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Assessment of In Vitro Skin Permeation of Ruxolitinib from OPZELURA (Ruxolitinib Phosphate) Topical Cream, EQ 1.5% Base to Support a Demonstration of Bioequivalence

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PURPOSE

In vitro permeation testing (IVPT) may be used along with other characterization studies to support a demonstration of bioequivalence (BE) of topical products (collectively referred to as "characterization-based BE approach"). An IVPT study may provide information related to the rate and extent to which a drug from a complex multiphasic topical product becomes available at or near the site of action in the skin. The current research evaluated the local bioavailability of ruxolitinib after application of its brand name cream formulation to dermatomed human cadaver skin samples. The feasibility of recommending IVPT as a component of characterization-based BE approach for complex generic ruxolitinib phosphate topical cream, EQ 1.5% base products was thereby assessed. The research highlights the importance of development and optimization of experimental conditions for an IVPT method for the specific drug product of interest to support a demonstration of BE using the characterization-based BE approach.

METHODS

Ruxolitinib permeation from non-occluded, finite doses of Opzelura (ruxolitinib phosphate) topical cream, EQ 1.5% base ("Opzelura") was assessed across dermatomed human cadaver skin samples mounted to vertical diffusion cells (VDCs), as the IVPT parameters were developed and optimized. The IVPT parameters used in each IVPT run are listed in Table 1.

In addition, drug solubilities in three candidate receptor solutions were studied by using a shaker flask method. The drug concentration in the solubility samples and the receptor solution were quantified using a validated HPLC-UV method.

Table 1: Testing conditions for developing the IVPT method

IVPT Parameters	Run 1	Run 2	Run 3	Run 4
Apparatus	Phoenix dry heat diffusion cell system, automated sampling	Microette automated system	Microette automated system	Phoenix dry heat diffusion cell system, manual sampling
Applied product dose	11.0 mg/cm^2 of skin	15 mg/cm^2 of skin	15 mg/cm^2 of skin	15 mg/cm^2 of skin
Receptor solution	1) PBS, pH 7.4; 2) PBS, pH 7.4 + 0.02% Oleth-20; and 3) PBS pH 7.4 + 4% BSA. Sodium Azide, 0.1% was added in each medium.	PBS, pH 7.4 + Sodium Azide, 0.1%	PBS, pH 7.4 + Sodium Azide, 0.1%	PBS, pH 7.4 + Sodium Azide, 0.1%
Skin integrity test	Transepidermal water loss (TEWL), 10 g/m^2/h or lower	TEWL, 10 g/m^2/h or lower	TEWL, 10 g/m^2/h or lower	TEWL, 10 g/m^2/h or lower
Receptor solution volume	15 mL	6.5 mL	6.5 mL	9 mL
Sampling time	30 m, 1, 2, 4, 8, 12, 16, 20, 24, 48 h	6, 12, 18, 24, and 48h	1, 6, 12, 18, 24, 36, 48, 60, 72, 84 and 96 h	1, 6, 12, 18, 24, 36, 48, 60, 72, 84 and 96 h
Study duration	48 h	48 h	96 h	96 h
Sampling and replacement volume	700 µL (sample collection volume = 500 µL+ prime volume = 200 µL)	2 mL(sample collection volume= 1.5 mL+ rinse volume = 0.5 mL)	2 mL(sample collection volume= 1.5 mL+ rinse volume = 0.5 mL)	1 mL
Testing type	Non-occlusive	Non-occlusive	Non-occlusive	Non-occlusive
No. of samples (Donor and repllicates)	n=3, skin replicates from one donor ("A") (one additional non-dosed cell)	n=6, skin replicates from one donor ("B")	n=4, skin replicates per donor, 3 donors ("C", "D" and "E")	n=3, skin replicates per donor, 3 donors ("F", "G" and "H") (one additional non-dosed cell)

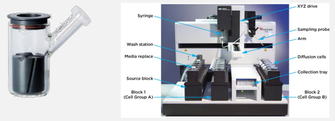

Figure 1: Images of (left) Phoenix vertical diffusion cell and (right) Phoenix dry heat test system.

Figure 2: Images of (left) Vision Microette vertical diffusion cell and (right) Vision Microette test system

Images adopted from : Phoenix RDS Automated Diffusion | Teledyne LABS and VISION® MICROETTE™ - Hanson Research Corporation - PDF Catalogs | Technical Documentation (medicalexpo.com)

RESULT(S)

Saturation Solubility

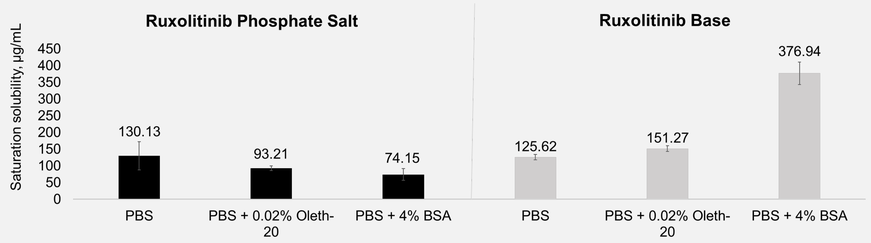

Figure 3: Saturation solubilities of ruxolitinib phosphate salt and ruxolitinib base in three candidate receptor solutions. Data are presented as mean ± SD, n=3.

