Impact of Cream Composition on Critical Quality Attributes of Miconazole Nitrate Vaginal Creams

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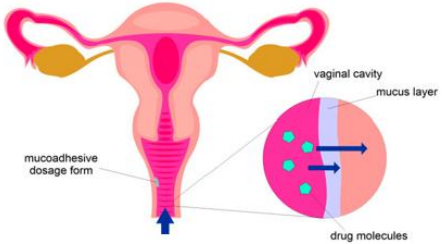
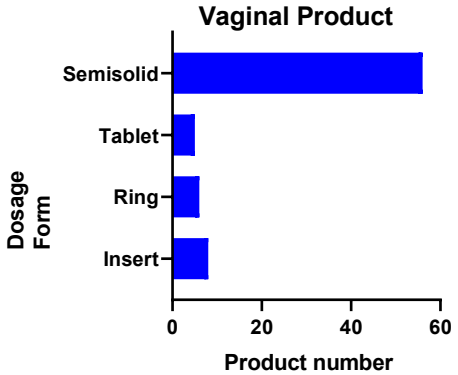
CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

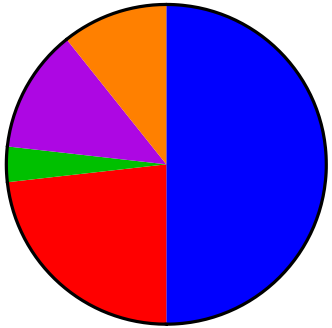
NEXT-GENERATION DELIVERY INNOVATIONS

Vaginal Cream Products



Vaginal drug delivery






Cream


Gel

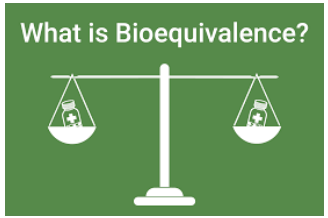

Ointment

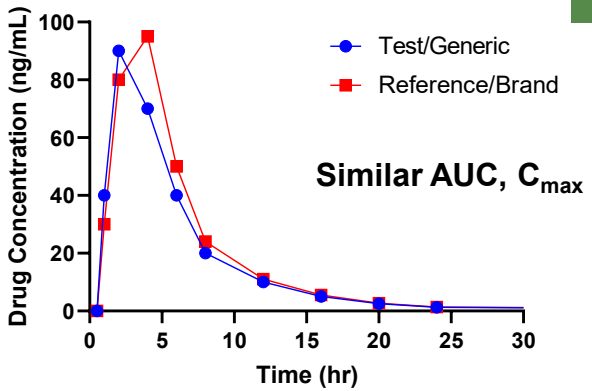

Suppository

[1] *FDA Orange Book Approved Vaginal Drug Products. Accessed in June 2025.*

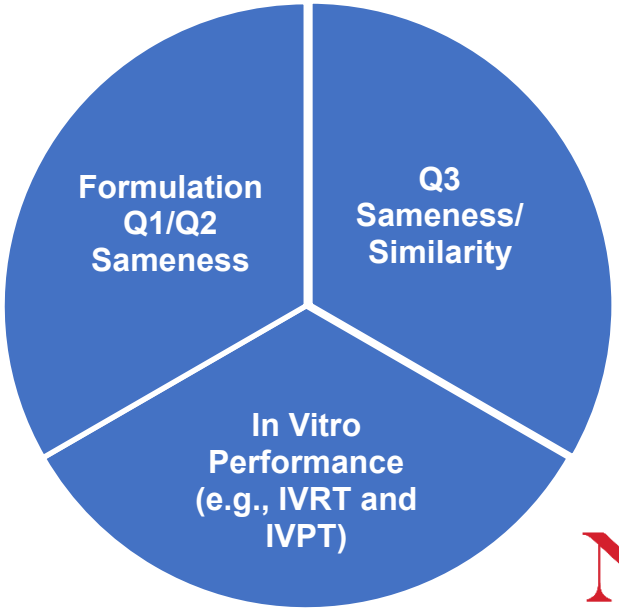
Bioequivalence (BE) Assessment of Locally Acting Topical Dosage Forms

- **BE for Systemically Acting Drugs**





- **BE for Locally Acting Dosage Forms (e.g., ophthalmic, nasal, dermal)**



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Miconazole Nitrate Vaginal Cream

