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Research paper

Development of medicated foams that combine incompatible hydrophilic and lipophilic drugs for psoriasis treatment

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Cocamidopropylbetaine (PubChem CID: 20280)
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ABSTRACT

The focus was on the development of medicated foam for incorporation of two incompatible active agents for psoriasis treatment; i.e., lipophilic cholecalciferol, and hydrophilic salicylic acid. Emphasis was given to formulation of a propellant-free foam, with sufficient foaming properties, physical and chemical stability, and low irritancy potential to maintain relevance for later translation into clinical practice. Various excipients and concentrations were examined to achieve suitable foam stability parameters, viscoelasticity, and bubble-size, which relate to foamability and spreadability. The major positive impact on these properties was through a combination of surfactants, and by inclusion of a viscosity-modifying polymer. Incorporation of the incompatible drugs was then examined, noting the instability of cholecalciferol in an acidic environment, with the design aim to separate the drug distributions among the different foam phases. Cholecalciferol was stabilized in the emulsion-based foam, with at least a 30-fold lower degradation rate constant compared to its aqueous solution. The composition of the emulsion-based foam itself protected cholecalciferol from degradation, as well as the addition of the radical-scavenging antioxidant tocopheryl acetate to the oil phase. With the patient in mind, the irritancy potential was also examined, which was below the set limit that defines a non-irritant dermal product.

1. Introduction

Psoriasis is a chronic, inflammatory, autoimmune skin disease of unknown etiology. It is characterized by scaly, erythematous patches, papules, and plaques, which are often itchy and painful. Its severity can vary from small and localized plaques, to full-body cover (Menter et al., 2008). Psoriasis represents one of the most common chronic inflammatory diseases worldwide, and it affects approximately 2%–3% of the population (Jacobi et al., 2015). More than 18% of patients with diagnosed moderate or severe psoriasis are dissatisfied with their treatment, as their health-related quality of life and work productivity are affected (Korman et al., 2015, 2016).

Dermal dosage forms are most commonly used in the treatment of psoriatic skin, and these usually contain anti-inflammatory, keratolytic, and emollient active pharmaceutical ingredients (APIs) (Jacobi et al., 2015). However, their low dermal bioavailability and the difficulties in their application can result in insufficient therapeutic effect. Nowadays, the interest in the development of new vehicles for topical delivery is steadily growing. Medicated foams represent one option of such new vehicles which might provide for more convenient and patient-friendly topical administration. This also represents an attractive drug delivery system that can have several advantages over the conventional delivery

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systems such as ointments, creams, lotions, gels or solutions. As well as their high marketing potential, foams have application advantages and an improved cosmetic appeal, and thus they promise improved patient acceptance and preference, compared to conventional drug delivery systems. Indeed, several surveys have shown significant patient preference for foam vehicles over conventional vehicles, in terms of their ease of application, uniform spreading, non-stickiness, and no greasy after feeling (Zhao et al., 2010). Furthermore, foams can provide quick release of APIs and instant absorption. Additionally, development and manufacturing costs are comparable to other forms of application (Bureiko et al., 2015; Shinde et al., 2013).

Foams are formulations that include large amounts of gas dispersed in a small amount of a liquid phase in the form of gas bubbles separated by thin viscoelastic film (Arzhavitina and Steckel, 2010). Surfactants are one of their essential components, as these provide the foaming agent. Foams can comprise one or more phases. The additional advantage of foams produced from oil-in-water emulsions is that it is possible to incorporate hydrophilic and lipophilic APIs into a single dosage form. Due to the large amount of surfactant, which can also act as a penetration enhancer, the dermal bioavailability of APIs in these foams is significantly improved (Som et al., 2012). Indeed, the superiority of foams in plaque psoriasis treatment has already been shown for topical administration of calcipotriol/betamethasone dipropionate, whereby a foam formulation promoted enhanced treatment results in comparison to ointments or topical suspensions of the same APIs (Kim and Frampton, 2016). Furthermore, foams have great value in their practical use, as they can be spread over large, sensitive and inflamed skin surfaces with no need for extensive rubbing (Shinde et al., 2013). As such, foams are also suitable as dosage forms for geriatric and pediatric patients in general.

