Impact of Fatty Acids on In Vitro Performance of Clindamycin Phosphate Vaginal Creams

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Introduction

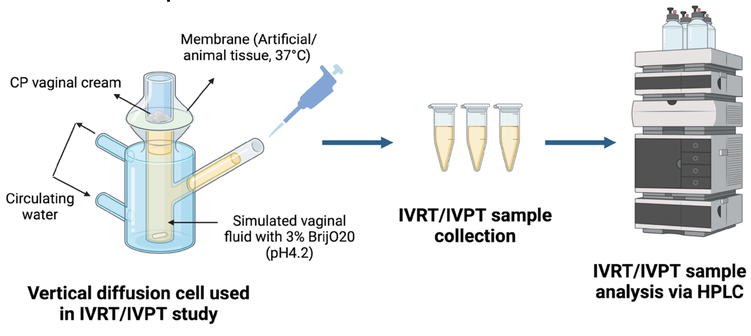
In vitro characterization-based bioequivalence (BE) approaches that mitigate the risks associated with potential failure modes for BE are successfully established for topical drug products applied to the skin. However, such BE approaches have yet to be established for locally-acting vaginal cream products. In order to develop characterization-based BE approaches for vaginal creams, it is essential to understand the influence of inactive ingredients on the critical quality attributes (CQA) and in vitro release and permeation of the active ingredients from vaginal creams. The objective of this study was to investigate the impact of variations in an inactive ingredient (stearic acid (SA)) on the CQAs and in vitro performance of clindamycin phosphate (CP) vaginal creams.

Learning Objectives

Obtain knowledge on the impact of material attributes on in vitro performance of CP vaginal creams.

Methods

Laboratory-made (LM) CP vaginal creams (2% w/w) prepared with SA containing different ratios of palmitic (PA) and stearic acid (SA) (LM-SA50 vs. LM-SA97) were compared to a marketed reference listed drug (RLD) CP vaginal cream. The quality attributes (drug content, rheological properties, and globule size) of the CP creams were characterized using established methodologies. The performance of the CP creams was evaluated via an in vitro drug release test (IVRT) and in vitro permeation test (IVPT) using vertical diffusion cell methods with polyethersulfone (PES) membrane (0.45 µm) and excised porcine vaginal tissue, respectively. Simulated vaginal fluid (SVF) containing 3% (w/v) Brij®O20 was used as the receptor solution for both studies. The IVRT and IVPT studies were conducted at 37°C for 6 h and 12 h, respectively. The CP release rate (n=6-9 cells per formulation) from the IVRT study and the cumulative CP amount permeated and maximum permeation flux (J_{max}) (n=3 cells per formulation per animal) from the IVPT study, were utilized to compare the CP creams.



IVRT/IVPT study conditions

Apparatus: Vertical diffusion cell

Receptor solution: SVF containing 3% w/v Brij®O20 (pH 4.2)

Membrane temperature: 37°C

IVRT: PES membrane

IVPT: Porcine vaginal membrane

Results

- **Drug content of CP creams**

Table 1. Composition of LM CP creams.

Ingredient	Concentration (%w/w)
Clindamycin phosphate	2.5
Purified water	71.5
Polysorbate 60	1.5
Benzyl alcohol	1.0
Propylene glycol	5.0
Cetostearyl alcohol	1.5
Mixed fatty acids esters	1.0
Mineral oil	12.0
Sorbitan monostearate	2.0
Stearic acid (SA)	2.0

Table 2. SA properties and drug content of the RLD and LM creams prepared with stearic acid containing different PA to SA ratios (Mean±SD, n=3 for RLD, n=9 for LM creams).

CP cream	RLD	LM-SA50	LM-SA97
SA Type	N/A	Stearic acid, 50%	Stearic acid, 97%
PA:SA (w/w)	N/A	54.8:44.8	<1.4:98.6
Drug content (%, w/w)	2.04±0.020	2.06±0.093	1.99±0.025

N/A: Not available

- **Globule size of CP creams**

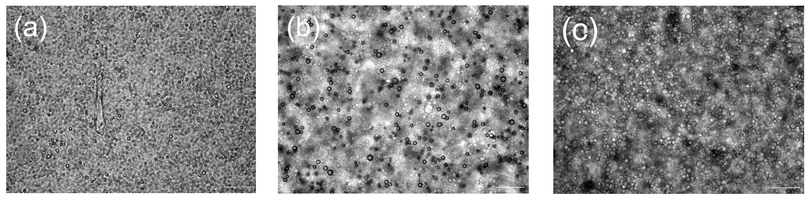


Figure 1. Optical microscope images of (a) the RLD cream, (b) LM-SA50 cream, and (c) LM-SA97 cream (scale bar = 100 µm).

