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Personalised medicine

Dilution of semi-solid creams: Influence of various production parameters on rheological properties and skin penetration

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ABSTRACT

In order to customise treatment for patients, topical formulations are often diluted with drug-free cream bases to adjust the drug dose and thereby the formulations' activity to the patients' needs. However, the process of dilution influences properties of the formulations. Stability can be reduced as well as the microbial stability and most importantly, efficacy and skin penetration behaviour can be severely and unpredictably changed.

The present study investigates the effects of production parameters on creams, namely incorporation of an API (active pharmaceutical ingredients) into an OW cream with prior mixing with propylene glycol or without and subsequent automated or manual dilution of the resulting creams with three different cream bases. Effects were measured by influence on microscopic appearance, measurement of chemical stability, skin penetration and rheological behaviour.

Result: suggest strong influence of the cream bases used for dilution of the formulations. Mixture of equal amounts of the employed OW and WO cream proved unfavourable due to inferior penetration behaviour and less appealing microscopic and macroscopic appearance. Prior mixing with PG was of negligible importance for the characteristics of the dilutions, however, the type of API and manner of dilution had an influence on the viscosity of the formulations.

1. Introduction

Dermal drug delivery is a favourable way of treatment for localised afflictions as it alleviates the conditions and simultaneously minimises the potential of systemic adverse effects (Hengge et al., 2006). Therefore, in Europe this approach is widely used for an eclectic variety of conditions and APIs (active pharmaceutical ingredients) including non-steroidal anti-inflammatory drugs in osteoarthritis (Barthel et al., 2009), antibiotics against acne vulgaris (Feucht et al., 1980) and foremost corticosteroids in the treatment of atopic dermatitis (Lucky et al., 1997; Maia et al., 2000).

In order to customise topical treatment for the individual, dermatologists often vary parameters of prescribed formulations like lipophilicity or drug content, for example. This therapeutic concept aims to adjust the properties of formulations in order to meet the patients' needs and therefore, well-established works summarise and collect pharmaceutical formulations in order to guide pharmacists in the preparation of such formulations and to ensure certain quality standards in personalised topical medical care (DAC/NRF, 2014). Accordingly, topical formulations are often diluted with cream bases not containing an API (active pharmaceutical ingredient) with the intention of adjusting the drug dose and thereby the formulations' activity to the patients' needs. In theory, this has the additional advantage of minimising the risk of adverse effects due to a dosage of drug reduced to the dose required. However, the process of dilution strongly influences various properties of the formulations. Stability of the resulting formulations can be reduced as well as the microbial stability and most importantly, the efficacy and skin penetration behaviour can be subject to severe and mostly unpredictable changes (Busse, 1978; Demana, 2014; Magnus et al., 1981; Refai and Müller-Goymann, 2002; Wiedersberg et al., 2008). These changes can lead to loss of effect or, contrary, to an effect much more pronounced than expected and wanted, which in turn may prevent the desired outcome of the treatment and lead to negative side effects of

Abbreviations: API, active pharmaceutical ingredient; OW, oil in water; PG, propylene glycol; SC, stratum corneum; WO, water in oil.

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the drugs and thereby reduce patient compliance due to lack of success with the treatment. Nevertheless, aforementioned practice of dilution of topical creams is frequently employed in dermal drug delivery, mostly without proof of concept and despite the references indicating unpredictable changes in the diluted systems and therefore advising against dilution of API-containing creams (Demana, 2014; Mitriaikina and Müller-Goymann, 2009; Refai and Müller-Goymann, 2002).

In consideration of this, the present study is aiming at gaining further insight into the effects of various production parameters, namely (I) prior mixing of the API for a model formulation with PG, (II) mixing the model formulation with different cream bases to simulate a dilution process and (III) mixing by hand or mechanically. The effects of these parameters on the homogeneity of the resulting cream systems was evaluated microscopically and furthermore on the chemical stability of three incorporated APIs being fludrocortisone acetate, diclofenac sodium, and erythromycin belonging to the commonly used drug classes corticosteroids, non-steroidal anti-inflammatory drugs, and antibiotics was studied. Moreover, the influence of the listed parameters on the rheological properties of the resulting formulations was studied.