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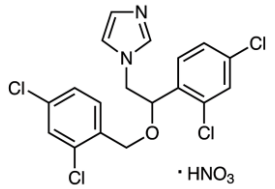
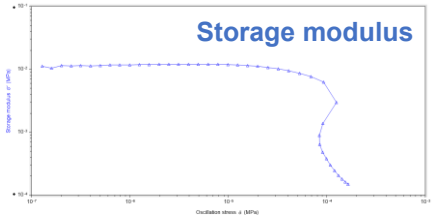
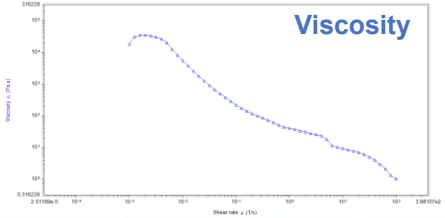
- **Reference listed drug (RLD): Monistat® 3**
  - API: miconazole nitrate
  - Strength: 4%
  - Indication: vaginal candida (yeast) infections

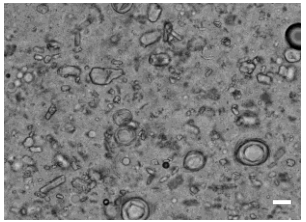


Water solubility: 0.000763 mg/mL
LogP: 5.86

Ingredients	
Miconazole nitrate	API
Cetyl alcohol	auxiliary emulsifiers
Stearyl alcohol	auxiliary emulsifiers
Isopropyl myristate	emollient and lubricant
Propylene glycol	humectant
Polysorbate 60	surfactant
Benzoic acid	preservative
Potassium hydroxide	pH adjustment
Water	media





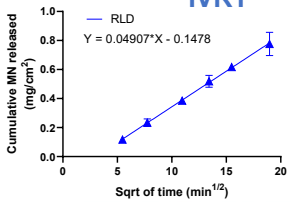


Droplet size

D50 (um)	6.99

Scale bar: 20 μm

IVRT



Data presented as mean±SD (*n*=3)

Laboratory-Made (LM) Vaginal Cream Preparation

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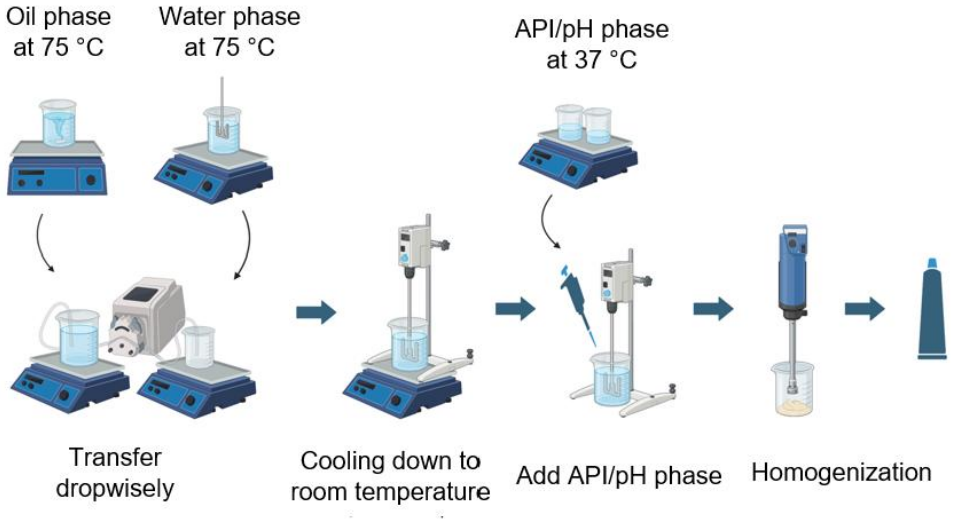
Key Variables	
Composition	Cetyl alcohol Stearyl alcohol Polysorbate 60
Processing Parameters	Cooling timeframe Homogenization duration Homogenization speed