Table 3. Globule size of CP vaginal creams prepared with different SA.

CP cream	RLD	LM-SA50	LM-SA97
Globule Diameter (d50, µm)	3.23	4.48	4.04
Span	0.87	1.11	1.01
Globule # Analyzed	3,540	1,383	2,635

- **Rheological properties of CP creams**
  - All three CP creams had shear-thinning property.
  - LM CP cream with SA97 had similar storage modulus and yield stress compared to the RLD product, which was lower than that of LM CP cream with SA50 (RLD ≈ LM-SA97 < LM-SA50).

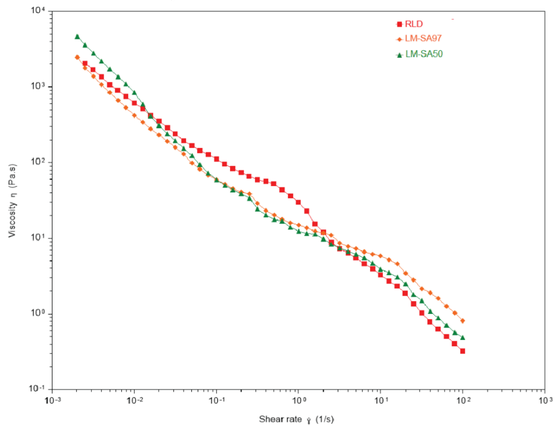


Figure 2. Viscosity vs. shear rate flow curves of LM-SA50, LM-SA97, and the RLD product.

- **IVRT and IVPT profiles**

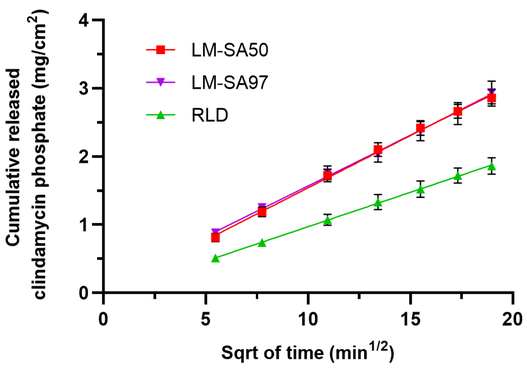


Figure 3. In vitro release profiles of CP creams analyzed using the Higuchi model (n=9 for LM creams; n=6 for the RLD, Mean±SD).

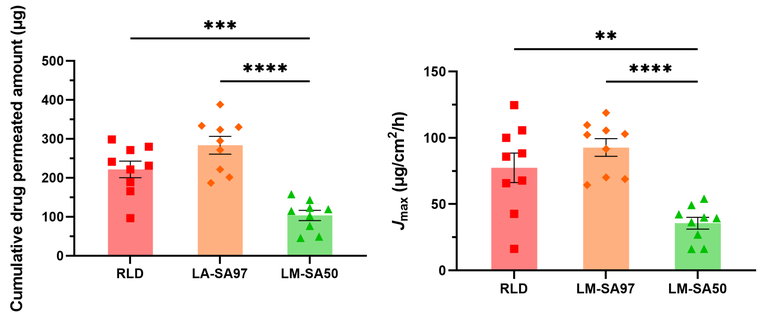


Figure 4. Cumulative permeated CP amount (12 hours) and maximum flux value (J_{max}) of CP creams (3 animals, n=3/animal, Mean±SEM). Statistical analyses were compared between each formulations, **p<0.01, ***p<0.001, and ****p<0.0001.

Conclusions

The present research demonstrated that differences in material attributes of SA may have the potential to influence the physicochemical and structural properties and in vitro performance of CP creams. However, additional analysis is necessary to understand the impact of such differences on the BE of vaginal cream drug products.

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