Oil-in-Oil-Emulsions with Enhanced Substantivity for the Treatment of Chronic Skin Diseases

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ABSTRACT: The therapy of chronic skin diseases often requires several applications of creams or ointments per day. This is inconvenient to the patients and frequently leads to poor acceptance and compliance. We therefore developed oil-in-oil-emulsions that deliver the active pharmaceutical ingredient (API) to the skin over a prolonged period of time. In this study, we compare the permeation of the API from a conventional formulation to its permeation from an oil-in-oil-emulsion under infinite and finite dosing. Furthermore, we evaluate the substantivity of the formulations. Our results show that the permeation from oil-in-oil-emulsions is constant over a prolonged time and that the emulsions show significantly higher substantivity than conventional formulations. Because of that, the treatment intervals can be extended substantially and compliance can be increased. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1515–1519, 2014

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INTRODUCTION

Chronic itch is a symptom that accompanies many skin diseases. It may be derived from different pathogenesis and is often difficult to treat.[1,2] If the conservative treatment failed, capsaicinoids may be used.[1,3,4] The mechanism of action involves TRPV1, a nonselective cation channel that is expressed on peripheral endings of Aδ and C-fibers in the dermis and viable epidermis. The binding of capsaicinoids to TRPV1 initially induces pain and burning. If the application of capsaicinoids is continued, defunctionalization of the neurons leads to long-lasting relief of pain and pruritus.[5–8]

Numerable dermal formulations that contain capsaicinoids exist for the treatment of pain. However, there is still no authorized product for the treatment of chronic itch on the market. A magistral formula[9] exists but it has to be applied several times per day as with most conventional formulations. The main cause of repetitive application of conventional semisolids is their low substantivity, that is, up to 90% of the formulation is withdrawn from the skin. The resulting need for multiple applications per day in turn leads to poor compliance and eventually even to therapeutic failure.[5] Furthermore, formulations that contain capsaicinoides may cause contamination of the patients' environment, which may lead to adverse reactions in the patient or other people as an unintended contact with the capsaicinoids may lead to an intense burning sensation.[7] Therefore, it is even more important to ensure sufficient substantivity.

Recently, the successful development of a film forming semisolid formulation has been reported.[10,11] This formulation contains the solution of a lipophilic active pharmaceutical ingredient (API) as the dispersed phase of an emulsion. Additionally, the continuous phase comprises water insoluble polymers that form a water insoluble film on the skin that encapsulates the drug loaded oil droplets. In the process, substantivity is enhanced and the API is delivered to the skin by diffusion through the polymeric matrix with a constant permeation rate over 12 h.[10,11]

As an alternative approach, we previously reported the successful development of castor oil-in-silicone oil-emulsions for the therapy of chronic skin diseases.[12] The emulsions consist of the lipophilic API dissolved in castor oil, which is in turn dispersed in a suitable silicone oil. The castor oil-in-silicone oil-emulsions are stabilized by a silicone surfactant. In this system, the silicone oil is intended to enhance the substantivity of the formulation. From an infinite dose of the emulsions, the API permeates the skin with a constant flux over 10 h.[12]

In order to further evaluate the suitability of oil-in-oil-emulsions for the treatment of chronic skin diseases, we compared the permeation of the API from the oil-in-oil-emulsion to its permeation from the magistral formula.[9] We employed an infinite dose approach in order to compare the permeation rates and a finite dose setup in order to investigate the duration of permeation under conditions that closely match treatment conditions. Furthermore, we investigated the substantivity of the oil-in-oil-emulsions in comparison with the magistral formula.[9]

Nonivamide, a synthetic analogue of capsaicin was used as the API instead of capsaicinoids as nonivamide exhibits equivalent pharmacodynamics and is, in contrast to capsaicinoids, a highly purified, chemically defined substance and may therefore be analyzed with higher precision.[13]

MATERIALS AND METHODS

Materials

Different materials used and their manufacturer information are as follows: nonivamide (Sigma–Aldrich Chemie GmbH, Steinheim, Germany), castor oil (Caesar & Loretz GmbH, Hilden, Germany), medium-chain triglycerides (Miglyol® 812;

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Sasol GmbH, Witten, Germany), glycerol monostearate (GMS) (Cutina GMS®; Cognis BASF SE, Ludwigshafen, Germany), cetyl alcohol (Henkel AG & Company KG aA, Duesseldorf, Germany), macrogol-20-GMS (PEG-20-GMS) (Tagat S2®; Evonik Goldschmidt GmbH, Essen, Germany), propylene glycol (PG) (BASF SE). The 1:1 dispersion of a silicone surfactant (BY 11-030) and polydimethyl siloxanes (Q7–9120 20 cst and 1000 cst) were kindly donated by (Dow Corning GmbH, Seneffe). Methanol and ethanol were of HPLC gradient grade. Disodium phosphate dodecahydrate, potassium dihydrogen phosphate, and phosphoric acid were of European Pharmacopeia (Ph. Eur.) grade.

Preparation of Emulsions

Oil-in-oil-emulsions containing 1% nonivamide were prepared by means of a "syringe to syringe technique" (Fig. 1). To this end, 2.35 g of polydimethyl siloxane, 0.2 g of silicone surfactant, and 2.45 g of castor oil that contained 51.45 mg nonivamide were weighed precisely into a syringe. This syringe was connected to a second syringe by an adapter. Homogenization was achieved by transferring the ingredients from one syringe to the other 70 times.