In a last step the influence of the aforementioned production parameters on the skin penetration of fludrocortisone acetate was investigated. This drug was chosen as a model drug to simulate the use of glucocorticoids in dermatological formulations. These have an important role in dermatological therapy and are amongst the most often prescribed drugs in dermatological treatment (Demana, 2014; Ring et al., 2012).

2. Materials and methods

2.1. Materials

Standard Corneofix F 20 adhesive tapes with a surface area of approximately 4.0 cm^2 were purchased from Courage+ Khazaka GmbH (Cologne, Germany).

The APIs fludrocortisone acetate (CAS: 514,363), erythromycin (CAS: 114-07-8) and diclofenac sodium (CAS: 15,307-79-6) were purchased from Sigma–Aldrich (St. Louis, USA), as well as ammonium acetate (CAS: 631-61-8). Potassium dihydrogen phosphate (KH_2PO_4) was purchased from ACROS Organics (Geel, Belgium).

All solvents as methanol (CAS: 67,561) and acetonitrile (CAS: 75-05-8) were of analytical grade and used as obtained from Sigma Aldrich.

The industrial cream bases representing the WO, OW 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:

WO 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 (Vienna, Austria).

OW 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 (Vienna, Austria).

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 (Vienna, Austria).

2.2. Skin tissue

For the skin penetration studies, fresh porcine ears were purchased from a local abattoir (EU Schlachthof Gantner, Hollabrunn, Austria). The age of the sacrificed pigs was about 6 months. The ears were removed before exposure of the carcass to high-temperature cleaning procedures to ensure integrity of the skin barrier (Herkenne et al., 2006). The excised ears were cooled during transport, carefully rinsed with cold water and dabbed dry before storage at −18 °C, which is a suitable storage method and does not affect the stratum corneum (SC) in ways that would interfere with the envisioned experiments (Hahn et al., 2010; Klang et al., 2011b; Stracke et al., 2006). All experiments were performed at room temperature after allowing the ears to thaw. The skin remained on the porcine ears for easier handling and prevention of skin contraction (Breternitz et al., 2007; Lademann et al., 2009).

2.3. Production of the formulations

In Table 1 codes for each formulation are presented. Various production parameters were investigated: the influence of mixing the API with PG prior to incorporation into the cream, the influence of manual (M) or automated (T) dilution on the homogeneity of the formulations and the type of cream base used for dilution of the

Table 1
Codes for the investigated cream dilutions. Based on the 1% API standard formulation from the OW basic cream containing 5% PG, 1:1 dilutions with WO, amphiphilic and OW creams were produced. OW is the first abbreviation in the code because of the standard formulation contained in every dilution. PG indicates prior mixing with PG, no means no prior mixing with PG, T means mechanical mixing with the TopiTec® system, M stands for mixing by hand, cream bases are indicated as follows: OW oil in water cream, A amphiphilic cream, WO water in oil cream.

	Prior mixing with PG		Means of mixing		Cream for dilution to 0.5% API		
Code	Yes	No	Manually	Automated	WO	A	OW
OW/PG/T/WO	+	–	–	+	+	–	–
OW/PG/M/WO	+	–	+	–	+	–	–
OW/no/T/WO	–	+	–	+	+	–	–
OW/no/M/WO	–	+	+	–	+	–	–
OW/PG/T/A	+	–	–	+	–	+	–
OW/PG/M/A	+	–	+	–	–	+	–
OW/no/T/A	–	+	–	+	–	+	–
OW/no/M/A	–	+	+	–	–	+	–
OW/PG/T/OW	+	–	–	+	–	–	+
OW/PG/M/OW	+	–	+	–	–	–	+
OW/no/T/OW	–	+	–	+	–	–	+
OW/no/M/OW	–	+	+	–	–	–	+