Development of An In Vitro Permeation Test (IVPT) Method for Vaginal Creams

Lingxiao Xie[1], Weizhou Yue[1], Megan Kelchen[2], Priyanka Ghosh[2], Mengmeng Niu[2], Sam G. Raney[2], and Jie Shen[1,3]

[1]University of Rhode Island, College of Pharmacy, Kingston, Rhode Island, 02881

[2]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993

[3]University of Rhode Island, College of Engineering, Kingston, Rhode Island, 02881

Introduction

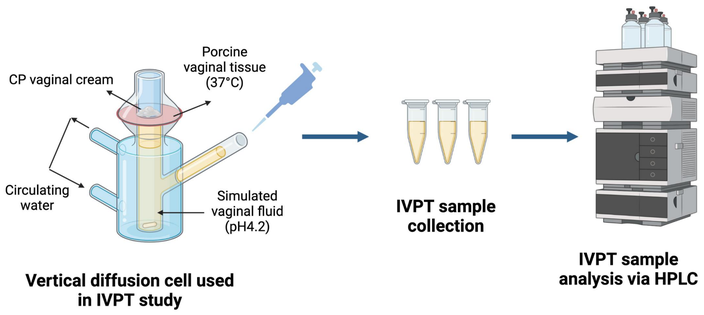
An in vitro permeation test (IVPT) can assess the rate and extent to which a drug permeates into and through a biological membrane. Validated IVPT studies can support a demonstration of bioequivalence (BE) for topical dermatological creams as part of a characterization-based BE approach that mitigates the risk of failure modes for BE through comprehensive comparisons of test and reference products. More than 50% of FDA-approved vaginal semi-solid drug products are creams. This research aimed to develop a reproducible and discriminating IVPT method using excised porcine vaginal tissues and to assess whether IVPT may be used to support characterization-based BE approaches for vaginal creams.

Learning Objectives

1. Explain the method development and validation of an IVPT method for vaginal creams.
2. Describe vaginal tissue permeation of clindamycin phosphate (CP) vaginal creams.

Methods

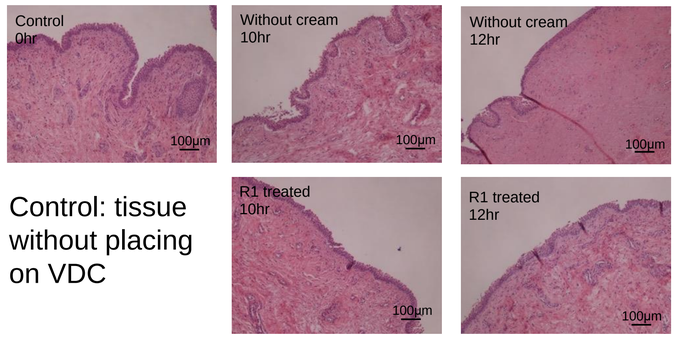
CP vaginal creams were chosen as the model drug products. The IVPT studies were conducted by mounting excised porcine vaginal tissues in a vertical diffusion cell (VDC) apparatus with a surface temperature of 37°C and simulated vaginal fluid (pH 4.2) containing 3% Brij O20 as the receptor solution. Samples were quantified using high pressure liquid chromatography (HPLC). Intra- and inter-day method reproducibility was assessed using a marketed 2% w/w CP vaginal cream (R1; *n*=3 cells/run, 3 independent runs (days)). The impact of variation in vaginal tissue between different animals on CP permeation was examined using tissues from 4 different animals (*n*=3 cells/animal tissue source). The discriminatory ability of the method was evaluated using 3 strengths (1%, 2%, and 3% w/w) of laboratory-made (LM) CP creams with the same components as R1 (*n*=3 cells/strength). The permeation of CP from R1 was compared with an approved generic for R1 (G) and a different marketed CP vaginal cream (R2).



Vertical diffusion cell used in IVPT study

Results

- Porcine vaginal tissues



Control: tissue without placing on VDC

Figure 1. H&E images of porcine vaginal tissues with or without CP cream (R1) treatment on VDC at 37℃.

- IVPT method reproducibility

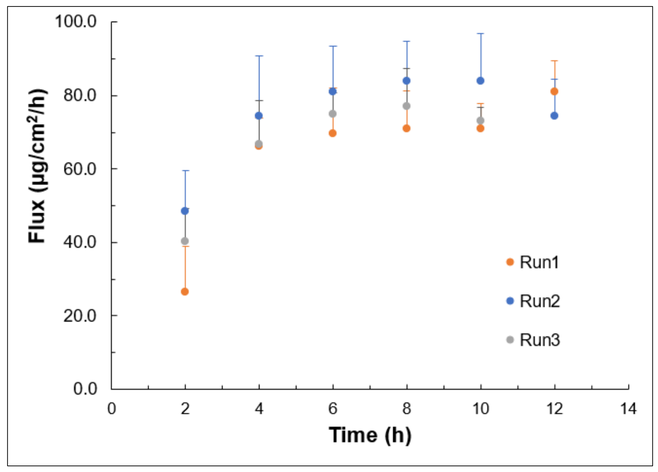


Figure 2. IVPT flux profiles of CP cream (R1) obtained from multiple runs using porcine vaginal tissues from the same animal (n=3 per run, mean ± SD)

