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Bioavailability of Topical Dosage Forms

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Introduction

As the largest organ in the human body, skin provides a unique and non-invasive platform to deliver active pharmaceutical ingredients into superficial lesions or even systemic circulation [1]. In recent years, topical drug agents are being employed for the local treatment of inflammation, infections (bacterial, viral or fungal) or to anaesthetise an area. The target site may be the outermost layer of the skin, the stratum corneum (SC), or deeper layers. Hence topical drug agents, to be effective should permeate through the skin more specifically the SC.

Drug product selection has emerged as a critical issue in therapeutics during the past few decades. Concern about health care costs has resulted in a tremendous increase in the use of generic drug products and currently about one half of all prescriptions can be substituted with a generic product. This is the obvious driving force for pharmaceutical industry to develop generic drug products [2]. The availability of generic versions of topical dermatological products remains constrained due to the limited methods accepted for bioequivalence evaluation of these products [3]. Since most of the topically applied molecules may not produce measurable concentrations in extra cutaneous biological fluids-the traditional method for assessing bioequivalence. Hence there is a need to assess the rate and extent of drug permeation into or through the skin as it is important not only to evaluate the usefulness of a drug for topical or transdermal delivery, but also to demonstrate bioequivalence (BE) for approval by regulatory agencies.

The acceptable approaches for assessment of bioequivalence of topical drugs include Clinical end point trials, pharmaco dynamic studies, dermatopharmacokinetic studies, in vitro methods such as Franz cell chamber, ex vivo methods such as isolated per fused skin models. However it should be clear that there is no single test that can be used to assess the bioavailability and bioequivalence of all topical dosage forms. The current review will delve into the strengths and limitations of the currently available methods to evaluate the performance and bioequivalence of topical dermatological products.

Clinical End Point Trials

The goal of the clinical endpoint bioequivalence study is to perform a comparison of clinical effects of a test and reference drug in order to infer bioequivalence. The clinical endpoint bioequivalence study is a complex compromise method of determining bioequivalence of products that cannot be evaluated by means of a pharmacokinetic or pharmaco dynamic study, or, in some cases, an *in vitro* study. A clinical study is subject to a very high degree of variability and sensitivity of clinical study to detect the difference between test product and the Reference listed drug (RLD) needs to be evaluated thoroughly. In some instances because of the lack of sensitivity of bioequivalence studies with clinical endpoints, additional tests, eg, flux measurement across human skin and in vitro dissolution may be needed to assure bioequivalence and drug product quality. The clinical studies used to support the RLD's regulatory filing are generally the foundation for the design of the clinical endpoint study for the generic drugs [4]. Even though it provides clinicians with a chance to directly evaluate the generic products, this method is the least sensitive and reproducible among all general approaches to demonstrate bioequivalence. Further, clinical endpoint trial is often costly, time-consuming, difficult to conduct, and entails large patient population [5].

Pharmacodynamics Studies

For certain topical drugs, specifically the corticosteroids, pharmaco dynamic measurements represent an accepted approach with which to establish bioequivalence between different formulations and are used, as well, in the development of new chemical entities in the same therapeutic class. In fact, the only accepted surrogate method to clinical trial by several regulatory agencies is the pharmaco dynamic study. They are much simpler than clinical end point studies and in volves less patient population. However, high inter-subject variability is the major limitation to this type of evaluation. With the exception of the vasoconstrictor assay for corticosteroids, no methodology to

quantify the rate and extent of drug delivery to the skin has been validated [6].

Corticosteroids produce skin blanching at the site of application and this response has been correlated with clinical efficacy. McKenzie and Stoughton developed the first documented, single reading time, visual-assessment procedure for comparing corticosteroid performance. As this approach is rather subjective, the methodology has been refined and improved over the decades to the point of using a chromameter to quantify the blanching response [7].

In addition to the vasoconstriction effects of dermatological corticosteroids, other pharmaco dynamic responses have also been reported. For instance, the vasodilatation effect of topical NSAIDs caused by nicotinic acid can be used to evaluate the absorption of topical NSAIDs by a laser Doppler velocimeter [8]. In addition, application of trans epidermal water loss (TEWL) effect in assessing the absorption of topical retinoid has also been reported [9].

Dermatopharmacokinetic Studies

Dermatopharmacokinetic -pharmacokinetic approach applied to drug concentrations in stratum corneum has recently evolved as a method to assess bioequivalence of topical products. It involves determination of drug concentration in the stratum corneum by sequential removal of thin layers of stratum corneum. This can be assessed by physical dermato techniques (skin washing, skin stripping), bioengineering techniques (trans epidermal water loss).

Tape stripping involves sequentially removing microscopic layers (~0.5-1.0µm thick) of SC by placing an adhesive tape strip onto the skin surface, followed by gentle pressure to ensure good contact and subsequent removal by a sharp upward movement [10], which may be repeated 10 to more than 100 times. Although, it is a relatively painless and non invasive technique, it might disrupt the integrity of the water barrier properties of the SC. Amongst the many variables that hamper the precision and reproducibility of this method is the fact that stratum corneum thickness differs between each individual - hence, normalization is necessary.

Micro Dialysis

The direct measurement of local drug concentration levels at discreet skin locations with minor trauma has recently become possible with the introduction of cutaneous micro dialysis. It is an in vivo sampling technique that allows real-time, continuous monitoring of the extracellular concentration of drug/metabolite in the dermis and hypodermis. When a topical formulation is applied onto the skin and perfusate is pumped through the implanted membrane system, drug molecules from the topical formulation present in the dermal interstitial fluid diffuse (driven by the concentration gradient) into the lumen of the membrane, resulting in the presence of drug in the perfusion medium collected as dialysate.The dial sate is sampled at various intervals of time and the drug concentration in the dialysate. The can be determined quantitatively [11]. The absorption profile of the drug (the Cmax, Tmax, absorption constant, AUC, and lag time) can be determined from the plot of free drug/metabolite concentration in the dermis or hypodermis as a function of time.

In vitro Techniques

Franz cell chamber

The most widely used in vitro technique to assess topical drug bioavailability is the Franz cell chamber: a two-compartment system, with a donor compartment and receptor compartment separated by human skin (preferred for most studies), animal skin (typically porcine skin), or an artificial membrane. When skin is used, it can be isolated into epidermis and dermis by enzymatic digestion, heat, chemicals, or dermatome to determine drug absorption parameters for each tissue subsection. To assess topical bioavailability using the Franz cell, the quantity of the drug/metabolite should be determined in the applicator (spreader, glass rod, loop), donor chamber, surface washings, stratum corneum (SC). Because the Franz cell is a static system, the receptor fluid needs to be regularly sampled, stirred, and replaced with new fluid. A variant of the Franz cell is the Bronaugh cell, which is a flow-through system with regular perfusion/collection of receptor fluid [12].

ExVivo Techniques

Isolated per fused skin models

Ex vivo techniques involving per fused skin models allow assessment of topical drug absorption with consideration for the effects of microcirculation and metabolism but without the subsequent consequences of systemic absorption. Commonly used models include the isolated per fused bovine udder, porcine forelimb, or porcine skin flap. The basic foundation of each of these models is the surgical isolation of a section of animal skin or organ with a vascular circulation that can be cannulised, per fused with tissue-culture medium, and continuously sampled for topical drug/metabolite [12].

Conclusion

Various approaches are being made to assess the bioavailability of various topical dosage forms. Each approach has its own merits and demerits and the intricacy of cutaneous drug delivery makes the bioequivalence studies of topical products a challenge to be faced by all stake holders.

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