DoE Study Design for LM MN Creams

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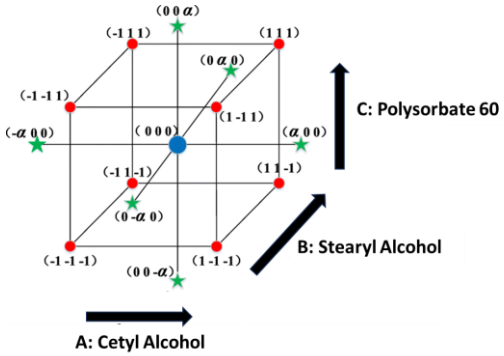
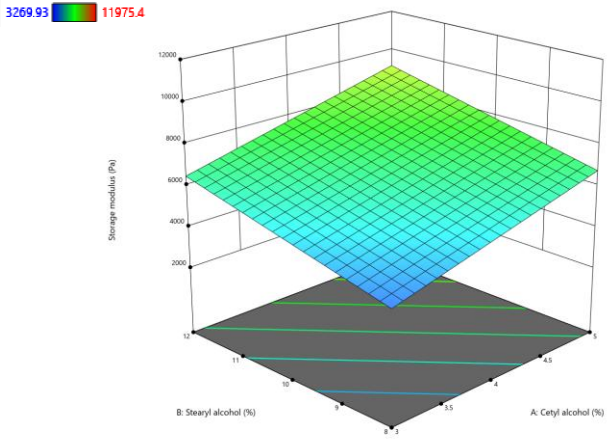
Input Variables	DoE Range				
	-α	-1	Center (0)	+1	+α
Cetyl alcohol (A)	2.318	3	4	5	5.682
Stearyl alcohol (B)	6.636	8	10	12	13.364
Polysorbate 60 (C)	1.318	2	3	4	4.682

Output Responses	Importance
Rheological properties	***
Cream droplet size distribution	***
In vitro release profile	***
MN particle size distribution	**
pH	*

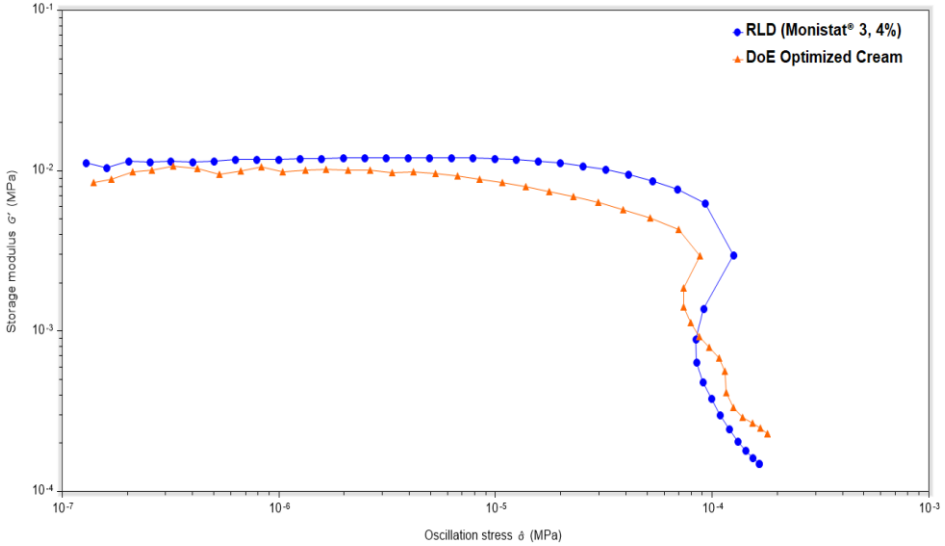


Run #	Block	Code	Factor A (Cetyl alcohol, %)	Factor B (Stearyl alcohol, %)	Factor C (Polysorbate 60, %)
1	Block 1	0, 0, 0	4	10	3
2	Block 1	-α, 0, 0	2.32	10	3
3	Block 1	+α, 0, 0	5.68	10	3
4	Block 1	0, 0, +α	4	10	4.68
5	Block 1	0, 0, -α	4	10	1.32
6	Block 1	0, -α, 0	4	6.64	3
7	Block 1	0, +α, 0	4	13.36	3
8	Block 2	0, 0, 0	4	10	3
9	Block 2	-1.-1.-1	3	8	2
10	Block 2	+1,+1,+1	5	12	4
11	Block 2	+1,+1,-1	5	12	2
12	Block 2	+1,-1,+1	5	8	4
13	Block 2	+1,-1,-1	5	8	2
14	Block 2	-1,+1,+1	3	12	4
15	Block 2	-1,-1,+1	3	8	4
16	Block 2	-1,+1,-1	3	12	2
17	Block 2	0, 0, 0	4	10	3

