



Approaches for Bioequivalence Assessment of Topical Dermatological Formulations



Syed Arman Rabbani*

Department of Clinical Pharmacy and Pharmacology, RAK Medical and Health Sciences University, United Arab Emirates

*Corresponding author: Syed Arman Rabbani, Department of Clinical Pharmacy and Pharmacology, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, United Arab Emirates

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Abstract

The assessment of the bioequivalence (BE) of topical dermatological formulations is a long standing challenge. There are only a limited number of acceptable methods for determining BE between the generic topical dermatological products and reference list products. To establish the BE of most topical dermatological products, barring dermatological corticosteroids, the only method to-date has been to undertake tedious, time consuming and expensive clinical endpoint trials. Therefore, significant efforts are being made to find alternative approaches for BE assessment of topical dermatological formulations. The pharmaceutical scientists, dermatologists and regulatory agencies are considering promising surrogate approaches like derma to pharmacokinetic study (DPK), dermal micro dialysis (DMD) and in vitro studies as prospective strategies for establishing BE of topical dermatological products. This short review focuses on these potential surrogate approaches for demonstration of BE of generic topical dermatological products with an emphasis on their strengths and limitations.

Introduction

Table 1: Approaches for bioequivalence assessment of topical dermatological formulations [1,3,4].

Approach	Examples
Acceptable	Clinical trials
	Pharmacodynamic studies (vasoconstriction assay)
Potential	Dermatopharmacokinetic study (tape stripping)
	Dermal microdialysis
	<i>In vitro</i> release
	Pharmacokinetic study
Unacceptable	Suction blister
	Skin biopsy

Regulatory acceptable approaches for the determination of bioequivalence (BE) in order of preference are pharmacokinetic (PK) approach involving systemic measurement of the drug, Pharmacodynamic approach, comparative clinical studies and finally *in vitro* studies [1,2]. BE assessment of topical dermatological formulations is quite challenging as the pharmacokinetic approach cannot be applied to these formulations and there are only a limited number of acceptable BE methods. As of now clinical studies are the lone acceptable method for establishing BE of topical dermatological products with an exception to dermatological corticosteroids, where BE can be assessed by specific Pharmacodynamic approach recommended by the US-FDA [1,3]. Comparative clinical trials are generally tedious to perform, insensitive, highly variable, and expensive and involve a large patient population. Pharmacodynamic study is limited to dermatological corticosteroids only. There is a

need, therefore, to look for alternative BE assessment approaches for topical dermatological products. The table summarizes the BE assessment approaches for topical dermatological formulations. Table 1: Approaches for bioequivalence assessment of topical dermatological formulations [1,3,4]

Approaches for Bioequivalence Assessment of Topical Dermatological

Formulations

Clinical trial approach

Clinical trial approach can be used to show BE between the generic product and its reference listed drug for most of the topical

drug products. Comparative clinical trials are generally difficult to conduct, highly variable, and insensitive [5]. For these reasons, the FDA acknowledged the need for more sensitive and more efficient surrogate approaches for the assessment of BE of dermatological formulations. In addition, for specific products FDA provides it's BE recommendations for guiding the sponsor to perform specific studies for regulatory filing. In the absence of specific BE recommendations from FDA or the sponsors intent to use alternative methods, sufficient data pertaining to the use of such method should be provided by the sponsor to assure the FDA [6].

Pharmacodynamic approach

Pharmacodynamic study is the only well-established surrogate method which is currently accepted by most regulatory agencies

[3]. This approach is restricted to the BE assessment of topical corticosteroid products only. It is based on the skin blanching or “skin whitening” response following the application of topical corticosteroids due to their vasoconstriction activity [7]. This Pharmacodynamic response is measured at various time periods by a chromameter. This approach involves a relatively small number of subjects than the clinical trials.

Dermatopharmacokinetic approach

This approach is similar to a blood, plasma, urine pharmacokinetic approach applied to the stratum corneum. Dermatopharmacokinetic approach, which is known as tape stripping, involves drug concentration measurements with respect to time and provides information on drug uptake, apparent steady-state levels, and drug elimination from the stratum corneum based on a stratum corneum concentration-time curve [8]. In 1998, the FDA published a draft guideline [1] on this approach to assess BE of topical formulations but the guideline was subject to criticism, primarily due to a number of limitations, in particular the sources of variability and control ultimately leading to the withdrawal of the proposed draft guideline in 2002. Significant efforts have been made to evaluate the sources of variability and improve the original Dermatopharmacokinetic study [9]. The focus has been to standardize the Dermatopharmacokinetic study procedure. The promising approach is still marred by several limitations.

Dermal micro dialysis

Dermal micro-dialysis is a promising technique for the estimation of BE of topical formulations and has enticed a great deal of interest among researchers and the industry [10]. It is an *in vivo* method for estimation of cutaneous drug penetration with continuous sampling of drug fraction in extracellular fluid in the skin. It gives real-time measurement of the rate and extent of drug penetration into the skin. The technique can estimate topical drugs penetrating across both healthy and diseased skins. It has some limitations in case of lipophilic protein-bound and high-molecular weight drugs as well as its invasive nature.

In vitro release approach

In vitro release testing can be used to monitor the release and diffusion of drugs from topical dosage forms [11]. This testing uses a vertical diffusion system which can be separated by an excised skin or a synthetic membrane [12]. This approach is easier to conduct as compared to the *in vivo* testing, and also provides useful information on drug permeation mechanism. Many studies have backed the application of *in vitro* testing for estimation of BE of many topical products [13].

Pharmacokinetic approach

The application of pharmacokinetic approach in the BE assessment of topical dermatological products is limited. However,

in some special cases where there is significant systemic absorption pharmacokinetic studies can be used to assess the BE of topical products. One such special case is of generic lidocaine patches for which the FDA issued a draft guideline recommending the use of pharmacokinetic approach in BE assessment [13,14].

Conclusion

In conclusion, collaborative efforts of regulatory, industry and academicians are needed for the improvement and standardization of the existing BE assessment approaches for topical dermatological formulations. Considerable efforts are also required for the development of new alternative approaches.

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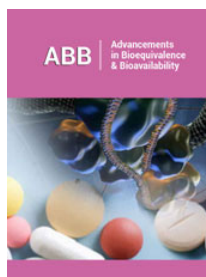
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