IVPT - Run 1

Similar drug levels were detected in PBS alone and PBS containing 0.02% Oleth-20, starting from 8 h for some cells. Slightly higher ruxolitinib levels were observed in PBS containing 4% BSA, but drug levels in this receptor solution were not detectable until the last sampling timepoint at 48 h. Adding Oleth-20 or BSA to PBS did not appear to increase the extent or rate of drug permeation. Based on these results, PBS was selected as the receptor solution for subsequent studies.

The IVPT results indicated that it was feasible to detect the drug levels in the receptor solution. However, to better characterize IVPT profiles, it was necessary to improve the drug permeation and/or the analytical method to capture data at earlier timepoints.

IVPT - Run 2

After increasing the product dose applied and reducing the receptor solution volume to facilitate drug quantification, detectable levels of drug were observed in all samples collected; however, IVPT flux profiles continued to rise with no declining phase, not ideal for capturing the maximum flux (J_{max}) as one of the IVPT BE endpoints.

The study duration may not be long enough or there may be a lack of data points between the last few sampling time points to accurately describe the trend of the profile in that area.

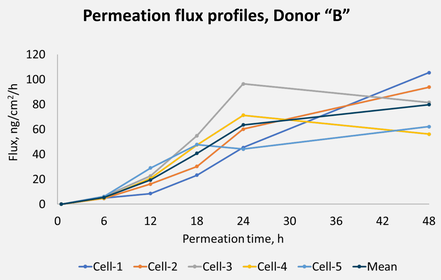

Figure 4: Individual cell/replicate and mean (n=5) permeation flux profiles for Donor "B".

Figure 5: Left Image: the skin appearance for five out of six replicates at the end of the 48 h IVPT study the skin remained flat. Right Image: One of the six skin sections exhibited a dome shape or upward deformation likely due to the positive pressure from auto-sampling and therefore the data from that replicate was excluded from data representation.

IVPT - Run 3

The extended study duration and more frequent sampling resulted in complete permeation flux profiles in some cells/replicates.

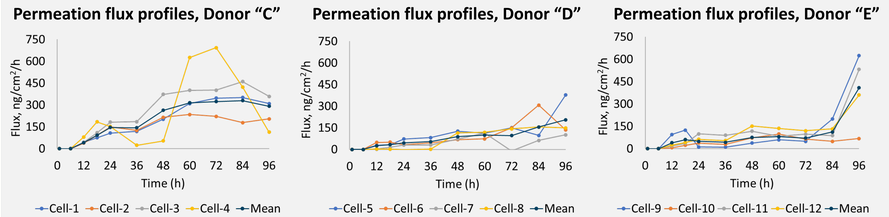

Figure 6: Individual cell/replicate and mean (n=4) permeation flux profiles for each of the three donors ("C", "D", and "E").

IVPT - Run 4

This repeat study was done with manual sampling compared to Run 3 and the results showed promising permeation flux profiles that might demonstrate a more obvious declining phase upon further method optimization (e.g., increasing study duration, or decreasing product dose). These results suggest that evaluation of drug permeation using an IVPT may be feasible for comparing the local availability of ruxolitinib phosphate topical creams.

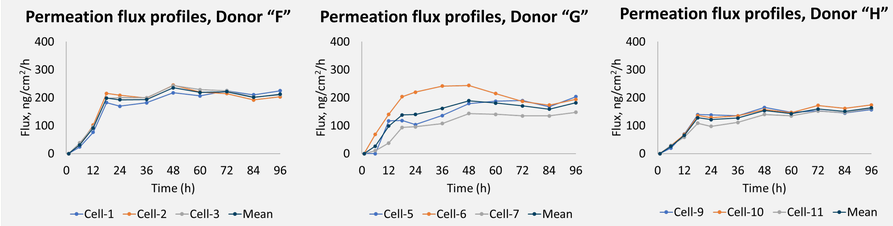

Figure 7: Individual cell/replicate and mean (n=3) permeation flux profiles for each of the three donors ("F", "G", and "H").

CONCLUSION(S)

This study demonstrated the feasibility of developing and optimizing an IVPT method for assessing ruxolitinib local bioavailability from complex cream formulations.

ACKNOWLEDGEMENTS & DISCLAIMER

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