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Pharmaceutical development of a generic corticoid semisolid formulation

F. Fernández-Campos*, M. Obach, M.C. Moreno, A. García, J. González

Reig Jofre Laboratories, Avda Gran Capita 6, 08970 Sant Joan Despi, Barcelona, Spain

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ABSTRACT

The development of bioequivalent topical products is still a challenge, partly due to a lack of general methods available to perform this assessment. Several tests are proposed to fulfil this objective, such as dermatopharmacokinetic and pharmacodynamic evaluation. The aim of this study is the evaluation of a topical corticoid emulsion as a candidate to undergo further skin blanching tests. 0.1% mometasone furoate pickering emulsion was produced and evaluated regarding appearance, pH, viscosity assay and impurity D values, under three experimental conditions, 25°C/60% HR, 30°C/65% HR and 40°C/75% HR., in vitro drug release and ex vivo skin absorption profiles have also been studied. All the parameters evaluated remained within specifications in time. Based on impurity D levels, expected shelf life is over five years for formulations stored at 25 °C and three years for formulations stored at 30 °C. A moderate range of viscosity (16785–94611 mPa s) was found between batches, but this variability did not lead to statistical differences in Higuchi's release constants. Mometasone skin absorption parameters were found to be statistically equivalent to the reference formulation (elocom® emulsion), therefore, the present formulation is a good candidate for skin blanching tests.

1. Introduction

Semisolid formulations remain the gold-standard pharmaceutical formulation used to treat skin diseases [1]. They can be self-administered and obtain compliance and acceptance from patients, despite having different textures (their greasy feeling is sometimes a drawback). The difficulty of finding new chemical entities to treat different diseases has led pharmaceutical companies to develop generic products, with savings in both time and costs. There is currently a great deal of knowledge regarding development of oral generic products, this is regulated and successful results have been achieved. But unfortunately, this is not the case in topical products [2].

When designing a generic topical product, firstly a Q1 (qualitative) and Q2 (quantitative) similarity to the reference formulation must be achieved [3]. When Q2 is not known, a factorial design should be carried out to check the effect of different levels of excipient percentage in the innovative product, in order to meet the measured parameter in the reference formulation. Lastly, work should focus on Q3 similarity (microstructure), which mostly depends on the manufacturing process and some characteristics of the raw materials. Only topical solutions [2] are supposed to reach Q3 (no experimental demonstration needed). In other cases, a factorial design is usually performed, by studying the effect of process parameters, such us agitation time and speed, temperature, mixing order, etc. [4]. Many techniques are used to evaluate the microstructure of both the reference and the innovative products. Differential Scanning Calorimetry (DSC) is used to study lipid crystalline state and polymorphisms [5]. Microscopy or laser dispersion techniques can study emulsion droplet size and distribution [6]. Rheological parameters determine drug release [7]. Visco-elasticity studies check organization of the system or microstructure [8], obtaining the fraction of solid-like and liquid-like state. Drug release is a determining factor to evaluate possible candidates for skin absorption tests. Drug skin permeability is a very sensitive assay, used to test the performance of the formulation, since drug absorption is influenced by all the mentioned formulation characteristics [9]. Variations in these parameters have a strong influence on transdermal flux. Unfortunately, in vitro methods to test topical bioequivalence cannot substitute the in vivo assessment, due to the lack of strong correlations between these two models.

* Corresponding author.
E-mail address: Francisco.fernandez@reigjofre.com (F. Fernández-Campos).

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In 1998, the FDA approved a topical bioequivalence guideline, based on drug dermatopharmacokinetics (DPK) [10]. Both products (reference and innovative) were applied in vivo and skin tape sprites were collected and analysed, to quantify drug amounts as a function of time. Statistical evaluation led to conclusions about equivalence between the formulations. Unfortunately, the hypothesis of using the kinetic profile to test bioequivalence failed, because contradictory results were obtained by different laboratories when a cross-validation was performed using this model [2]. The FDA subsequently removed this guideline. Further investigation in the DPK method was performed to ascertain the reason for this failure and to reduce assay variability. N'Dri-Stempfer et al. [11] proposed several improvements to achieve this goal, such as including the two first strips in the DPK analysis, improving drug quantification, cleaning method for excess formulation applied to the skin and sampling methodology, ensuring that the whole stratum corneum was removed. Although these modifications made tape stripping a more robust assessment, it seems that DPK is still limited to testing drug bioequivalence when its target site is the stratum corneum, such as antifungals.

Other promising equivalence methods have been proposed for use when the action of the drug occurs in deeper skin layers (epidermis and dermis), such as microdialysis [12], open flow microperfusion [13], confocal raman spectroscopy [14], but none of them have been approved yet.

There is only one authorized method to evaluate topical bioequivalence, skin blanching induced by corticosteroids [15]. Which is a pharmacodynamic test; after a topical application of a corticoid, vasoconstriction takes place, leading to an area of skin-whitening. This blanching effect can be measured with a skin-colorimeter [16], and a dose-response curve can be obtained. Additionally, equivalence in a clinical trial endpoint between the reference product and innovative product could lead to a generic topical product approval.

