cell culture of melanocytes. Black pepper, widely used with spice flavors, is listed by the US Food and Drug Administration (FDA) as Generally Recognized as

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Safe (GRAS). It contains 5–9% of active alkaloid piperine (Bajad et al., 2002). Faas et al. (2008) have noticed that piperine and its synthetic derivatives can stimulate pigmentation in mice skin especially when combined with ultraviolet radiation treatment. Such potential effect of piperine attracted our attention to explore the skin delivery characteristic of piperine using different solvent systems.

Piperine,1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]pi peridine (Fig. 1), has molecular formula $C_{17}H_{19}NO_3$, molecular weight 285.34 Dalton, and *p*Ka 12 at 18 °C. Piperine is slightly soluble in water (Maryadele and Neil, 2006).

One of the main criteria of successful pharmaceutical formulation is to deliver the therapeutic substance to the target organ at therapeutically acceptable levels with the least harm and/or side effects on the patients (Kreilgaard, 2002). The target site for most dermatological diseases is located in the viable epidermis or upper dermis. For vitiligo disorder, piperine must permeate stratum corneum (SC) and reach basal layer (the location of melanocyte) to exert its action. Therefore, passing the SC is an important aspect of topical drug therapy. Basically, two principal approaches have been introduced to optimize the skin permeability of topically applied drugs. The first approach relies on increasing the thermodynamic activity of the drug in a vehicle which could be achieved by increasing its concentration (Kunst and Lee, 2016). The second approach is based on reducing the barrier function of the skin (Rambharose et al., 2017). Alternative chemicals have augmented the permeation of substances through skin and thus been termed "chemical permeation enhancers". Among these chemical permeation enhancers, water, ethanol, propylene glycol, polyethylene glycol, and oleic acid were selected to investigate their effects on piperine permeation through the skin. The selection was based on their potential to enhance the permeation of a number of drugs through skin (Lopes et al., 2015) and their frequency of use in skin products.

Accordingly, the main objective of this study is to investigate the effect of these vehicles in neat and combined form on the cutaneous delivery of piperine. This can be considered as the first step in the development of optimized topical formulation of piperine.

2. Materials and methods

2.1. Materials

Piperine was purchased from Sigma-Aldrich Company, Steinheim, Germany. Oleic acid (OA) was obtained from LOBA Chemi PVT. Ltd., India. Propylene glycol (PG) was from WINLAB, UK. Polyethylene glycol 400 (PEG) was imported from Fluka AG, Germany. Methanol, acetonitrile, and ethanol 99% (Eth) were obtained from BDH laboratory supplies, Poole, England. All other reagents and chemicals were of analytical grade.

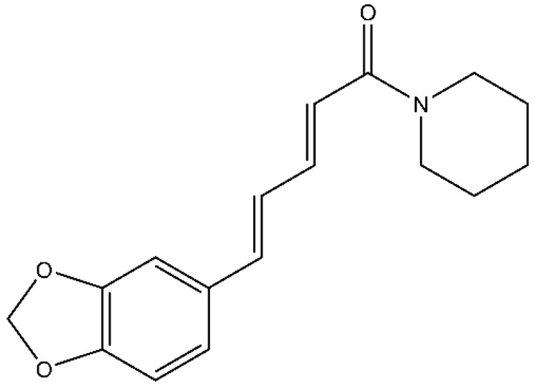

Fig. 1. Piperine chemical structure.

2.2. High pressure liquid chromatography (HPLC)

Piperine was analyzed using HPLC method of assay. The HPLC system consists of a Waters Model 1515 HPLC pump, a Waters autosampler Model 717 plus, and a Waters 2487 dual absorbance UV detector (Waters Inc., Bedford, MA, USA) governed by a computer running Empower software (version 1154). The detector wavelength was set at 309 nm. Separation was achieved by isocratic elution with a mobile phase of acetonitrile and water (52:48) adjusted to pH 3.5 with glacial acetic acid. This was pumped at a flow-rate of 1.2 ml/min at ambient temperature through a C_{18} analytical, μ-Bondapack column (150 mm length × 4.6 mm i.d., 10 μm particle size) (Badran et al., 2015).

2.3. Equilibrium solubility

Piperine solubility was conducted by adding excess amounts of piperine to the vehicle systems (water, ethanol, oleic acid, polyethylene glycol and propylene glycol alone and/or combined as ethanol-oleic acid, ethanol-propylene glycol, and propylene glycol-oleic acid) followed by equilibration in a shaking water bath (Julabo – SW 22) for 7 days; it was maintained at 32 °C (mimic skin temperature) with shaking rate of 80 rpm. The excess powder was then removed by centrifugation at 8000 rpm for 10 min before determining the drug content by HPLC after suitable dilution.

2.4. Preparation of piperine in vehicle

Saturated solution of piperine was prepared using different vehicle systems (water, ethanol, oleic acid, polyethylene glycol and propylene glycol alone and/or combined as ethanol-oleic acid, ethanol-propylene glycol, and propylene glycol-oleic acid). The saturated solutions of piperine were equilibrated by continuous shaking in water bath (Julabo – SW 22) adjusted at 32 °C (mimic skin temperature) for 7 days at 80 rpm. Excess powder was added to maintain saturation.

2.5. In vitro drug release

The in vitro release experiments were conducted using the FDC-6 Transdermal Diffusion Cell Drive Console (Logan Instrument Corp., Somerset, NJ, USA). The artificial membrane (Cellulose Tubing, Spectrum Medical Industries, USA, with cut off of 8000–12,000) was soaked in the receptor fluid for one hour before the test was performed to hydrate the membrane. The membrane was mounted between the donor and receptor compartments of the diffusion cells. These cells have a diffusional area of 1.7 cm^2 with each receptor compartment having a capacity of 12 ml. The receptor fluid was a 30% v/v Eth in water (Fang et al., 2008). This is believed to maintain sink conditions. The heater was adjusted to maintain the surface temperature of the membrane at 32 ± 1 °C to mimic skin permeation experimental conditions. The tested systems (1 ml) were loaded into the donor compartment before occluding the donor compartments using a parafilm. Receptor samples (5–10 ml) were collected at predetermined time intervals (1, 2, 3, 4, 6, 10 and 24 h) and fresh receptor fluid was used to compensate the collected samples. Piperine content in each sample was determined by HPLC.

2.6. Skin permeation studies

The ear skin of the rabbit (healthy male rabbits weighing about 2 kg) was used as a skin model for in vitro skin permeation of