Bioequivalence of Topical Dermatological Drug Products

Kasha PC and Banga AK

Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, 3001 Mercer
University Drive, Mercer University, Atlanta, GA 30341

*To whom correspondence should be addressed:

Ajay K. Banga, Ph.D.
Professor and Chairman
College of Pharmacy and Health Sciences
3001 Mercer University Drive
Mercer University, Atlanta, GA 30341
E-mail: banga_ak@mercer.edu
Tel. 678-547-6243; Fax 678-547-6423
1. Introduction

Topical dosage forms are liquid or semisolid dosage forms, which are not intended for systemic absorption. These dosage forms comprise solutions, lotions, gels, ointments, patches, and foams; that are applied onto the skin either to elicit therapeutic effect within the skin or underlying subcutaneous tissue.

The Code of Federal Regulations: 21 CFR § 320.1 has the following definitions:

a) **Drug product** means a finished dosage form, e.g., tablet, capsule, or solution, that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.

b) **Bioavailability (BA)** is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, BA may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

c) **Pharmaceutical equivalents (PE)** means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.
d) **Pharmaceutical alternatives (PA)** means drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

e) **Bioequivalence (BE)** is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents (PE) or pharmaceutical alternatives (PA) becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Establishing BE for Topical Dermatological Drug Products has been a topic of discussion for many years between scientific community and the regulatory agency. Despite great advances in addressing the issues related to topical bioequivalence, many challenges remain due to the complexity of drug transport through the skin from different formulations and lack of harmonized guidance documents. Siewert *et al.* (2003) have acknowledged that no single test procedure would be suitable for the development, biopharmaceutical characterization, and quality control of all semi-solid topical dosage forms.

The FDA’s current approval strategy for most of the topical drug products (New Drug Application/Abbreviated New Drug Application) is based on clinical studies. Clinical trials to prove BE often lack sensitivity and require large and costly trials (FDA’s Critical Path Initiative § 4.3.3, 2004; Narkar, 2010). It may not be cost effective for generic manufacturers to conduct large clinical trials. Several surrogate methods have been in development to
address this issue as summarized in this review. However, adoption by industry is limited. The reason could be less competition for a relatively smaller market of topical dosage forms when compared to other dosage forms. The Federal Trade Commission (FTC) has put conditions on Novartis AG's Acquisition of Fougera Holdings, Inc. in order to protect the competition in the skin care market for certain products.

The scope of this review is to summarize different methods that can facilitate establishing BE of Topical Dermatological Drug Products.

2. Regulations Governing Bioequivalence in USA

The Code of Federal Regulation (CFR), Title 21, describes how the Food and Drug Administration (FDA) regulates food, drugs, cosmetics, biologics, tobacco products, veterinary products, radiation emitting products, and medical devices in the US. As part of Department of Health and Human Services (DHHS), the FDA’s mandate is to protect and promote public health. There have been significant amendments to the Food, Drug and Cosmetics legislation ever since the Sulfanilamide Elixir tragedy in 1937 (Skelly, 2009; Table 1). The US enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (DPCA 1984), widely known as the Hatch-Waxman Act, to lower the raising costs of prescription drugs by increasing the competition among manufacturers. The generic industry has flourished by the virtue of this legislation. However, due to lack of reliable alternative methods, clinical studies are required to establish BE of Topical Dermatological Drug Products (FDA’s Critical Path Initiative § 4.3.3, 2004). Topical BE has been a topic of much discussion among researchers, industry, and agency (Table 1).

Table 1 Regulatory information pertaining to BE of Topical Dermatological Drug Products

<table>
<thead>
<tr>
<th>Year</th>
<th>Comments</th>
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<tr>
<td>1906</td>
<td>The Food and Drugs Act</td>
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3. **BE of Topical Dermatological Drug Products**

In order to get an approval to market a generic copy of “pioneer or innovator drug product” must demonstrate bioequivalence to the Reference Listed Drug (RLD) in compliance with DPCA 1984. Simple solutions or liquid dosage forms may be exempted from this requirement through bio-waivers.

3.1. New Drug Products

3.1.1. NDA via 505(b)(2)

The new drug application relies on already existing safety and/or efficacy data of already approved drug product, but must demonstrate non-inferiority to the RLD,
for example, seeking approval of cream dosage form to the RLD (ointment or lotion).

3.1.2. Abbreviated New Drug Application (ANDA)

The new drug products intended for approval through the § 505(j) of DPCA 1984 (Table 1) must demonstrate PE and BE.

