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Influence of drug content, type of semi-solid vehicle and rheological properties on the skin penetration of the model drug fludrocortisone acetate

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ABSTRACT

Throughout Europe, topical creams containing corticosteroids are diluted with various neutral cream bases to meet the specific needs of patients. Even though this practice has been common for years, its effect has not been thoroughly investigated and so the effectiveness of the diluted topical steroidal creams is difficult to predict. In the present study, the model drug fludrocortisone acetate was incorporated into three cream bases of different hydrophilicity that are commonly used in Austria. Different final drug concentrations were chosen for comparative studies. Additionally, a semi-solid preparation developed by our group was investigated for comparison. These formulations were tested in diffusion and tape stripping experiments. Diffusion cell studies showed that changes in drug concentration do not necessarily change the skin permeation behaviour in vitro. The tape stripping protocol was successfully optimised for investigation of semi-solid preparations to provide reproducible and accurate results despite the challenges of investigating semi-solid formulations. The results showed that tape stripping experiments are more suitable to elucidate subtle differences between formulations. The composition of the cream bases exhibited stronger effects on the skin penetration of the steroidal drug irrespective of its concentration than the rheological properties. No correlation between formulation viscosity and skin penetration was found.

1. Introduction

In dermal drug delivery and skin care, industrial cream bases are frequently employed for the delivery of anti-inflammatory drugs such as corticosteroids, which are a very important part of topical approaches to treating various diseases. Throughout Europe, potent topically applicable, ready-to-use steroid formulations are diluted with various industrially produced cream bases in order to adjust their potency to the individual needs of patients. However, only few details are known about the actual skin penetration of corticosteroids once the formulations have been diluted. Various research efforts have shown that the penetration behaviour of corticosteroids from diluted vehicles cannot be predicted easily as it is not proportional to the degree of dilution; diluting a steroid formulation to 50% of the original drug content does not necessarily cause a corresponding decrease in drug uptake by 50% (Mitriaikina and Müller-Goymann, 2009; Wiedersberg et al., 2008). The penetration behaviour depends on a number of characteristics of the vehicle as well as on the drug incorporated, as for example solubility of the drug within the vehicle or the composition of the vehicle itself (Jacobi et al., 2006). In accordance, the penetration behaviour is expected to be different for each combination of drug and vehicle, but it is tremendously difficult to predict the occurring changes in diluted formulations. Moreover, diluting ready-to-use preparations may render them more prone to microbial deterioration (Busse, 1978; Magnus et al., 1981).

The aim of the present work is to elucidate the effects of different vehicles and different drug concentrations on the skin permeation and penetration of the model steroid fludrocortisone acetate. For this purpose, three industrially produced cream bases were employed, representing a W/O, an O/W and an amphiphilic cream. Fludrocortisone acetate was added to the vehicles in final concentrations of 0.25, 0.5, 0.75, and 1% (w/w). Skin permeation was investigated by using Franz-type diffusion cells. Additionally, tape stripping experiments were performed to evaluate the penetration of the model drug from the different formulations into porcine ear skin. Various groups have reported that lipophilic cream components may remain on the surface of the skin and may therefore

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have a negative influence on the adhesiveness of tape strips (Jacobi et al., 2003; Klang et al., 2011b; Teichmann et al., 2007). To account for this obstacle in the investigation of semi-solid formulations by tape stripping, the working protocol was adapted and optimised to obtain reliable results even when studying semi-solid formulations with a considerable amount of lipophilic compounds retained on the skin surface. In comparison to the O/W cream a semi-solid O/W formulation recently developed by our group and based on a eudermic sugar-surfactant was termed preparation A and was tested at a concentration of 1% of model drug. Furthermore, the rheological properties of all produced formulations were analysed since an adequate viscosity and a certain viscoelasticity is desirable in topically applied formulations (Jaksic et al., 2011; Savic et al., 2011). These parameters were also inspected regarding their influence on the skin penetration of the model drug from the formulations.

2. Materials and methods

2.1. Materials

Standard Corneofix adhesive tapes with a surface area of 4.0 cm^2 were purchased from Courage + Khazaka GmbH (Cologne, Germany), γ-Cyclodextrin (Cavamax® W8 Pharma) was obtained from Wacker Chemie AG (Munich, Germany). Potassium sorbate (CAS: 0024634615) and fludrocortisone acetate (CAS: 0000514363) were purchased from Sigma–Aldrich (St. Louis, USA). Tegosoft® liquid (cetearyl ethylhexanoate) was kindly donated by Evonik Industries (Essen, Germany). Sucrose stearate (Ryoto Sugar Ester® S-970) was supplied by Mitsubishi-Kagaku Food Corporation (Tokyo, Japan). All solvents as methanol (CAS: 0000067561) and acetonitrile (CAS: 75-05-8) were of analytical grade and used as obtained from Sigma–Aldrich.

The industrial cream bases representing the W/O, O/W and amphiphilic cream were kind gifts from Bayer Austria GesmbH (Vienna, Austria). According to the manufacturer, the ingredients for the cream bases are as follows.

