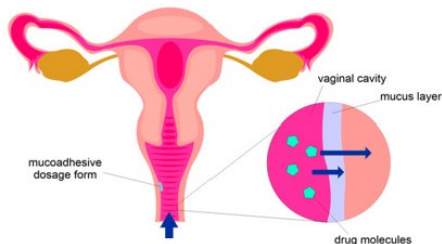


Impact of Cream Composition on Critical Quality Attributes of Miconazole Nitrate Vaginal Creams

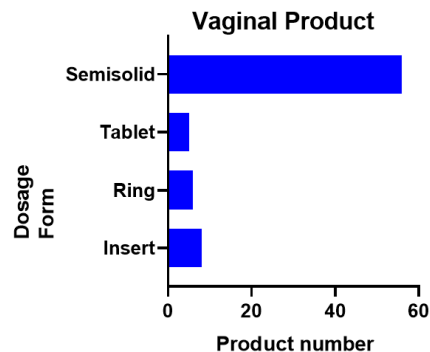
Presenter: Dr. Zizhao Xu

School of Pharmacy and Pharmaceutical Sciences
Northeastern University

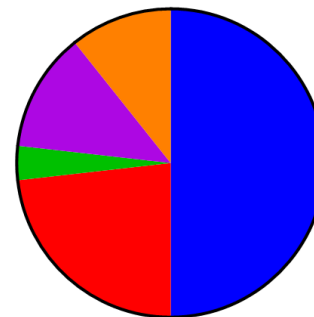
Vaginal Cream Products



Vaginal drug delivery



Semisolid Dosage Forms



- 50.00% Cream
- 23.21% Gel
- 3.57% Ointment
- 12.50% Suppository
- 10.71% Combination Products



Cream



Gel



Ointment

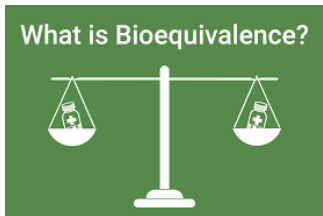
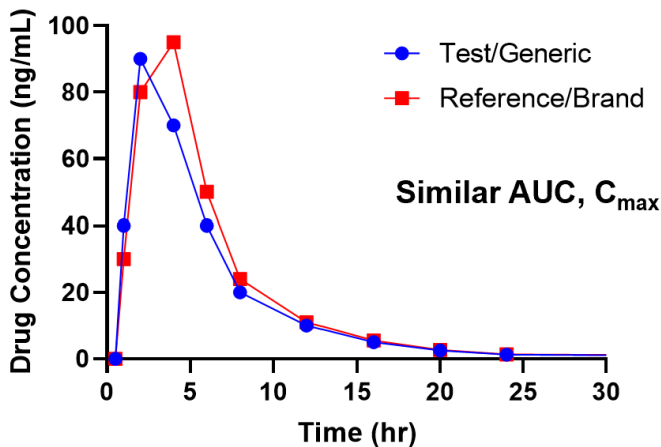


Suppository

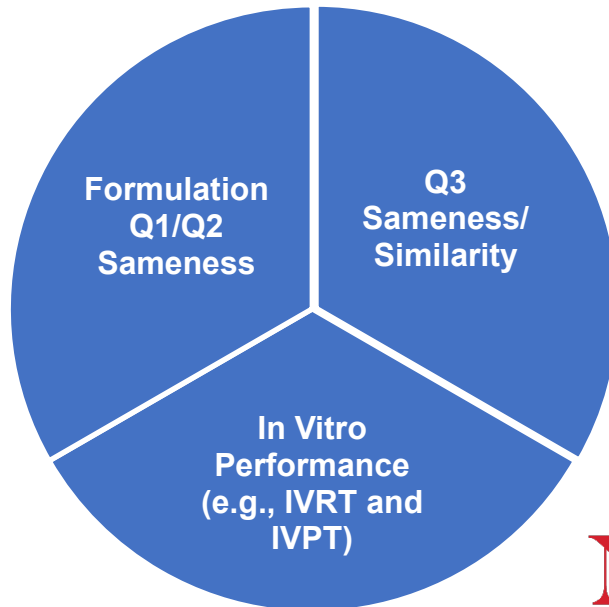
¹ FDA Orange Book Approved Vaginal Drug Products. Accessed in June 2025.