3.2. Approved Drug Products (NDA/ANDA)

“Same drug product formulation” means the formulation of the drug product submitted for approval and any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the agency’s determination of bioequivalence” (21 CFR § 320.1). In the case of any changes to the already approved product (same drug formulation), the NDA or ANDA holder may document BE with respect to unchanged formulation. The FDA’s Guidance for Industry: Nonsterile Semisolid Dosage Forms Scale-Up and Post Approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and Bioequivalence (SUPAC-SS, 1997) provides recommendations for pharmaceutical sponsors. The guidance defines “(1) the levels of change; (2) recommended chemistry, manufacturing, and controls (CMC) tests to support each level of change; (3) recommended in vitro release tests and/or in vivo bioequivalence tests to support each level of change; and (4) documentation to support the change.”

4. Demonstration of BE for Topical Dermatological Drug Products

Demonstration of PE and BE for Topical Dermatological Drug Products must be based on the intuitive choice from several available techniques. As envisaged by Franz (2011), a systematic approach for selecting an appropriate surrogate test can be adapted to establish BE
(Figure 1). The choice primarily depends on the therapeutic target and secondly the type of vehicle in which drug is formulated with emphasis on Q3 equivalence (Lionberger, 2004). Skin being the largest organ of the body, has several biologically and chemically distinct layers. To simplify the structure of skin with respect to partitioning of drugs, the outermost layer (stratum corneum) is lipophilic and protects the underlying dermis, which is hydrophilic. Thus, drug release from various vehicles (creams, lotions, gels, ointments, and foams) and diffusion into or through the skin is complex.

**Figure 1** Systematic approach to selecting an appropriate surrogate test to establish Bioequivalence of Topical Dermatological Drug Products (Franz TJ, AAPS Annual Meeting, October 2011); IVRT: In Vitro Release Testing, TEWL: Trans Epidermal Water Loss, IVPT: In Vitro Permeation Testing

4.1. Pharmaceutical Equivalence

Lionberger (2004) has classified the pharmaceutical equivalence of semisolid dosage forms as:
- Q1 equivalence – qualitative similar components as RLD
- Q2 equivalence – quantitatively similar components as RLD
- Q3 equivalence – Q1 and Q2 with structural similarity as RLD

4.2. In Vitro Release Testing (IVRT)

IVRT utilizes widely accepted Franz diffusion cells to estimate rate of drug release from drug products. It involves the application of a drug product on to a membrane (synthetic membrane, excised animal skin, or excised human skin) that separates the donor and receiver chambers. The receiver chamber simulates sink conditions in vivo. The rate of delivery obtained from these studies is assumed to be similar to the in vivo situation. The method has been widely employed in discovery research for screening formulations and understanding mechanism of cutaneous drug transport (Narkar, 2010). However, it is not recognized as a surrogate for in vivo BA/BE of new drug products (SUPAC-SS, 1997). However, Franz et al. (2009) have reported substantial evidence of in vitro – in vivo correlation (maximum rate of absorption, total absorption, and time to maximum rate of absorption) using dermatomed cadaver human trunk skin (0.5 – 0.9 mm; finite dose model) for glucocorticoids and retinoid dosage forms of different vehicles when compared to respective RLD. (Glucocorticoid formulations: Alclometasone dipropionate cream and ointment 0.05%, Halobetasol cream and ointment 0.05%, Mometasone ointment 0.1%; Retinoid formulations: Tretinoin gels 0.01%, 0.025%) It is important to note that in vitro excised human skin model provided discriminatory evidence across different vehicles (Alclometasone dipropionate cream versus Ointment; Betamethasone valerate foam versus lotion) in contrast to non-discriminatory vasoconstriction assay (Franz TJ et al., 2009). In addition, Lehman et al., in their recent evaluation of literature,
have concluded that using excised human skin would establish better in vitro – in vivo
correlation, provided the study protocols are harmonized.
SUPAC–SS (1997) provides a detailed description of the method along with
recommended instructions in the event of any changes to the already approved drug
product.

4.3. Tape Stripping (TS)

Tape stripping provides information on drug uptake, apparent steady-state levels, and
drug elimination from the stratum corneum based on a stratum corneum concentration-
time curve (FDA’s Draft Guidance, 1998). This method is also known as the
dermatopharmacokinetic (DPK) approach similar to blood, plasma, and urine analysis
for drug concentrations as a function of time.
Though the draft guidance document was withdrawn in 2002, the FDA has
recommended it as surrogate method for certain class of drugs, for example antifungals
that target the stratum corneum itself (Narkar, 2010). However, Au et al. (2010) have
illustrated the potential of standardized TS methods; demonstrating the BE of two 0.05%
clobetasol propionate cream formulations and bio-in-equivalence of cream and ointment
formulations. Pershing et al. (2003) have shown direct correlation between DPK
parameters in healthy patients and clinical safety/efficacy of tretinoin gel products in
patients with acne.

