T1130-09-49

Development of In Vitro Skin Permeation Testing Method to Assess Bioequivalence of Topical Roflumilast Cream Formulations

Nahid Kamal*[1], Tasmin Ara Sultana[1], Muhammad Ali[1], Jackson Russo[2], Ying Jiang[2], Priyanka Ghosh[2], Ahmed Zidan[1], Muhammad Ashraf[1]

1. Office of Pharmaceutical Quality and Research V/Office of Pharmaceutical Quality/CDER/FDA.
2. Office of Research and Standards/Office of Generic Drug/CDER/FDA.

*Presenting and corresponding author

aaps PharmSci 360

DISCLAIMER: This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

CONTACT INFORMATION: Nahid Kamal (Email: nahid.kamal@fda.hhs.gov)

PURPOSE

A characterization-based approach may be used for demonstration of bioequivalence (BE) of topical drug products. This approach relies on establishment of a group of evidence which may include results of in vitro BE studies, such as in vitro permeation test (IVPT) and in vitro release test (IVRT), as well as other physicochemical and structural (Q3) characterization tests, such as characterization of visual appearance and texture, phase states and microstructure, rheological behavior, pH, and specific gravity. ZORYVE (roflumilast) topical cream (0.3%) has been approved for the treatment of plaque psoriasis in patients 6 years of age and older. As a complex multiphasic topical formulation, a demonstration of BE of generic roflumilast topical creams may be achieved using the characterization-based BE approach. In this regard, the current study evaluated the dermal availability of roflumilast after application of the drug product to dermatomed human cadaver skin samples. The feasibility of recommending IVPT as a component of a characterization-based BE approach for roflumilast topical cream products was also assessed.

METHODS

Roflumilast solubility in various solvents at both 25°C and 32°C was assessed to identify a suitable receptor solution for an IVPT study. The receptor solutions evaluated were phosphate buffered saline (PBS) (pH 7.4) with 0.02% Oleth-20, PBS (pH 7.4) with 4% bovine serum albumin (BSA), and PBS (pH 7.4). Sodium azide was added to each receptor solution at a 0.02% w/v concentration to prevent bacterial growth. Permeation of roflumilast from ZORYVE topical cream was then assessed using IVPT conditions listed in Table 1. Roflumilast in receptor solution and solubility samples were quantified using a validated HPLC-UV method.

Table 1: Testing conditions for developing the IVPT method

IVPT conditions	
Apparatus	Phoenix dry heat diffusion cell system
Formulation	ZORYVE (roflumilast) topical cream, 0.3%
Applied dose	15.0 mg/cm² of skin (equivalent to 79.65 µg of roflumilast)
Skin type	Disease-free human cadaver dermatomed skin, Male/Female donors of age < 65 yrs., thickness ~500 ± 100 µm
Receptor solution	Receptor solution will be selected based on solubility study results
Skin integrity test	TEWL, 10 g/m²/h or lower
Receptor solution volume	15 mL
Testing temperature	32 ± 1 °C
Stirring rate	600 rpm
Cell orifice area	1.77 cm²
Sampling time points	1, 6, 12, 18, 24, 30, 48, 60, 72, 84, and 96 h post dose application
Length of testing	96 h
Sampling and replacement volume	700 µL (sample collection volume = 500 µL + prime volume = 200 µL)
Testing type	Non-occlusive
Experiment donor and replicate	Four skin donors, 3 replicate skin sections for each donor

a b

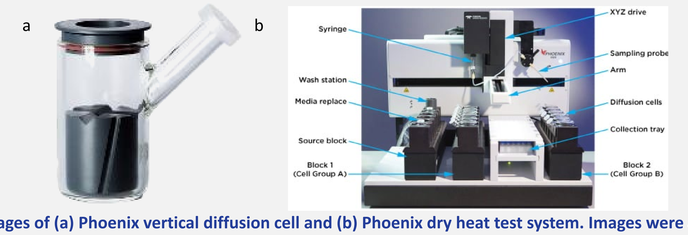

Figure 1: Images of (a) Phoenix vertical diffusion cell and (b) Phoenix dry heat test system. Images were adopted from Phoenix RDS Automated Diffusion | Teledyne LABS.

RESULT(S)

Saturation Solubility

The highest solubility of roflumilast was observed in PBS with Oleth-20 at both temperatures (Figure 2) and thus it was expected to provide the best solubility sink condition among the three receptor solutions evaluated. Therefore, PBS with Oleth-20 was chosen for the IVPT study.