Bioequivalence (BE) Assessment of Locally Acting Topical Dosage Forms

- BE for Systemically Acting Drugs



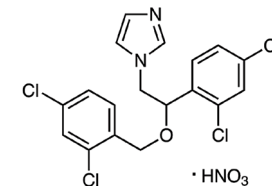
- BE for Locally Acting Dosage Forms (e.g., ophthalmic, nasal, dermal)



Miconazole Nitrate Vaginal Cream

— Reference listed drug (RLD): Monistat® 3

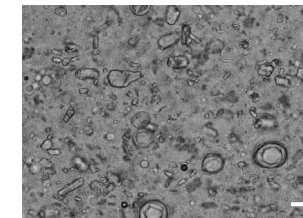
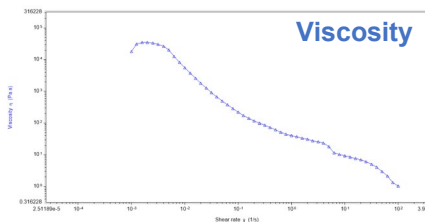
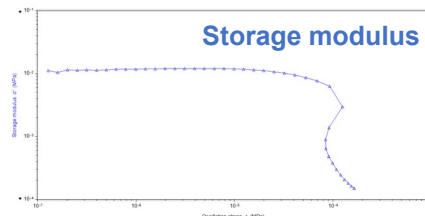
- API: miconazole nitrate
- Strength: 4%
- Indication: vaginal candida (yeast) infections



Water solubility: 0.000763 mg/mL
LogP: 5.86

Ingredients

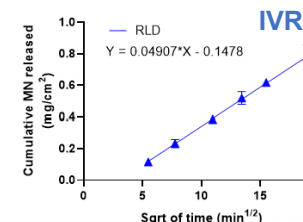
Miconazole nitrate	API
Cetyl alcohol	auxiliary emulsifiers
Stearyl alcohol	auxiliary emulsifiers
Isopropyl myristate	emollient and lubricant
Propylene glycol	humectant
Polysorbate 60	surfactant
Benzoic acid	preservative
Potassium hydroxide	pH adjustment
Water	media



Droplet size

D50 (um)	6.99
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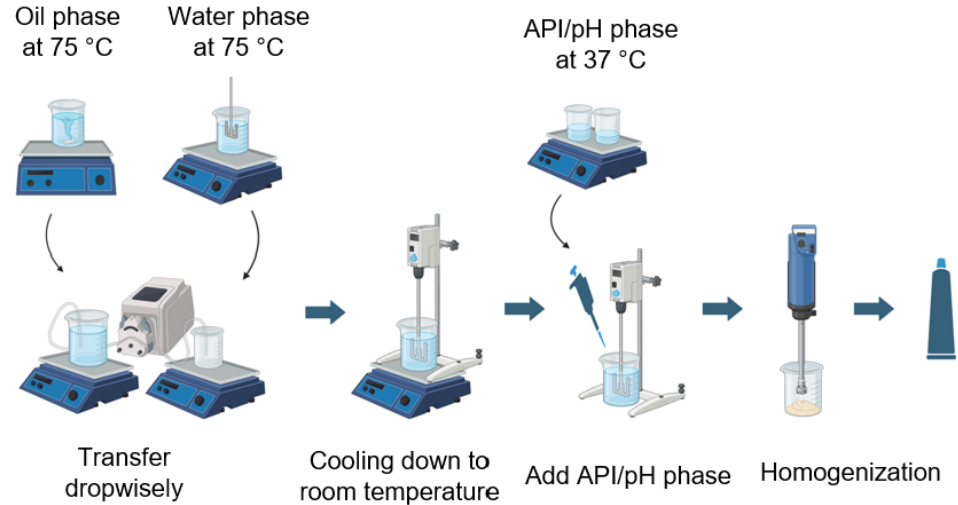
Scale bar: 20 µm



