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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, as very small amount of drug (dispersed in an appropriate vehicle) is applied to the skin and the amount of drug that actually reaches the systemic circulation is too small to be quantified. In this paper we discuss, various comparative clinical studies those are used currently to establish bioequivalence for topical drug formulations. The method of establishing pharmacokinetics of topical drugs is generally termed as Dermatopharmacokinetics. The dermatological, cosmetical formulations are simply and efficiently assessed for quality and efficacy by the most common method of Dermatopharmacokinetics i.e. skin stripping technique, but it's not an easy task as it is difficult to make a large number of precise measurements due to the limited area of application to the skin. In this technique, after topical application and penetration of drug, 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 drug 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-time profiles will be identical without significant statistical differences. The United States, Food and Drug Administration (FDA) has defined bioequivalence as, "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study". [8] 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 because of the rate limiting barrier of the stratum corneum. This route of drug delivery has gained popularity because it avoids first-pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration. Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Percutaneous absorption of drugs from topical formulations involves the release of the drug from the formulation and permeation through skin to reach the target tissue. The release of the drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed. In order to enhance drug release and skin permeation, various methods such as the selection of a suitable vehicle [9], co-administration of a chemical enhancer [10], and iontophoresis [11] have been studied. There are various topical gel formulations available in the market for both local and systemic delivery of drugs and several others are in clinical trials. [12] These formulations are targeted to deliver both small molecules and large macromolecules. 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. [4, 7] The structure of the stratum corneum has been described as a "brick and mortar" type structure. In this analogy, the corneocytes are the bricks. A corneocyte is a protein complex that is made of tiny threads of keratin in an organized matrix. The keratin can hold large amounts of water between the fibers / threads. The stratum corneum contains about 12-16 layers of corneocytes and each corneocyte has a mean thickness of 1 micrometer, which depends upon the following factors:

- Age
- Anatomical location
- Frequency of exposure to UV radiation. [13]

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The determination of the bioequivalence of topical products involves the Dermatopharmacokinetic (DPK) approach. The dermatopharmacokinetic (DPK) approach is comparable to a Blood, Plasma and Urine Pharmacokinetics approach. DPK encompasses 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. When applied to diseased skin, topical drug products induce one or more therapeutic responses, where onset, duration, and magnitude depend on the relative efficiency of three sequential processes, namely, (1) the release of the drug from the dosage form, (2) penetration of the drug through the skin barrier, and (3) generation of the desired pharmacological effect. Because topical products deliver the drug directly to or near the intended site of action, measurement of the drug uptake into and drug elimination from the stratum corneum can provide a DPK means of assessing the Bioequivalence (BE) of two topical drug products. Two formulations can produce comparable stratum corneum concentration-time curves may be Bioequivalent, just as two oral formulations are judged Bioequivalent, if they produce comparable plasma concentration-time curves. Though the target site of action for topical dermatologic drug products in some instances may not be the stratum corneum, the topical drug must still pass through the stratum corneum, except in instances of damage, to reach deeper sites of action. In certain instances, the stratum corneum itself is the site of action, e.g. in fungal infections of the skin, fungi reside in the stratum corneum and therefore DPK measurement of an antifungal drug in the stratum corneum represents direct measurement of drug concentration at the site of action. In condition where the stratum corneum is disrupted or damaged, in vitro drug release may provide additional information toward the BE assessment. In this context, the drug release rate may reflect drug delivery directly to the dermal skin site without passage through the stratum corneum. For antiacne drug products, target sites are the hair follicles and sebaceous glands. In this setting, the drug diffuses through the stratum corneum, epidermis, and dermis to reach the site of action. The drug may also follow follicular pathways to reach the sites of action. The extent of follicular penetration depends on the particle size of the active ingredient if it is in the form of a suspension. Under these circumstances, the DPK approach is still expected to be applicable because studies indicate a positive correlation between the stratum corneum and follicular concentrations. Although the exact mechanism of action for some dermatological drugs is unclear, the DPK approach may still be useful as a measure of BE because it has been demonstrated that the stratum corneum functions as a reservoir, and stratum corneum concentration is a predictor of the amount of drug absorbed. For reasons cited above, DPK principles should be generally applicable to all topical dermatological drug products including antifungal, antiviral, antiacne, antibiotic, corticosteroid, and vaginally applied drug products. The DPK approach can thus be the primary means to document BA/BE. Generally, BE determinations using DPK studies are performed in healthy subjects because skin where disease is present demonstrates high variability and changes over time. Use of healthy subjects is consistent with similar use in BE studies for oral drug products. A DPK approach is not generally applicable when (1) a single application of the dermatological preparation damages the stratum corneum, (2) for otic preparations except when the product is intended for otic inflammation of the skin; and (3) for ophthalmic preparations because the cornea is structurally different from the stratum corneum. The following sections of the guidance provide general procedures for conducting a BA/BE study using DPK methodology. [14] 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. [1-2, 4]

SUPAC-SS

It is the FDA guidance for **"**Non-sterile 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. [4]

It defines three levels of changes which are as follows:

Level 1 Changes: - 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 are likely to have significant impact on formulation quality and performance. [4]

Various Techniques and Methods Practiced in Dermatopharmacokinetic

There are many in vitro, 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*; 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, 6]

Microdialysis

Microdialysis technique has been introduced to study the amount of drug after topical drug administration. The method consists of placing an ultra thin 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. [1, 4]

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. [4]

***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* 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. [4, 7]

Confocal Laser Scanning

Confocal laser scanning microscopy appears to be a permissible 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. [4]

Validation of Dermatopharmacokinetic 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. [1, 4]

Cadaver Skin Permeation

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 section's integrity is verified by measuring its permeability to titrated water. Subsequently test product is applied to a required number of sections and multiple donors are used for each section. At different time intervals the solution is replaced with fresh solution, and aliquot taken for assay by HPLC. [6]

Vasoconstrictor Assay

The vasoconstrictor potency of the test product and positive control are tested using normal human volunteers. The test product and the control are applied and after a specific time it is removed and site's skin color is evaluated using Minolta Chroma Meter. The change in scale value between pre-dosing and post dosing, after the specified time is calculated for each site. [6]

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