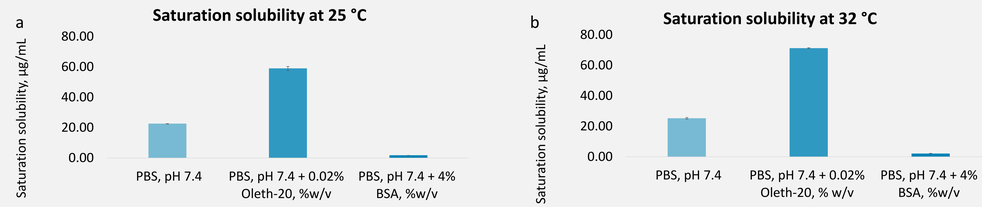

Figure 2: Saturation solubilities of roflumilast in the three candidate receptor solutions at (a) 25 °C and (b) 32 °C. Data are presented as mean ± SD, n=3.

IVPT Feasibility

Roflumilast permeated into the receptor solution was detected across all diffusion cells with a consistent lag time of 6 hours (Figure 3), likely due to the analytical sensitivity issues related to low drug detection for earlier timepoint samples. Mean cumulative amount permeated from all four donors was 1.09 µg/cm². Roflumilast flux profiles typical to finite dosing were clearly observed for roflumilast in data from all donors (A-D) (Figure 5). Both IVPT endpoints for BE evaluation (i.e., total cumulative amount (AMT) permeated and the maximum flux (J_{max}) at the peak of the drug flux profile) can be appropriately captured with the current IVPT conditions.

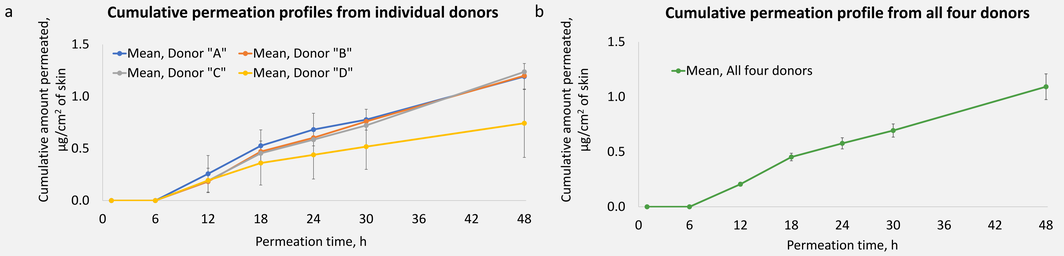

Figure 3: Cumulative permeation profiles of roflumilast across human cadaver skin samples from (a) individual skin donors (Donors "A-D", n=3 for each donor) and (b) all four skin donors. Data are presented as mean ± SD for each skin donor in sub-figure a and mean ± SE for all skin donors in sub-figure b.

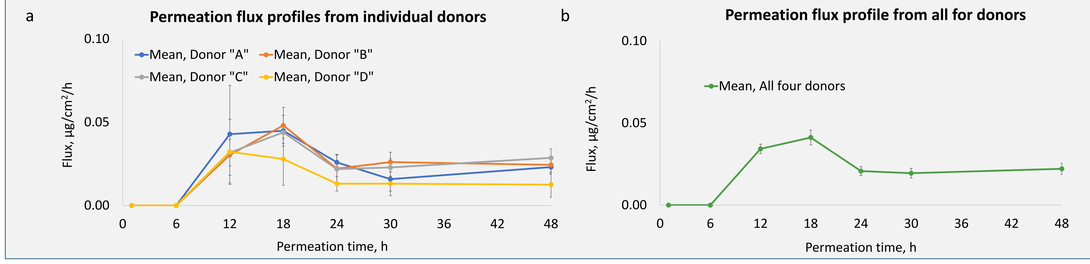

Figure 4: Permeation flux profiles of roflumilast across human cadaver skin samples from (a) individual skin donors (Donors "A-D", n=3 for each donor) and (b) all four skin donors. Data are presented as mean ± SD for each skin donor in sub-figure a and mean ± SE for all skin donors in sub-figure b.

CONCLUSION(S)

The results suggest that it is feasible to conduct an IVPT as a component of the characterization-based BE approach for roflumilast topical creams, following adequate development and optimization of an IVPT method.

ACKNOWLEDGEMENTS

This project was supported in part by an appointment (Muhammad Ali and Jackson Russo) to the Research Participation Program at the Center for Drug Evaluation and Research, U.S. Food and Drug Administration, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA. The views expressed in this poster are those of the authors and should not be construed to represent FDA's views or policies.