Data presented as mean ± SD (n=3)

Laboratory-Made (LM) Vaginal Cream Preparation

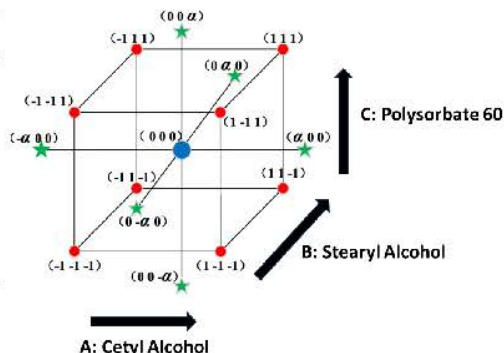
Key Variables	
Composition	Cetyl alcohol
	Stearyl alcohol
	Polysorbate 60
Processing Parameters	Cooling timeframe
	Homogenization duration
	Homogenization speed



DoE Study Design for LM MN Creams

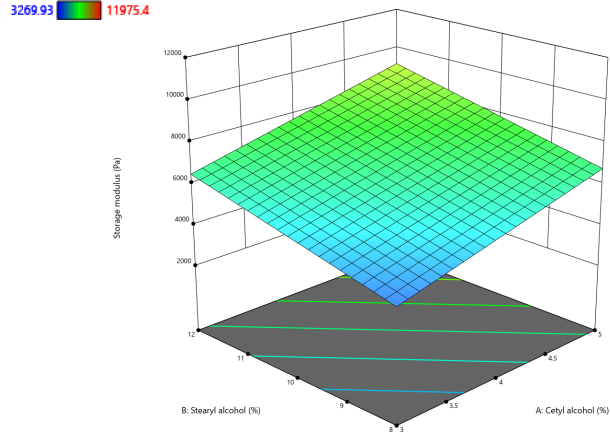
Input Variables	DoE Range				
	$-\alpha$	-1	Center (0)	+1	$+\alpha$
Cetyl alcohol (A)	2.318	3	4	5	5.682
Stearyl alcohol (B)	6.636	8	10	12	13.364
Polysorbate 60 (C)	1.318	2	3	4	4.682

