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Development of performance matrix for generic product equivalence of acyclovir topical creams

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ABSTRACT

The effect of process variability on physicochemical characteristics and in vitro performance of qualitatively (Q1) and quantitatively (Q2) equivalent generic acyclovir topical dermatological creams was investigated to develop a matrix of standards for determining their in vitro bioequivalence with reference listed drug (RLD) product (Zovirax®). A fractional factorial design of experiment (DOE) with triplicate center point was used to create 11 acyclovir cream formulations with manufacturing variables such as pH of aqueous phase, emulsification time, homogenization speed, and emulsification temperature. Three more formulations (F-12–F-14) with drug particle size representing RLD were also prepared where the pH of the final product was adjusted. The formulations were subjected to physicochemical characterization (drug particle size, spreadability, viscosity, pH, and drug concentration in aqueous phase) and in vitro drug release studies against RLD. The results demonstrated that DOE formulations were structurally and functionally (e.g., drug release) similar (Q3) to RLD. Moreover, in vitro drug permeation studies showed that extent of drug bioavailability/retention in human epidermis from F-12–F-14 were similar to RLD, although differed in rate of permeation. The results suggested generic acyclovir creams can be manufactured to obtain identical performance as that of RLD with Q1/Q2/Q3.

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1. Introduction

Zovirax® cream was approved by US/FDA in 2002 for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents. It is a topical dermatological product containing 5% w/w of acyclovir in aqueous cream base formulated with cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum as inactive ingredients (Zovirax, 2002). Acyclovir is a synthetic purine nucleoside analog with in vitro and in vivo inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV) (Acosta and Flexner, 2011). There are no generic acyclovir topical dermatological cream products available at this time in the market. The possible generic products of acyclovir topical cream have to conform to the same standards of quality as that of Zovirax® cream (reference listed drug product, RLD) and demonstrate clear bioequivalence (BE) by in vivo or in vitro methodologies. The availability of product quality metrics is critical to demonstrate that generic pharmaceutical drug products are therapeutically equivalent and interchangeable with their associated innovator's product.

A list of in vivo and in vitro methods have been provided to establish the BE under regulation 21CFR320.24(b) 44 (21CFR320.1, 2014; 21CFR320.24, 2014). In vivo studies in humans comparing drug/metabolite concentrations in an accessible biological fluid, in vivo testing in humans of an acute pharmacological effect, and controlled clinical BE trials in humans to establish ability to achieve an equivalent clinical endpoint with no evidence of differing safety profile are to be chosen as the first, second, and third approaches. The in vitro methods are to be chosen as the next available choices. The sponsors may choose any other rational approach and provide data to convince FDA on the use of such approach in demonstrating bioequivalence. One or more of these approaches might be used to demonstrate BE. For example, the

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bioequivalence of solid oral dosage forms intended for systemic delivery is established by in vivo pharmacokinetic (PK) studies with a support of comparative in vitro drug release data. This approach has been successfully applied to a large number of drug products (Kryscio et al., 2008). However, the conventional in vivo BE study with PK endpoints such as C_{max} and AUC is neither appropriate nor feasible for establishing BE of topically applied dermatological products. Determination of topical bioequivalence for locally acting drugs in skin is more complicated as local drug concentrations cannot be measured directly. The guidance on bioavailability and bioequivalence drafted by Committee of Proprietary Medical Products (CPMP) of the European regulatory authorities stated "for medicinal products not intended to be delivered into the general circulation, the common systemic bioavailability approach cannot be applied" (EMA, 2000). The US FDA provided certain recommendations with respect to the establishment of BE for such specific products (FDA, 2010). Draft guidance documents on locally acting topical drug products such as cyclosporine ophthalmic emulsion and acyclovir ointment have been developed by FDA to provide recommendations to sponsors to meet statutory and regulatory requirements (FDA, 2012, 2013). Generally, FDA addresses the issue on a case by case basis as outlined by the drug-specific guidance. Therefore, it is necessary to identify the key scientific principles for consistent and efficient identification of bioequivalence methods for locally acting topical dermatological products.