Corticoids are still one of the most popular treatments for a wide variety of skin disorders, from allergy reactions and contact dermatitis to psoriasis, vitiligo and other autoimmune diseases with skin symptoms. Mometasone furoate is a high potency corticoid presented in topical and nasal formulations.

The aim of this work is the development and evaluation of a 0.1% mometasone furoate emulsion, in terms of appearance, pH, viscosity and drug and impurity levels over time. The Release and skin absorption profile was studied and compared with a reference product, elocom®. In vitro equivalence of the reference and the innovative product was statistically evaluated after estimation of permeation parameters. This equivalence guided the choice of candidate to undergo a skin blanching test, in order to perform a future bioequivalence assessment.

2. Material and methods

2.1. Materials

Mometasone furoate (Newchem S.A Verona, Italy), white soft paraffin (Dilube, S.A. Olive Group, Gava Spain), propylene glycol monostearate (Quimidroga, Barcelona, Spain), stearyl alcohol and ceteareth-20 (Gattefose S.A.S. Saint Priest, France), hexylene glycol and titanium dioxide (Sucesores de Jose Escuder S.A., Barcelona, Spain), aluminium starch octenylsuccinate (Safic Alcan Specialities, Barcelona, Spain) and purified water were used to produce an emulsion.

To analyze mometasone furoate in the semisolid formulation, acetonitrile (ACN) (Panreac, Barcelona, Spain), beclometasone dipropionate (Sigma-Aldrich, Madrid, Spain) and impurities 9,11-Dexaepoxide (8-DM), impurity 8-DM-21-Mesylate, impurity Mometasone, impurity 8-DM-21-Chlorine, impurity 8-DM-21-Chlorine-17-Furoate (impurity D) (from Newchem S.A Verona, Italy) and specific impurity 1 (Siemsgluss Iberica S.A. Sant Vicenç dels Horts, Sapin) were used. Elocom® (Merck Sharp & Dohme, Spain) was used as a reference formulation (white soft paraffin, propylene glycol monostearate, stearyl alcohol and ceteareth-20, hexylene glycol, titanium dioxide, aluminium starch octenylsuccinate and water).

2.2. Methods

2.2.1. Preparation of the formulation (RJ emulsion)

0.1% mometasone furoate RJ emulsion was prepared as follows.

Oil phase components composed of white soft paraffin, propylene glycol monostearate, stearyl alcohol and ceteareth-20, were melted at 70-75 °C and mixed. Water phase components (hexylene glycol and purified water) were heated at the same temperature and pH was adjusted to 4.0 with phosphoric acid. Mometasone furoate was added to the water phase at 70 °C and when dissolved, the water phase was added to the oil phase and mixed. Titanium dioxide previously sieved and aluminium starch octenylsuccinate were added to the blend. They were added after the mixture of the two phases since these excipients are suspended in the cream. The mixture was homogenized for 10 min and allowed to cool to 25-30 °C. As a result, a white homogeneous W/O emulsion was obtained.

The bulk emulsion was packed in 30 g aluminium tubes and subject to stability studies.

2.2.2. Analysis and validation of mometasone and its degradation products

Quantification of parent drug and degradation products were performed and validated (ICH Q2A) [17] using a High performance liquid chromatography Alliance 2695 provided with UV-Vis detector PDA 2996, Waters (Spain).

Mometasone analysis. Mobile phase was composed by miliQ water: ACN (45:55, v:v) flowing at 1.8 mL/min through a C8 chromatographic column coupled with a C8 pre-column heated at 30 °C. The wavelength was set at 254 nm and injection volume was 20 μL. A solution of beclometasone dipropionate, 50 mg/mL in ACN, was used as an internal standard (IS) to quantify and validate mometasone furoate in emulsion. Linearity samples were prepared by weighing an appropriate amount of mometasone furoate and diluted with ACN (to reach 80–120% of nominal concentration). 5 mL of IS were added to each working solution and diluted to 10 mL with ACN. A calibration curve, composed of 5 standards, was prepared in triplicate. To assess linearity, the correlation coefficient (r) was evaluated, as well as the ANOVA of response factors and coefficients of calibration equation.

The recovery of the analytical method was evaluated by comparing the HPLC response between the mometasone standards in ACN and the response of mometasone spiked in placebo cream (at 80%, 100% and 120% of nominal concentration). Approximately 0.7 g of spiked emulsion were accurately weighed in a screw-capped centrifuge tube and 5 mL of mometasone furoate solution and 5 mL of IS were added and mixed. The tube was centrifuged for 10 min at 3000 rpm. 4 mL of the supernatant was diluted to 10 mL with ACN.

Selectivity was determined by examining chromatograms of placebo samples for interfering peaks at retention times of mometasone or beclometasone.

Repeatability and accuracy were assessed using 9 determinations, covering the procedure specified range (3 concentrations/3 replicates each). The same solutions were prepared and analysed in a different day by a different person to study the

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