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

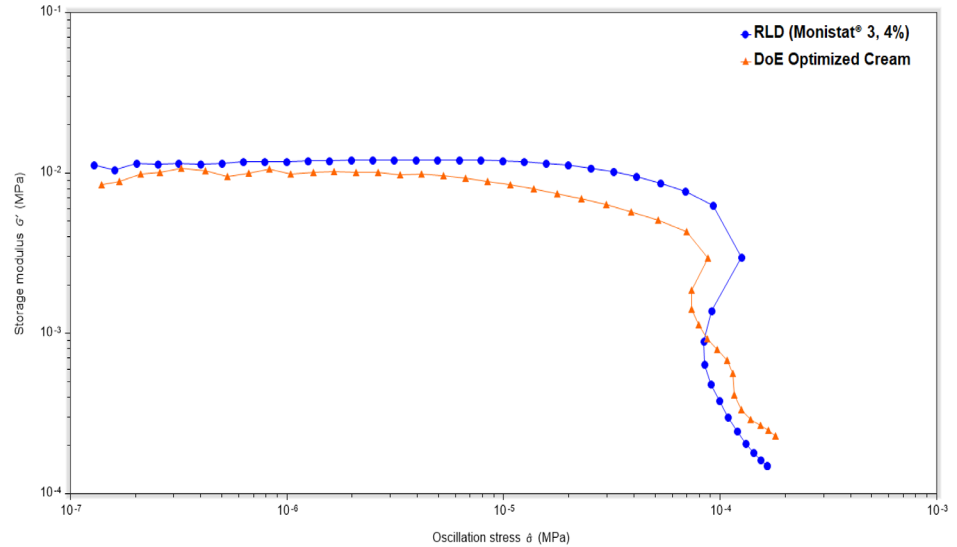


Run #	Block	Code	Factor A (Cetyl alcohol, %)	Factor B (Stearyl alcohol, %)	Factor C (Polysorbate 60, %)
1	Block 1	0, 0, 0	4	10	3
2	Block 1	$-\alpha$, 0, 0	2.32	10	3
3	Block 1	$+\alpha$, 0, 0	5.68	10	3
4	Block 1	0, 0, $+\alpha$	4	10	4.68
5	Block 1	0, 0, $-\alpha$	4	10	1.32
6	Block 1	0, $-\alpha$, 0	4	6.64	3
7	Block 1	0, $+\alpha$, 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

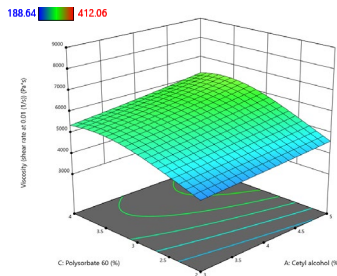
Impact on Storage Modulus



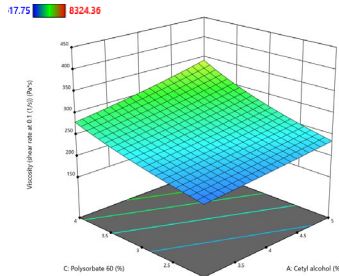
Storage Modulus
 $= 1341.72 * \text{Cetyl alcohol} + 604.13$
 $* \text{Stearyl alcohol} - 4773.82$



