# Impact of Formulation and Manufacturing on Drug Delivery from Topical Drug Products Applied to the Skin

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## INTRODUCTION

The bioavailability of an active ingredient from a drug product is typically evaluated using pharmacokinetic studies in which the rate and extent to which a drug becomes available at or near the site of action (in the blood/plasma) is measured. However, for locally acting topical products applied to the skin, it has been historically challenging to evaluate bioavailability at or near the site of action in the skin, and thereby establish bioequivalence (BE) of prospective generic drugs.

In an effort to identify new in vitro, in vivo, and in silico methodologies that can be utilized to evaluate drug bioavailability at or near the site of action in order to establish BE, a multimillion-dollar research program under the Generic Drug User Fee Amendments (GDUFA) through the Office of Generic Drugs at the U.S. Food and Drug Administration was designed to advance public health by enhancing patient access to safe and effective generic drugs.

This poster provides an overview of case studies within the scope of the GDUFA science and research program that were conducted to better understand how differences in topical drug product formulation and manufacturing processes can impact bioavailability of the active ingredient at or near the site of action in the skin. The data were subsequently supported the development, and implementation of efficient, characterization-based approaches, for evaluation of drug product equivalence for topical drug products applied to the skin.

## GDUFA research program: Useful links

- **Generic Drug Research Priorities & Projects**

  https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects

- **Generic Drug Research-Related Guidances & Reports**

  https://www.fda.gov/drugs/generic-drugs/generic-drug-research-publications-resources

- **Generic Drug Research Collaborations and Fellowship Opportunities**

  https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

**Collaboration opportunities**

**Post-doctoral fellowships**

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## METHODS and RESULTS

### Case study on effect of formulation differences on drug delivery

To evaluate the effect of formulation differences on drug delivery, three gel formulations containing 0.5% w/w diclofenac sodium were manufactured with variations in polyethylene glycol 200 (PEG-200) concentration using the same manufacturing process. An in situ drying study was performed on human cadaver skin in Franz diffusion cells for selected formulations. A semi-infinite dose in vitro permeation test (IVPT) study was performed using human cadaver skin mounted in Franz diffusion cells.

The three gels demonstrated differences in degree of saturation of a model drug (diclofenac sodium) in the drug product during drying (Figure 1), which led to differences in product performance in vitro (Figure 2).

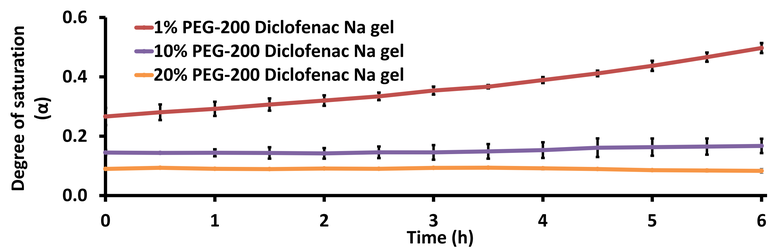


**Figure 1.** Degree of saturation profiles of diclofenac sodium in the PEG-200 gels (n=3 ± SD)

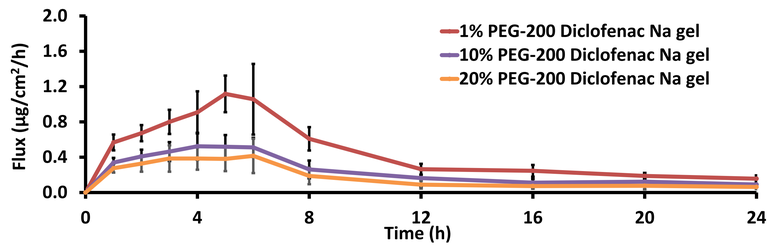


**Figure 2.** Flux profiles of PEG-200 diclofenac sodium gels through excised human cadaver skin using a semi-infinite dose (n=6 replicates per donor; 3 donors; data presented as mean ± SEM)

Data courtesy of Dr. Narasimha Murthy, Grant U01FD006507

### Case study on effect of manufacturing processes on drug delivery

To evaluate the effect of differences in manufacturing processes on product performance, seven creams with identical formulations were prepared with systemic variations in manufacturing. Nile Red, a hydrophobic dye that served as a model compound, was incorporated in the oil phase to facilitate microscopic visualization of the globules. The globule sizes were evaluated for each emulsion by confocal microscopy using a Zeiss LSM 510.

The seven creams showed differences in microstructure (e.g., globule size) due to the changes in manufacturing process (Figure 3), which in turn led to differences in product performance in vitro (data not shown).

