

Pharmacokinetic Studies of Topical Formulations - A Review

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Abstract

Pharmacokinetic assessment of topical formulation is represented as crucial and a challenging task to confront, as very small amounts of drug dispersed in an appropriate vehicle is applied to the skin and the amount of drug that actually reaches the systemic circulation is usually too small to be quantified. Various comparative clinical studies are used currently to establish bioequivalence for most drug formulations. The pharmacokinetics of topical drugs is generally termed as Dermatopharmacokinetics. The dermatological and cosmeceutical formulations are simply and efficiently assessed for quality and efficacy by the skin stripping technique, but it's not an easy task as it is difficult to make a large number of precise measurements due to limited area of application to the skin. After topical application and penetration of formulation, the cell layers of Stratum Corneum are successively removed from the same skin area using adhesive tapes. These tape strips contain the amount of corneocytes and the corresponding amount of penetrated formulation which can be determined by classical analytical chemical methods.

Keywords: Dermatopharmacokinetic; Stratum corneum; Bioequivalence; Skin stripping

Introduction

Bioequivalence is a relative term which denotes that the drug substance in two or more identical dosage forms, reaches the systemic circulation at the same relative rate and to the same relative extent i.e. their plasma concentration profiles will be identical without significant statistical differences. Thus in the case of topical formulations the drug has to penetrate through the layers of skin to reach the local site of action which is a complex process only due to the rate limiting barrier of the Stratum Corneum [1]. Stratum Corneum is the external layer of the skin composed of mainly corneocytes which are embedded in complex lipid matrix comprising of ceramides, cholesterol, and free fatty acids. This explains the behavior of Stratum Corneum as a barrier to the transport of hydrophilic substances.

The determination of the Bioequivalence of topical products involves the DermatoPharmacokinetic (DPK) approach [2]. The DPK approach includes any measure of drug concentration in the skin, whether directly or indirectly related to the drug's therapeutic action, which can be determined continuously or intermittently for a period of time. This may include the measurement of either drug concentration in Stratum Corneum over time and or drug concentration in serial biopsy samples. The measurement of the change in the Stratum Corneum drug concentration as a function of time is the objective of DPK approach and thus is a valid means of comparing a generic and innovator product for their ability to deliver drug to the deeper layers of the skin.

DPK studies offer certain advantages as it is painless, the active drug substances (moieties) are protected from gastric enzymes, it avoids first pass effect, and it is simple to terminate if any adverse or undesired effect is observed.

SUPAC-SS: It is the FDA guidance for "Nonsterile Semisolid Dosage Forms, Scale -U and Post Approval Changes: Chemistry, Manufacturing and Controls; *In Vitro* Release Testing and *In Vivo* Bioequivalence Documentation" (SUPAC-SS). It is intended to lower the regulatory burden while assuring the safety and effectiveness of the products under post approval changes. It defines three levels of changes they are:-

Level 1 change: These are the changes that don't have any detectable impact on formulation quality and performance.

Level 2 changes: These are the changes that could have a significant impact on formulation quality and performance.

Level 3 changes: These are changes that that are likely to have significant impact on formulation quality and performance.

Materials and Methods

Various techniques and methods practiced in dermatopharmacokinetics

There are many *in vitro* and *in vivo* methods for pharmacokinetic assessment of the dermal products, of which the most important and easy method is *in vivo* tape stripping technique, which and some other techniques are discussed below.

Tape stripping technique: The method consists of the standardized protocol of repeated applications and removal of adhesive tape on the skin surface, whereby consecutive layers of Stratum Corneum cells are sampled. As discussed by J Lademann et al. [3] Tape stripping is a standard measuring method for the investigation of the dermatopharmacokinetics of topically applied substances using adhesive films. These tape strips are successively applied and removed from the skin after application and penetration of topically applied substances; thus, the layers of the corneocytes and certain amount of topically applied substances are removed. The amount of the substances and the amount of Stratum Corneum removed with the single tape strip is to be determined for calculation of the penetration profile. The topically applied substances removed from the skin can be thus determined by various analytical methods like HPLC, Mass Spectroscopy and other spectroscopic measurements [4].

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Microdialysis: Microdialysis technique has been introduced to study the amount of drug after topical drug administration. The method consists of placing an ultrathin semi permeable hollow fiber called the probe in the dermis and per fusing this fiber with a tissue compatible sterile buffer at a very low rate with a Microdialysis pump. The probe functions as an artificial vessel in the dermis and thus exchanges small, diffusible molecules from the probe to tissue and vice versa. The recovery of the given compound closely reflects the concentration of unbound, that is, pharmacologically active compound in the intracellular fluid of the tissue surrounding the probe.

Pharmacodynamic approach: Pharmacodynamic approaches for certain selected corticosteroid drugs have already proved useful to document Bioequivalence, which is based upon the well-known skin blanching effects of corticosteroids. Also another endpoint which proves useful is the increase in Trans Epidermal Water Loss (TEWL) and desquamation rate of the Stratum Corneum following the application of retinoic acid dose. This happens over the course of several days and the phenomenon is readily followed with respect to time.

In Vitro permeation assessment: *In-Vitro* experiments are performed using artificial membranes or excised skin (from humans or an animal model) to screen and optimize topical formulations. The artificial membranes such as silicone membrane or even pig ear skin are used to serve the purpose. As mentioned by Shah et al. [5] the evidence available suggests that the rate of permeation of drugs from their formulations and the temporal profiles of such permeation may be similar as long as the formulation themselves are the same. Though there are differences in clinical end points the permeation rates have shown to vary and these finding still need investigation. In this method all comparisons must be performed with skin membranes cut from the same section of unblemished excised skin.

Confocal laser scanning: Confocal laser scanning microscopy appears to be a promissable tool for future DPK studies. This tool allows an investigator to focus a beam to a given depth within a tissue and to take reading of the concentration of an agent at the level of focus, thus a concentration profile can be generated following topical application of drug product [6].

Validation procedures: DPK method should be validated and verified. Method validation should include all aspects of sampling e.g. Stratum Corneum stripping and measurement of drug concentration

in Stratum Corneum, or any other analysis. At every critical step in the method development accuracy, precision, sensitivity, specificity, and other standard aspect of validating an assay methodology should be established. Following methods are used for assessing the validity of Stratum Corneum tape stripping method to determine the BE of topical formulations.

Cadaver skin permeation: As mentioned by the authors, this method validation procedure is done by selecting multiple sections of dermatome human trunk skin and mounted on Franz cells and placed in diffusion apparatus consisting of dermal receptor solution which is constantly stirred and maintained at optimal temperature. Each sections integrity was verified by measuring its permeability to titrated water. Subsequently test product was applied to a required number of sections and multiple donors were used for each section. At different time intervals the solution is replaced with fresh solution, and aliquot taken for assay by HPLC.

Vasoconstrictor assay: The vasoconstrictor potency of the test product and positive control are tested using normal human volunteers. The test product and the control were applied and after a specific time it was removed and sites skin color was evaluated using Minolta Chroma Meter. The change in scale value between pre-dosing and post dosing after the specified time was calculated for each site.

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