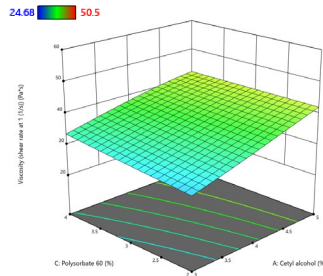
Impact of on Viscosity



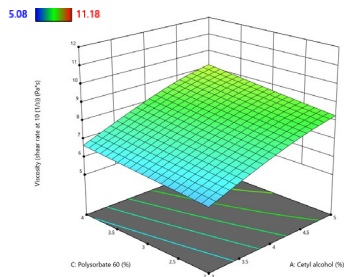
Shear rate: 0.01 s^{-1}



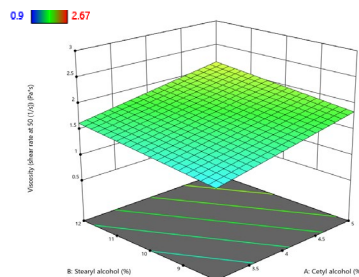
Shear rate: 0.1 s^{-1}



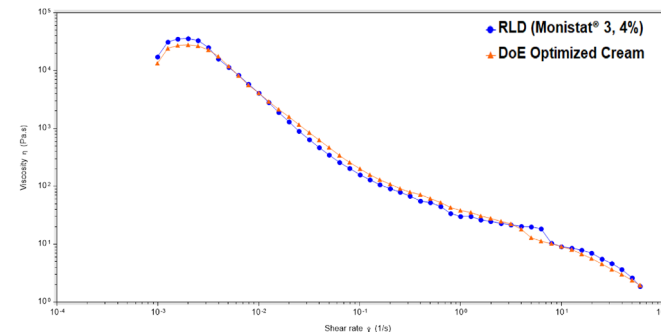
Shear rate: 1 s^{-1}



Shear rate: 10 s^{-1}

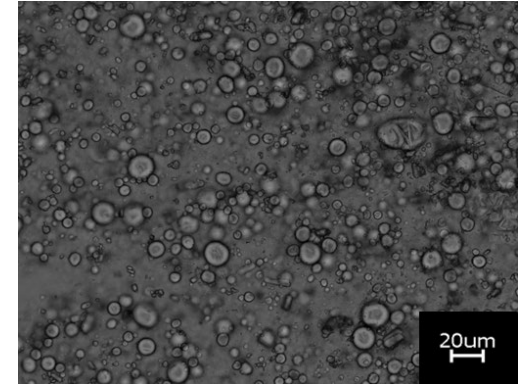
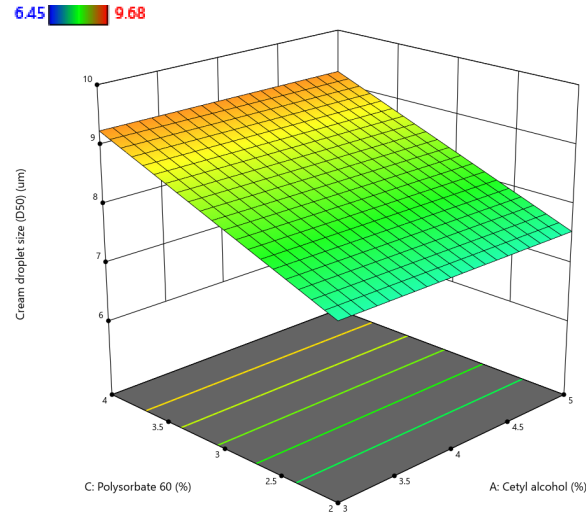


Shear rate: 50 s^{-1}



- 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



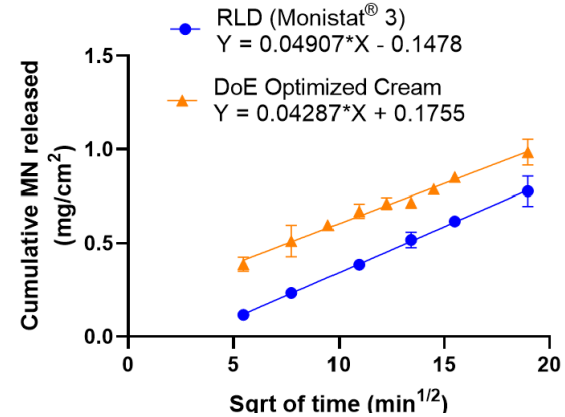
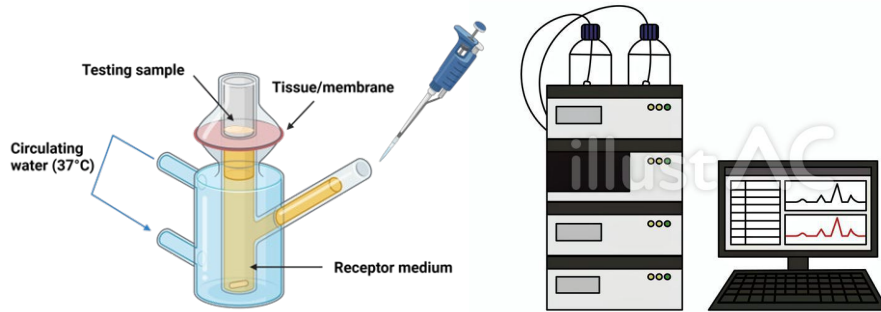
$$\text{Cream droplet size distribution (D10)} = 0.17 * \text{Polysorbate 60} + 4.87$$

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

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

D50 (representative) vs. Polysorbate 60

In Vitro Drug Release Performance of MN Creams



Data presented as mean $\pm$ SD (n=3)

- The DoE optimized cream exhibited CQAs within $\pm 10\%$ 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

- ✓ 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

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Dr. Sam Raney



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