Impact of Material Attributes on In Vitro Performance of Clindamycin Phosphate Vaginal Creams

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PURPOSE

Unlike topical drug products applied to the skin, characterization-based bioequivalence (BE) approaches that can mitigate the risks associated with potential failure modes for BE have yet to be established for locally acting vaginal drug products. Differences in material attributes of inactive ingredients (such as differences in grade, sources, etc.) have the potential to influence the physicochemical and structural attributes of vaginal creams, which may impact product performance. Therefore, it is essential to investigate and understand the influence of material attributes on the critical quality attributes (CQA) and in vitro release and permeation of the active ingredient(s) from vaginal creams to support characterization-based BE approaches. The objective of this study was to investigate the impact of variations in an inactive ingredient (cetostearyl alcohol (CSA)) on the CQAs and in vitro performance of clindamycin phosphate (CP) vaginal creams.

METHODS

Laboratory-made (LM) CP vaginal creams (2%, w/w) were prepared with CSA containing different ratios of cetyl alcohol (CA) and stearyl alcohol (SA) (LM-CSA50 vs. LM-CSA70) and compared to a marketed reference listed drug (RLD) CP vaginal cream. The drug content and rheological properties of the CP creams were determined using high performance liquid chromatography (HPLC) and a rheometer, respectively. The droplet size of the CP creams was characterized using an optical microscope; the data were analyzed using ImageJ. The performance of the CP creams was evaluated via an in vitro drug release test (IVRT) and in vitro permeation test (IVPT). The studies were conducted using vertical diffusion cell (VDC) methods with polyethersulfone (PES) (0.45 µm, contact area: 1.77 cm^2) and excised porcine vaginal tissue (contact area: 0.2 cm^2) for the IVRT and IVPT studies, respectively. Simulated vaginal fluid (SVF, pH 4.2) containing 3% (w/v) Brij®O20 was used as the receptor solution for both IVRT and IVPT studies. The IVRT and IVPT studies were conducted at 37°C (measured at the surface of the membrane or tissue) for 6 hours and 12 hours, respectively. The animal tissue integrity and thickness were monitored before and after the 12-hour IVPT study. Tissues from three animals were utilized for the IVPT study (n=3 cells per formulation per animal). The in vitro release rate (from the IVRT study, n≥6 cells per formulation) and the cumulative amount permeated and maximum permeation flux (J_{max}) for CP (from the IVPT study) were utilized to compare the products.

CONCLUSIONS

An understanding of the impact of material attributes on the physicochemical and structural attributes of the dosage form and thereby its influence on product performance of CP vaginal creams can facilitate the development of characterization-based BE approach for such products. The present research suggests that differences in material attributes of the inactive ingredient may have the potential to influence the physicochemical and structural properties (such as rheology). Additional analysis would be necessary to understand the impact of differences in CSA on the permeation mechanism(s) of CP across the vaginal mucosal membrane.

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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 (CSA)	1.5
Mixed fatty acids esters	1.0
Mineral oil	12.0
Sorbitan monostearate	2.0
Stearic acid	2.0

Table 2. CSA properties and drug content of RLD and LM creams manufactured with CSA with different CA to SA ratios (Mean±SD, n=3)

CP cream	RLD	LM-CSA50	LM-CSA70
CSA Type	N/A	Kolliwax® CSA 50	Kolliwax® CSA 70
CS:SA (w/w)	N/A	1:1	3:7
Drug content (%w/w)	2.04±0.020	2.04±0.100	2.05±0.073

N/A: Not available

➢ Droplet size of CP creams

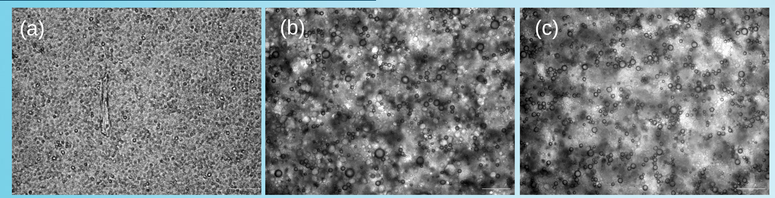


Figure 1. Optical microscope images of (a) the RLD cream, (b) LM-CSA50 cream, and (c) LM-CSA70 cream (scale bar = 100 µm).

Table 3. Droplet size of CP vaginal creams manufactured with different CSA.