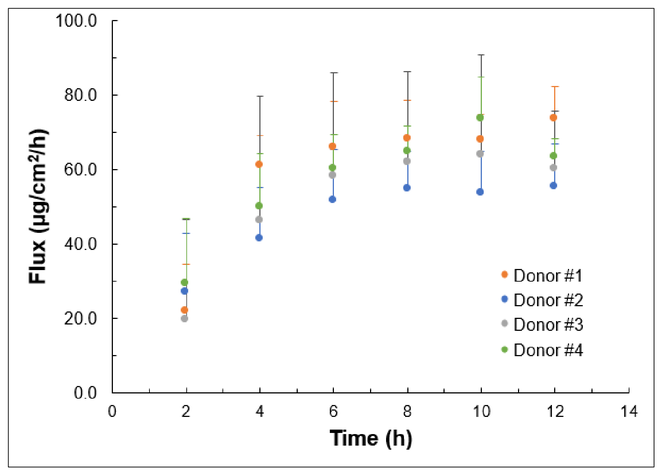


Figure 3. IVPT flux profiles of CP cream (R1) obtained from multiple runs using porcine vaginal tissues from different animals (n=3 per animal, mean ± SD).

- IVPT method discriminatory ability

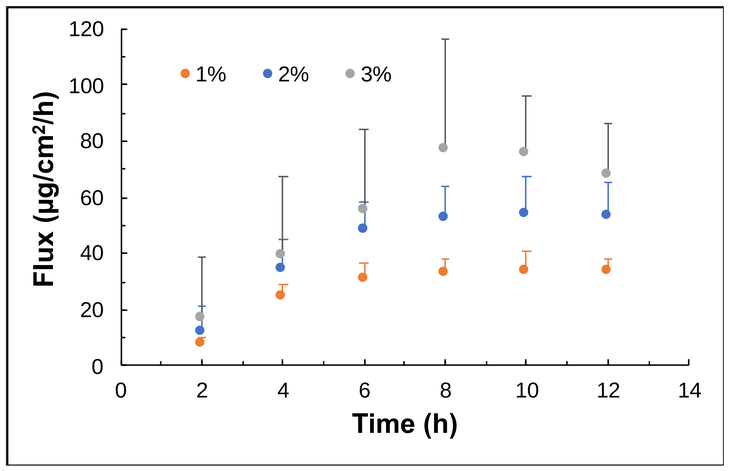


Figure 4. IVPT flux profiles of LM CP creams with different drug content (1%, 2%, and 3%, w/w) using porcine vaginal tissues from the same animal (n=3 cells/strength, mean ± SD).

- IVPT pivotal study

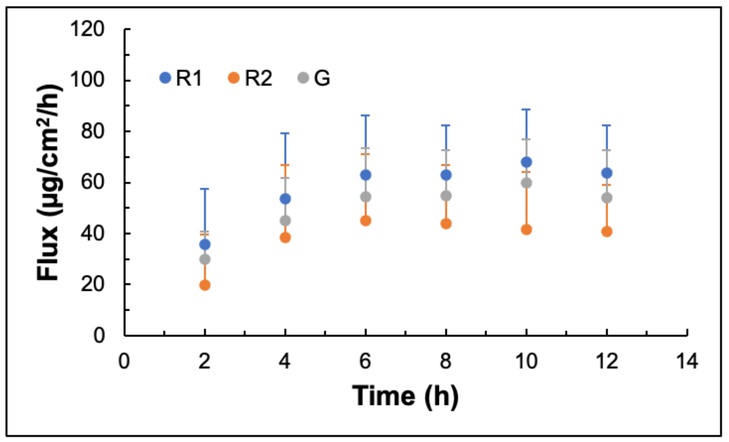


Figure 5. IVPT flux profiles of commercial CP cream products R1, R2, and G (generic product of R1) using porcine vaginal tissues from three animals (3 animals, n=3/animal, mean ± SEM).

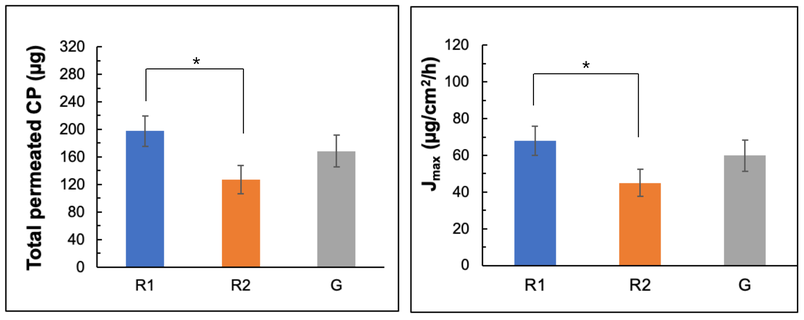


Figure 6. Cumulative permeated CP amount (12 hours) and maximum flux value (J_{max}) of CP cream products R1, R2, and G (3 animals, n=3/animal, mean ± SEM). Statistical analysis was compared between each formulations, *p<0.05.

Conclusions

A reproducible and discriminating IVPT method using porcine vaginal tissue was successfully developed for CP vaginal creams, suggesting that it may be feasible to develop IVPT methods that may support characterization-based BE approaches.

Acknowledgement

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