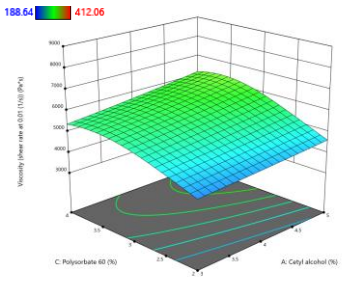
Impact on Storage Modulus



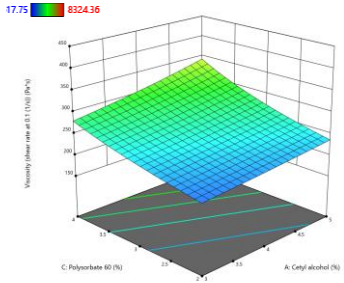
Storage Modulus
$= 1341.72 * Cetyl\ alcohol + 604.13$
$* Stearyl\ alcohol - 4773.82$



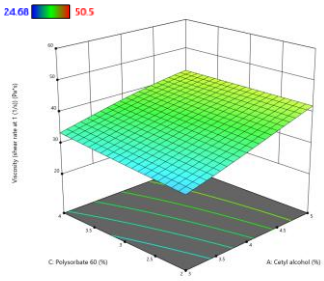
Impact of on Viscosity



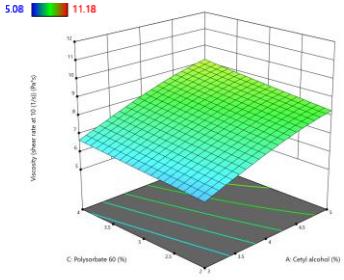
Shear rate: 0.01 s^{-1}



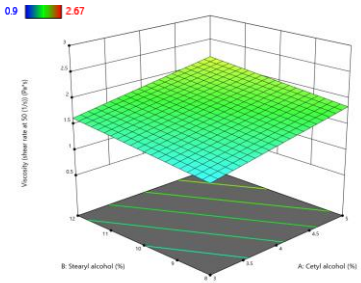
Shear rate: 0.1 s^{-1}



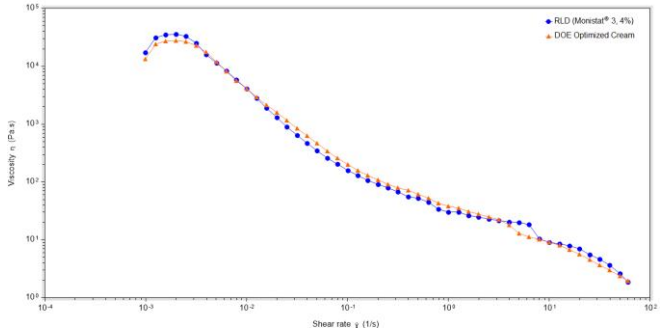
Shear rate: 1 s^{-1}



Shear rate: 10 s^{-1}



Shear rate: 50 s^{-1}



- Power-law or linear relationship was observed between viscosity at shear rates ranging from 0.01 to 50 s^{-1} and the formulation compositions (i.e., cetyl alcohol, stearyl alcohol, or polysorbate 60).

Impact of Cream Droplet Size Distribution

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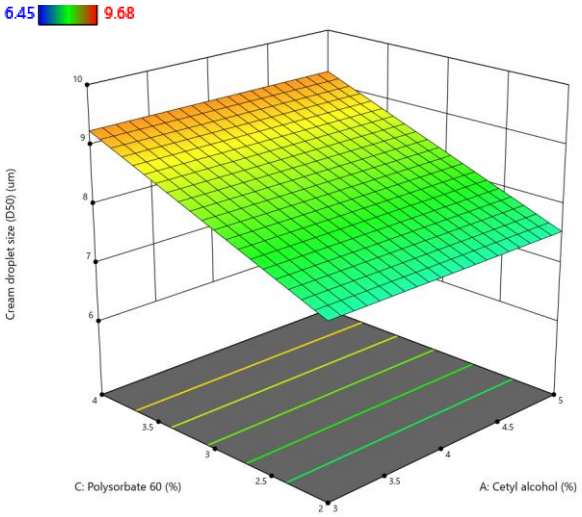
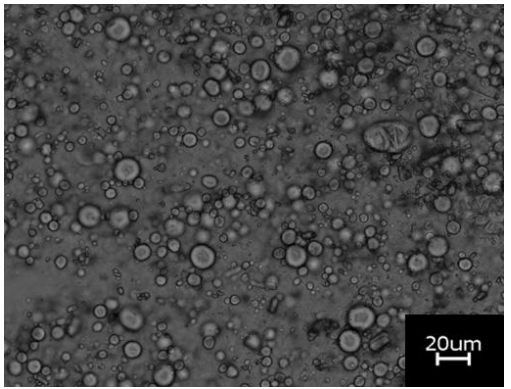
$$Cream\ droplet\ size\ distribution\ (D10) = 0.17 * \boldsymbol{Polysorbate\ 60} + 4.87$$