W/O cream: purified water, white petrolatum, liquid paraffin, Dehymuls E (dicocoyl pentaerythrityl distearyl citrate, sorbitan sesquioleate, cera alba, aluminium stearate), white wax, perfume oil. Water content is approximately 30% (w/w). This corresponds to Ultrabas® of Bayer Austria GesmbH.

O/W cream: purified water, white petrolatum, liquid paraffin, stearylalcohol, macrogolstearate 2000, polyacrylic acid, sodium EDTA, sodium hydroxide, methyl-4-hydroxybezoate (E 218), propyl-4-hydroxybenzoate (E 216), perfume oil. Water content is approximately 70% (w/w). This corresponds to Ultrasicc® of Bayer Austria GesmbH.

Amphiphilic cream: purified water, white petrolatum, liquid paraffin, glycerol distearate, glycerol monostearate, polyoxyethylene 100 stearate, polyoxyethylene-2 and polyoxyethylene-21 stearyl alcohol, benzyl alcohol, perfume oil. Water content is approximately 40% (w/w). This corresponds to Ultraphil® of Bayer Austria GesmbH.

Recently, a eudermic, semi-solid preparation was developed in our group (Klang et al., 2011c). This formulation was termed preparation A and consisted of the following ingredients (% w/w): purified water (approximately 70%), cetearyl ethylhexanoate (Tegosoft® liquid, 30%), sucrose stearate S-970 (5%), potassium sorbate (0.1%).

2.2. Skin tissue

For the skin penetration studies, fresh porcine ears were purchased from a local abattoir (Totzenbach, Austria). The age of the sacrificed pigs was about 6 months. To ensure integrity of the skin barrier, the ears were removed before the carcass was exposed to any high-temperature cleaning procedures (Herkenne et al., 2006). The excised ears were cooled during transport, carefully rinsed with cold water and blotted dry before storage at −18 °C, which does not influence the stratum corneum regarding the envisioned experiments (SC) (Hahn et al., 2010). All experiments were performed at room temperature after allowing the ears to thaw. The skin remained on the porcine ears, as this renders handling easier and prevents contraction of the skin (Breternitz et al., 2007; Lademann et al., 2009).

The model membrane for the skin diffusion studies using Franz-type diffusion cells was porcine abdominal skin acquired from a local stockbreeder (Purkersdorf, Austria).

2.3. Production of the formulations

2.3.1. Formulations based on industrial cream bases

Three different industrially produced cream bases were employed to produce the formulations for the present study; namely, an O/W cream, W/O cream and an amphiphilic cream. The model drug fludrocortisone acetate was incorporated into the cream bases by means of a device for homogenisation of pharmaceutical formulations (TopiTec®, Austria). A pre-installed programme was employed to homogenise the formulations in a controlled manner, mixing the components for 30 s at 2000 rpm, then 3 min at 1000 rpm. In this manner, four different formulations per vehicle were produced, matching final concentrations of fludrocortisone acetate of 0.25, 0.5, 0.75, and 1% (w/w), respectively.

2.3.2. Preparation A

Potassium sorbate was dissolved in water (aqueous phase), whereas both the model drug fludrocortisone acetate and the emulsifying agent sucrose-stearate S-970 were suspended in the oil phase (Tegosoft® liquid). These phases were stirred separately at 50 °C with magnetic bars at a speed of 500 rpm for 15 min. Then they were combined and stirred further for 10 min at a speed of 1000 rpm. After this, the mixture was homogenised using an ultraturrax (Omni 500, 2500 rpm, 4 min). The resulting preparation named A was allowed to cool and during this process, a semi-solid preparation was formed. The preparations were stored at 4 °C. By this procedure, formulations of final concentrations of 0.25, 0.5, 0.75, and 1% (w/w) model drug were produced.

2.4. Skin diffusion studies

In vitro skin permeation studies were performed using standard Franz-type diffusion cells (Permegear, USA). Porcine abdominal skin was chosen as the model membrane because of its similarity to human skin regarding morphology and permeability (Schmook et al., 2001). Visible hairs were removed from the porcine abdominal skin and the skin was dermatomed to a thickness of 0.7 mm (GB 228R, Aesculap). The dermatomed skin was stored at −18 °C thawed prior to the experiments. Appropriate skin pieces were clamped between the donor and acceptor chambers of the diffusion cells with a permeation area of 1.13 cm^2. The acceptor compartment was filled with 2 ml of phosphate buffer of pH 7.4 containing γ-Cyclodextrin (γ-CD) in a final concentration of 0.1% (w/v) to compensate for the poor water solubility of fludrocortisone acetate (Cisternino et al., 2003; Loftsson and Masson, 2001). An accurately weighed amount of 500 mg of formulation was placed onto the excised skin in the donor compartment and the compartment was closed with Parafilm® and aluminium foil. The cells were kept at 32 °C in a temperature-controlled water bath for up to 24 h and the receptor fluid was stirred with magnetic bars. At certain time points, namely after 2, 4, 6, 8, and 24 h, the receptor fluid was replaced by fresh phosphate buffer containing γ-CD. At least 4