**Table 1.** Composition of emulsions

| Ingredients | Quantity (% w/w) |
|---|---|
| Cetostearyl alcohol | 7 |
| Mineral oil | 12 |
| Cremophor® A25 | 1.5 |
| Cremophor® A6 | 1.5 |
| Propylene glycol | 8 |
| Water purified | 70 |

**Table 2.** Process variables used to manufacture formulations (F1-F7)

| Formulation code | Homogenization speed (rpm) | Homogenization time (minutes) |
|---|---|---|
| F1 | 500 | **20** |
| F2 | 1000 | **20** |
| F3 | **3000** | **20** |
| F4 | 5000 | **20** |
| F5 | **3000** | 10 |
| F6 | **3000** | 40 |
| F7* | **3000** | **20** |

*A controlled cooling protocol (ramping from 80 °C to 25 °C in 25 min) was followed for all the emulsions, except F7 which was allowed to cool to room temperature in an uncontrolled manner.

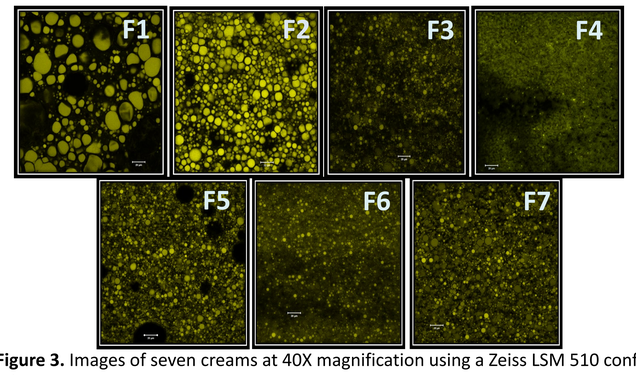


**Figure 3.** Images of seven creams at 40X magnification using a Zeiss LSM 510 confocal microscope.

Data courtesy of Dr. Narasimha Murthy, Grant U01FD005223

**The results of these case studies support the hypothesis that differences in formulation and manufacturing processes, which in turn affects the microstructure of a drug product, can impact the drug delivery of an active ingredient. Based on these results, characterization-based BE approaches for topical products applied to the skin that consider the impact of formulation and microstructure drug delivery have been developed and successfully utilized to support the approval of generic topical drug products.**

### Methodologies to support an assessment of BE for topical generic drug products

| | |
|---|---|
| Comparative clinical endpoint (CCEP) BE study | • In vivo BE study comparing the efficacy of a prospective generic product and the reference standard (RS), and both products are assessed to be superior compared to a placebo<br>• Can be used for: Majority of topical products |
| Vasoconstrictor (VC) study | • In vivo clinical BE study comparing the pharmacodynamic effect (i.e., skin blanching) of the prospective generic product and the RS<br>• Can be used for: Corticosteroid products |
| Waiver of in vivo BE studies | • Comparison of the formulation and/or dosage form of the prospective generic product and the RS<br>• Can be used for: Simple topical products (e.g., solutions) |
| Characterization-based BE approach | • Combination of in vitro and, in some cases, in vivo BE studies comparing formulation, microstructure, and performance of the prospective generic product and the RS<br>• Can be used for: Semisolid (e.g., gels, creams, etc.) topical products with certain formulations |

**Figure 4**. Common BE approaches for topical products applied to the skin.

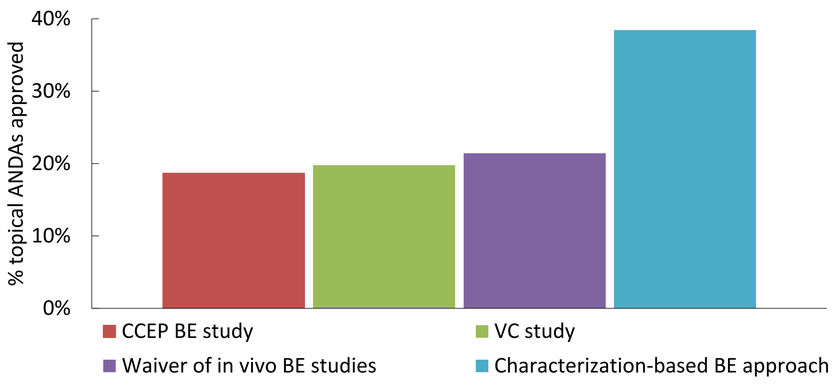


**Figure 5**. Approved topical abbreviated new drug applications (ANDAs) received between fiscal year (FY) 2018-FY 2023 by the four most common BE approaches for topical products (as of 03/20/2024). Bars represent approved ANDAs using a given BE approach normalized by the total number of approved topical ANDAs that were received between FY 2018-FY 2023.

## CONCLUSIONS

The results from the GDUFA-funded research supports the importance of considering the influence of both formulation and manufacturing processes when designing topical drug products applied to the skin, in addition to the mechanism of action of the active ingredient. This work has supported the development of efficient methodologies to demonstrate BE of prospective generic drugs to their respective brand name drugs, leading to increased availability of high-quality generic drugs for patients.