CP cream	RLD	LM-CSA50	LM-CSA70
Droplet diameter (d50, µm)	3.20	4.60	4.53
Span	0.87	0.97	0.88
Droplet number	3540	3257	3774

➢ Rheological properties of CP creams

- All three CP creams had shear thinning property.
- LM CP creams had a lower storage modulus and yield stress compared to the RLD product (RLD > LM-CSA70 > LM-CSA50).

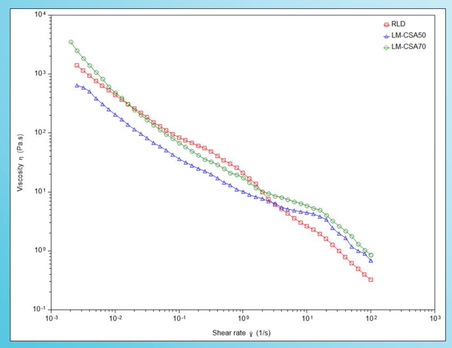
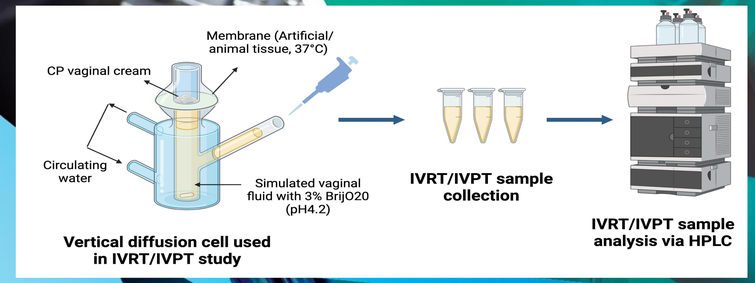


Figure 2. Viscosity vs. shear rate flow curves of LM-CSA50, LM-CSA70, and the RLD product.

➢ In vitro performance test of CP creams



IVRT/IVPT study conditions

- Apparatus: VDC
- Receptor solution: SVF containing 3% w/v Brij®O20 (pH 4.2)
- Membrane temperature: 37°C
- IVRT: PES membrane; IVPT: Porcine vaginal membrane

IVRT

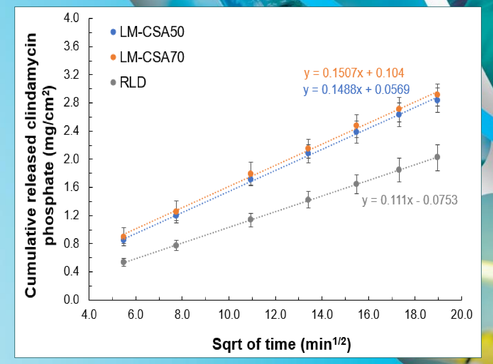


Figure 3. In vitro release profile of CP creams analyzed using the Higuchi model (n=9 for LM creams; n=6 for the RLD, Mean±SD)

IVPT

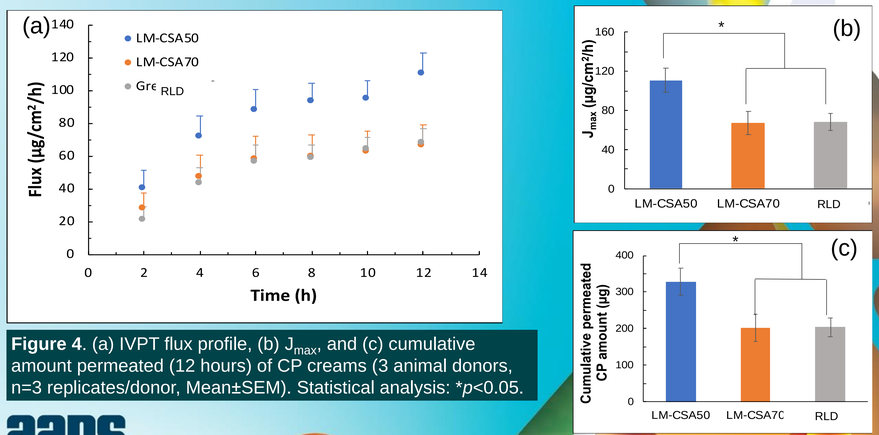


Figure 4. (a) IVPT flux profile, (b) J_{max}, and (c) cumulative amount permeated (12 hours) of CP creams (3 animal donors, n=3 replicates/donor, Mean±SEM). Statistical analysis: *p<0.05.

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