Preparation of Hydrophilic Nonivamide Cream 0.1% and 1%

Hydrophilic nonivamide cream (HNC) was prepared according to the monograph of "Hydrophile Capsaicinoid Creme NRF 11.125."[9] Capsaicinoids were replaced by nonivamide. In brief, Cremor Basalis DAC was made by melting white soft paraffin, cetyl alcohol, and GMS. In parallel, polyoxyethylene-20-monostearate and PG were dissolved in hot water and incorporated into the oily phase to give an amphiphilic cream. A 10% or 1% (w/w) solution of nonivamide in ethanol 90% (v/v) was added to a solution of PG in water and this mixture was given to Cremor Basalis in aliquots to form HNC 1% or 0.1%.

Preparation of Dermatomed Pig Ear Skin

Fresh pig ears were washed with isotonic saline. Postauricular skin was excised. Skin samples were cleaned off blood with isotonic saline and cotton swabs, patted dry with tissue, wrapped in aluminum foil, and stored at −30°C. On the day of the experiment, the skin was thawed at room temperature, cut into strips of approximately 3 cm width and fixed to a block of Styrofoam with pins. The skin was dermatomed to a thickness of 1 mm (Dermatom GA 630; B. Braun Melsungen AG, Melsungen, Germany).

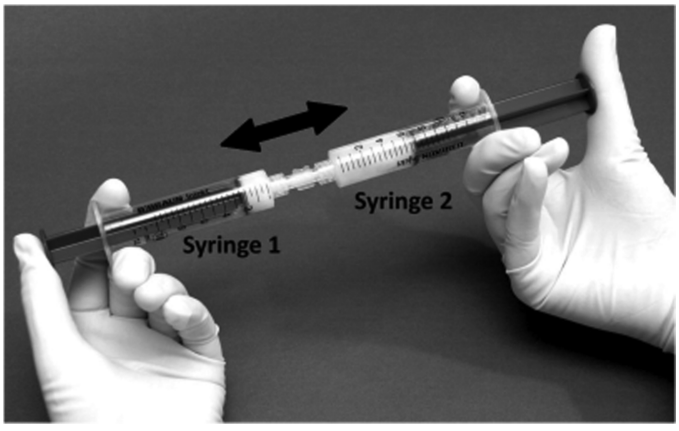

Figure 1. Illustration of syringe to syringe technique.

Permeation Through Pig Ear Skin

Ex vivo permeation tests were conducted using modified Franz diffusion cells (Gauer Glas, Püttlingen, Germany) with a receptor volume of 12 mL. Phosphate-buffered ethanol (phosphate buffer pH 7.4 containing 50% (v/v) ethanol) was used as the receptor fluid. Degassed, prewarmed (32°C) receptor medium was filled into Franz diffusion cells. Thereafter, Franz diffusion cells were equipped with dermatomed pig ear skin (thickness: 1 mm, diameter: 25 mm) and donor compartments. Subsequently, 0.4 g (infinite dose) or 4 mg (finite dose) of the formulation were applied to the skin surface. In infinite dose experiments cells were capped with Parafilm™ to prevent the evaporation of water. In finite dose experiments cell were not capped. *Ex vivo* permeation experiments were performed at 32°C, stirring speed was 500 rpm. Nonivamide was allowed to diffuse across the skin over a period of 28 h. Aliquots of 0.6 mL were withdrawn at five time points and the sample volume was replaced by fresh, prewarmed receptor medium. Samples were analyzed by HPLC. Cumulative permeated amounts were plotted against time. Permeation rates were calculated by linear regression; permeation coefficients were calculated by dividing permeation rates by initial drug concentration in the vehicle according to Eq. (1):

$$K_p = J_{ss}/c_0 \quad (1)$$

where K_p = permeation coefficient (mg/cm^2 h), J_{ss} = steady-state flux through skin (μg/cm^2 h), and c_0 = initial nonivamide concentration in the formulation (μg/mg). The experiments were performed in quintuplicate.

Water Resistance Test

For water resistance testing, 8–15 mg oil-in-oil emulsion or HNC were applied to the surface of pig ear skin (thickness: 1 mm, diameter: 25 mm). The vessels of a dissolution test apparatus (apparatus 2, Ph. Eur. 7) were filled with 100 mL deionized water and heated to 32°C. Skin samples were placed into the vessels with the stratum corneum facing upward. The dissolution medium was stirred at 50 rpm. Skin samples were removed from the apparatus after 20 min. Nonivamide content in the dissolution medium was determined by HPLC. The experiments were performed in sextuplicate.

Nonivamide Quantification

Nonivamide was quantified using the "LC-20A prominence" HPLC system (Shimadzu, Duisburg, Germany). The HPLC-column "Nucleosil 100–5C 8 CC 125/4" (Macherey-Nagel, Dueren, Germany) was used in combination with the HPLC-precolumn "Nucleosil 100–5 C8CC 8/3" (Macherey-Nagel). The column-oven temperature was set to 50°C. For *ex vivo* permeation experiments the eluent consisted of 50% methanol and 50% phosphoric acid pH 3.0. The flow was set to 1.15 mL/min. Then, 200 μL per sample was injected and the UV absorbance was measured at 230 nm. Nonivamide was eluted after approximately 9.7 min. For water resistance experiments, the eluent consisted of 59.5% methanol and 40.5% phosphoric acid pH 3.0. The flow was set to 1.125 mL/min. Twenty microliters per sample was injected and UV absorbance was measured at 230 nm. Nonivamide was eluted after approximately 3.7 min.