Corticosteroids, vitamin D analogs, retinoids, tar, anthralin, tazarotene, and salicylic acid are the most common active substances for topical treatment of psoriasis (Weinberg, 2008). These APIs can be hydrophilic as well as hydrophobic, and their actions help to reduce the scale load. They also have supportive roles for the normalization of cell hyperproliferation, differentiation, and apoptosis, along with anti-inflammatory effects; consequently, they help to reduce the severity of this disease (Fluhr et al., 2008; Jacobi et al., 2015). Cholecalciferol, or vitamin D3, is known to inhibit cell proliferation, stimulate keratinocyte differentiation, and alter inflammatory responses, and thus it can be used in psoriatic therapy. Salicylic acid is also widely used in the treatment of psoriasis as a keratolytic agent, as it reduces intercellular bonding in the horny layer, and softens psoriatic lesions by lowering the pH of the *stratum corneum* (Weinberg, 2008). However, cholecalciferol and its synthetic analog calcipotriol are incompatible with salicylic acid, which decreases the pH of the formulation and consequently affects their stability. The precise mechanism of this destabilization remains unknown.

In the present study, we focused on oil-in-water emulsion-based foams with incorporated cholecalciferol and salicylic acid. The hypothesis was that cholecalciferol loads into the oil phase and salicylic acid into the water phase, whereby the salicylic acid does not affect the chemical stability of cholecalciferol. Various excipients were selected at various concentrations for their effects on the appearance and stability of the foam produced and on patient compliance. Stability of cholecalciferol in the foam formulations was determined over a period of 1 month, using HPLC. Tocopheryl acetate was also incorporated into the foams as a lipophilic radical-scavenging antioxidant, to protect the skin and the product from free radicals, to promote positive effects on psoriasis treatment (Rangarajan and Zatz, 2001).

A 'downside' of high surfactant concentrations in foams is their irritancy potential, which is another aspect that was addressed in the present study. The pig-ear test is efficient for the detection of potential irritancy of dermal products. Here, the transepidermal water loss (TEWL) was determined, which serves as a sensitive measure of skin barrier function, the disturbance of which results in higher TEWL (Bárány et al., 2000; Welss et al., 2004).

The aim was thus to develop a propellant-free foam formulation that can incorporate two otherwise incompatible APIs. For application to psoriasis treatment, this formulation required sufficient foaming properties, physical and chemical stability, and low irritancy potential.

2. Materials and methods

2.1. Materials

2.1.1. Foam formulation

2.1.1.1. Surface active agents. Disodium laurethsulfosuccinate (DLS), polyethylene glycol $(PEG)_7$-glycerylmonococoate, cocamidopropyl betaine (CAPB), and ceteareth-20 were from Making Cosmetics, USA, and sodium dodecyl sulfate (SDS) from Merck, Germany (for chemical structures, see Fig. 1).

2.1.1.2. Additives. Cetyl alcohol was from Fagron, Spain, hydroxypropylmethyl cellulose (HPMC; Methocel K4M Premium CR) from Colorcon, England, and glycerol and sodium methylparaben from Lex, Slovenia (for chemical structures, see Fig. 1).

2.1.1.3. Oil phase. Olive oil (refined) was from Farmalabor, Italy, and caprylic/capric triglyceride (Miglyol 812) from Sasol, Germany.

2.1.1.4. Active pharmaceutical ingredients. Cholecalciferol and salicylic acid were from Merck, Germany, sodium salicylate from Sigma Aldrich, USA, and tocopheryl acetate from BASF, Germany (for chemical structures, see Fig. 1).

2.1.2. Other chemicals

Acetonitrile and methanol of HPLC grade and sodium chloride were from Sigma-Aldrich (Steinheim, Germany). Ultra-pure water was from a Milli-Q water purification system (A10 Advantage; Millipore Corporation, Bedford, MA, USA).

2.2. Methods

2.2.1. Foam preparation

Depending on the composition of the foam formulation (see Table 1, F1-F17), water, ceteareth-20, cetyl alcohol, SDS or DLS, HPMC, sodium methylparaben, salicylic acid, and sodium salicylate were weighed out and added into a plastic mortar. These were mixed for approximately 30 min in a heated water bath (70 °C), until a clear solution was obtained. The mortar was removed from the water bath, and when the solution reached room temperature, PEG_7-glycerylmonococoate, CAPB, glycerol, olive oil or Miglyol were added (one by one) to the solution while it was gently stirred. Cholecalciferol and tocopheryl acetate were initially dissolved in the selected oil, and then added to the cooled mixture at room temperature. Once prepared, the oil-in-water emulsions that formed were inserted into an Airspray foam pump, which was used to generate the foams without the use of gas propellants. The amounts of ionic surfactant, polymer, oil phase, and emollient varied.