4.4. Microdialysis (MD)

Microdialysis is a continuous sampling technique in which the molecule of interest is
collected from the target tissue; thus providing insight into the time course of drug action
or biochemical monitoring of the tissue. The technique can be imagined as an artificial
capillary, in which a hollow semipermeable probe is carefully inserted into the site of
interest: brain, muscle, eye, and skin. Therefore, it provides valuable information of
unbound drug concentrations or biomarkers at the site closer to the pharmacological
action compared to the conventional plasma/blood drug concentration versus time.
Though it was developed for neurological research, it has gained acceptance in other
areas of research. Stenken et al. (2010), in their quest to answer, “how minimally
invasive is microdialysis in human skin,” have concluded that “probe insertion in the
skin leads to inflammatory responses, both acute and chronic, and an immunological
probe rejection response, all of which have the potential to affect experimental
microdialysis in different ways.” However, with respect to sampling of drug molecules
from the skin, perturbation of blood flow to the local tissue is critical which would
recover to normal in approximately two hours. The technique has been successfully
adopted and demonstrated for dermatological research as well as for demonstrating the
BE of topical dosage forms (Narkar, 2010, Stenken et al., 2010). The technique has
shown promise in published and unpublished research in our laboratories for monitoring
intradermal and subcutaneous tissue drug concentrations after application of transdermal
drug formulations (Chaturvedula et al., 2005; Katikaneni et al., 2011; Paturi et al, 2010;
Siddoju et al, 2011).
Benfeldt et al. (2007) have estimated, based on the variability component of dermal
microdialysis of Lidocaine cream and ointment products, the number of subjects as 27
for demonstrating BE with 90% CI and 80 –125% BE limits using two probes in each
test area, or 18 subjects using three probes per formulation application site. The required
number of subjects using dermal microdialysis is relatively smaller compared to traditional clinical efficacy trials requiring as many as 300 patients for demonstrating BE (Shah et al., 1998).

Dermal microdialysis technique is appealing, however, faces many limitations; such as technical difficulties, protein binding, variability associated with the recovery, and tissue trauma caused by probe insertion.

4.5. Spectroscopy

Various spectroscopic methods, including ATR-FTIR, NIR, and Raman, have been investigated for non-invasive measurement of the drug in the skin. Not all molecules can have quantifiable spectral features, which can be used to distinguish from the stratum corneum (Narkar, 2010). NIR has been widely explored as one of the process analytical technology tools in the pharmaceutical industry. The promising feature of NIR is relatively rapid data acquisition and in vivo applicability.

4.6. Pharmacological Response to Demonstrate BE

Pharmacodynamic approaches based on pharmacological response are more appropriate for dosage forms intended for local action at the site of application. Topical glucocorticoids (TG) are formulated in various vehicles to treat atopic dermatitis and psoriasis (Wiedersberg S, 2008). FDA Guidance recommends demonstrating in vivo BE of topical dermatologic corticosteroids based on the pharmacodynamics approach, Stoughton-McKenzie vasoconstrictor assay (Table 1). This test is based on the chromameter readings of skin blanching effect resulting from vasoconstrictive action of corticosteroids.
Several other tests were reported in the literature, for example, laser Doppler flow meter for measuring the blood flow to assess topical NSAIDs; Trans Epidermal Water Loss (TEWL) to evaluate absorption of retinoids; skin temperature increase by nicotinic acid esters (Narkar, 2010; Wiedersberg et al., 2008).

5. **Conclusion**

The intricacy of cutaneous drug delivery is very well addressed in the literature. Nevertheless, there is a knowledge gap between industry and regulatory agencies. It will not be possible to have a single step solution for demonstrating the BE of all Topical Dermatological Drug Products. However, FDA’s Guidance documents on surrogate methods could not only reduce US healthcare costs by encouraging competition among companies, but also increase the emphasis on product quality, in particular Q3 equivalence.
6. References

Note: Please refer the following references for detailed information.


Holmgaard R, Benfeldt E, Nielsen JB, Gatschelhofer C, Sorensen JA, Höfferer C, Bodenlenz M, Pieber TR, Sinner F. Comparison of open-flow microperfusion and microdialysis methodologies when sampling topically applied fentanyl and benzoic