The current regulation requires conducting clinical endpoint trials for demonstrating BE between topical generic and RLD products when alternative methods, such as pharmacodynamic endpoint measures are not feasible (21CFR320.1, 2014; 21CFR320.24, 2014). Topical glucocorticoids (Chang et al., 2013b) are an example of products where a clear pharmacodynamic endpoint (skin blanching) is possible. Clinical endpoint bioequivalence studies with topical drug products are lengthy and expensive (Shah et al., 1998). These studies are subjected to greater variability than other in vivo methods for determining bioequivalence. Thus, the large inter-subject variability and dichotomous nature of these clinical endpoint bioequivalence studies demand the enrollment of several hundred subjects to achieve sufficient statistical power (Bhandari et al., 2002; Donner and Eliasziw, 1994). In order to determine BE of acyclovir topical cream products for treating herpes simplex labialis, the primary endpoint is the time to complete healing of lesions. This is particularly challenging for three reasons: (1) the severity of lesions is confounding; (2) lesions last a short period of time and heal rapidly regardless of treatment; and (3) the effectiveness of therapy is related to the rapidity with which treatment is initiated. In two clinical studies conducted for Zovirax® cream, no significant difference was observed between subjects receiving Zovirax® cream or vehicle (Zovirax, 2002). The mean duration of the recurrent herpes labialis episode was approximately half a day shorter in the subjects ($n = 682$) treated with Zovirax® cream (4.5 days) compared with subjects ($n = 702$) treated with placebo (5 days). The considerable variability in clinical endpoints is common and renders the BE clinical design difficult to detect the small difference in therapeutic response between generic and RLD (Chang et al., 2013b; Yacobi et al., 2014).

A variety of surrogate methods such as skin stripping/dermatopharmacokinetics (DPK), dermal microdialysis (DMD), in vitro permeation studies and near infrared (NIR) spectroscopy have been explored to demonstrate the BE of topical dermatological products (Lionberger, 2008; Narkar, 2010; Yacobi et al., 2014). Yet these surrogate methods are even more prone to failures in detecting low drug concentration in skin due to their limited sensitivity, technical difficulty, and high variability. The scope and limitations associated with these techniques have been reviewed (Herkenne et al., 2008; Mateus et al., 2013; Narkar, 2010; Yacobi et al., 2014). For example, skin stripping has been used for testing BE of topical dermatological products acting in stratum corneum (N'Dri-Stempfer et al., 2008, 2009; Navidi et al., 2008; Parry et al., 1992). But this is unsuitable for studying the BE of topical dermatological products whose site of action is a compromised skin (e.g., cold sores due to herpes labialis).

The in vitro drug permeation across human skin and in vitro drug release testing may be suitable to test the sameness (Q3) of Q1/Q2 equivalent topical dermatological products with respect to their performance. Such in vitro tests have been recommended to test the product sameness under certain scale-up and post-approval changes (SUPAC) as it is believed to collectively reflect any differences due to several physicochemical properties such as solubility, particle size of drug, and rheological properties of vehicle (FDA, 1997). The present study was carried out to understand and identify the appropriate in vitro quality metrics that can discriminate the effect of process and formulation variables on critical quality attributes (CQA) of possible generic acyclovir topical cream formulations having the same Q1/Q2 to that of Zovirax®.

Quality by design (QbD) approach was used to study the effect of process and formulation variables on CQA of acyclovir topical cream formulations. The preparation of acyclovir cream typically involves homogenization of oil-soluble and water-soluble components along with the drug to form oil-in-water cream at 70 °C. Based on the preliminary process understanding, three process parameters (emulsification time, homogenization speed, and temperature of oil/water phases) were identified as critical process parameters (CPP). Moreover, the HSV-1 infection and replication occurs in the basal cell layer of the epidermis (Parry et al., 1992). Therefore effectiveness of acyclovir topical dermatological creams depends on drug permeation across skin and drug retention in epidermis (DRE), which in general is a function of the aqueous phase drug concentration (thermodynamic activity). The equilibrium water solubility of acyclovir was reported to be influenced by pH with the highest solubility being at pH < 3 and at pH > 9 (Shojaei et al., 1998). Thus pH of acyclovir cream products was chosen as a formulation variable in addition to the above three CPPs for studying their influence on CQA. A fractional factorial design (2^{4-1}) with triplicate center point was chosen to study the effects of process and formulation variability on product CQA. This is a Resolution IV design where estimation of the main effects is not confounded by two-factor interactions (Chang et al., 2013a). Accordingly 11 formulations were prepared and subjected to physicochemical characterization and in vitro performance testing to test the sameness (Q3) of Q1/Q2 equivalent acyclovir creams.

2. Materials and methods

2.1. Materials

Zovirax® cream was obtained from Bradley Drugs, Bethesda, MD, USA. Acyclovir (>99%) was purchased from RIA International LLC, East Hanover, NJ, USA. Propylene glycol USP, white petrolatum USP, mineral oil USP, glacial acetic acid USP and sodium lauryl sulfate (SLS) NF were purchased from Fischer Scientific, Norcross, GA, USA. Poloxamer 407 NF and cetostearyl alcohol NF were purchased from Spectrum Chemical Manufacturing Co., New Brunswick, NJ, USA.

2.2. Preparation of acyclovir cream formulations

Four process/formulation variables (pH of aqueous phase, emulsification time, homogenization speed and emulsification temperature) were studied using a fractional factorial design with