$$Cream\ droplet\ size\ distribution\ (D50) = 0.84 * \boldsymbol{Polysorbate\ 60} + 5.87$$

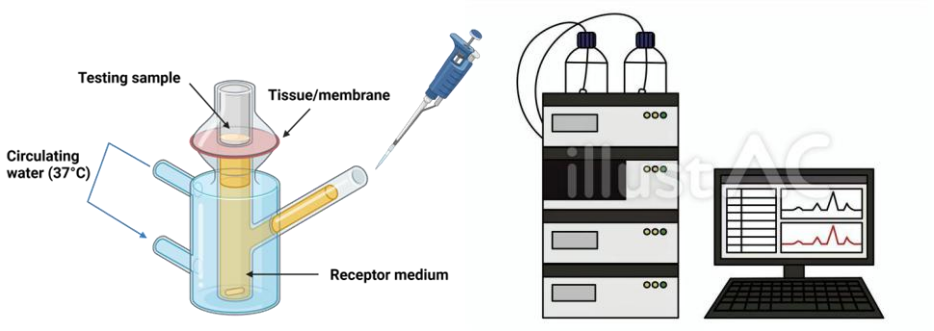
$$Cream\ droplet\ size\ distribution\ (D90) = 2.80 * \boldsymbol{Polysorbate\ 60} + 6.81$$

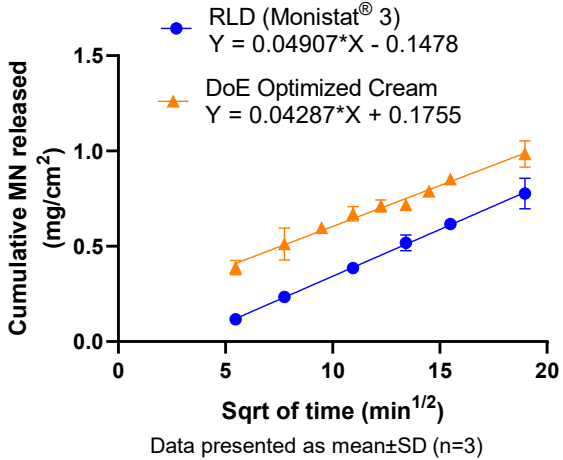


D50 (representative) vs. Polysorbate 60



In Vitro Drug Release Performance of MN Creams





Data presented as mean±SD (n=3)

- The DoE optimized cream exhibited CQAs within ±10% of the predicated values based on DoE software analysis.
- The DoE optimized cream showed similar in vitro MN release rate compared with the RLD cream.

Take Home Messages

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- ✓ The key formulation components of LM MN vaginal creams, specifically cetyl alcohol, stearyl alcohol, and polysorbate 60, significantly influenced critical quality attributes (CQAs) such as storage modulus, viscosity, and droplet size, while showing minimal effect on yield stress, cream pH, and API particle size distribution.

- ✓ Cream formulation compositions within the ranges selected for safe vaginal use showed limited impact on the in vitro MN release, and their effect on product performance (e.g., in vitro permeation test (IVPT)) will be further investigated.

- ✓ Quality by Design (QbD), implemented through Design of Experiments (DoE), successfully optimized the MN vaginal cream composition to achieve Q3 similarity compared with the RLD cream.

Acknowledgements

Shen Team

PI: Dr. Jie Shen

Dr. Weizhou Yue

Anjali Chauhan

Zekun Li

Shiqing Zhou

Krisha Hardik Desai

Chenfei Zhou

FDA Collaborators:

Dr. Megan Kelchen

Dr. Priyanka Ghosh

Dr. Lingxiao Xie

Dr. Tannaz Ramezanli

Dr. Sam Raney

This project is supported by the FDA of the U.S. Department of Health and Human Services (HHS) under grant **1U01FD007656**. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.