

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

Zizhao Xu¹, Chenfei Zhou¹, Krisha Hardik Desai¹, Megan Kelchen², Lingxiao Xie², Priyanka Ghosh², Jie Shen¹

¹Northeastern University, School of Pharmacy and Pharmaceutical Sciences, Boston, Massachusetts, 02115

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



Background

In vitro characterization-based bioequivalence (BE) approaches have been well-established for topical dermatological products. However, these have yet to be developed for locally-acting (LA) vaginal cream products. A comprehensive understanding of how critical material attributes influence critical quality attributes (CQAs) of LA vaginal creams is essential for the development of such BE strategies. The present study aims to elucidate the impact of cream composition on the CQAs and in vitro performance of LA vaginal creams, using miconazole nitrate (MN) vaginal creams as the model product.

METHODS

Laboratory-made (LM) MN vaginal creams (4% w/w) with varying formulations were prepared using a hot emulsification congealing method (**Figure 1**). The CQAs were systemically evaluated and compared to the reference listed drug (RLD). Drug content was determined using high performance liquid chromatography (HPLC), and rheological properties were assessed using a TA Discovery HR 20 rheometer. The drug particle size was imaged using an optical microscope and analyzed by ImageJ. The in vitro release performance of the MN creams was evaluated using a vertical diffusion cell (VDC) method with polyethersulfone (PES) membranes (0.45 μm , contact area: 1.77 cm^2) at 37°C. Simulated vaginal fluid (SVF, pH 4.2) containing 3% (w/v) Brij® O20 served as the receptor solution.

A design of experiment (DoE) study was conducted to evaluate the impact of three cream composition variables (cetyl alcohol, stearyl alcohol, and polysorbate 60) on the Q3 properties of MN creams, and to identify an optimized formulation with Q3 characteristics and in vitro performance comparable to the RLD cream. A central composite design (CCD) was employed to evaluate five levels ($-\alpha$, -1, 0, +1, $+\alpha$) of the selected input variables with a limited number (17) of experimental runs (**Figure 2**). Following the preparation and comprehensive Q3 characterization of all 17 LM cream formulations, the data were analyzed using Design Expert software to identify trends and correlations between formulation composition and Q3 properties.

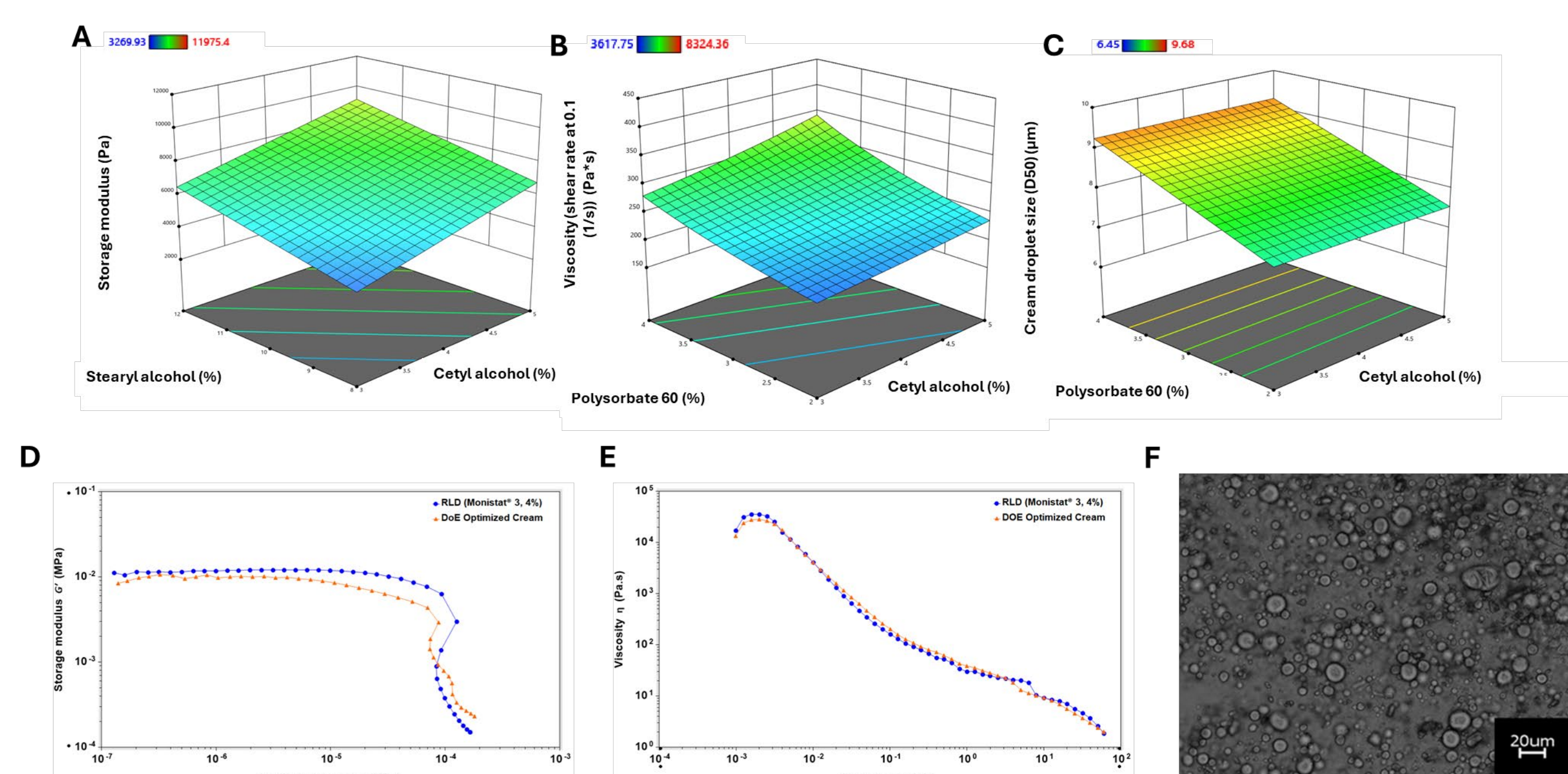


Figure 3. Q3 attributes of LM cream formulations based on the variation of the three input composition variables. (A) storage modulus, (B) viscosity at a shear rate of 0.1 s^{-1} (representative of the five shear rates tested), and (C) droplet size distribution (D50 as the representative). (D) Storage modulus profile of the RLD and DoE-optimized formulation. (E) Viscosity profile of the RLD cream product and the DoE-optimized formulation. (F) Representative microscopic image of DoE-optimized formulation.

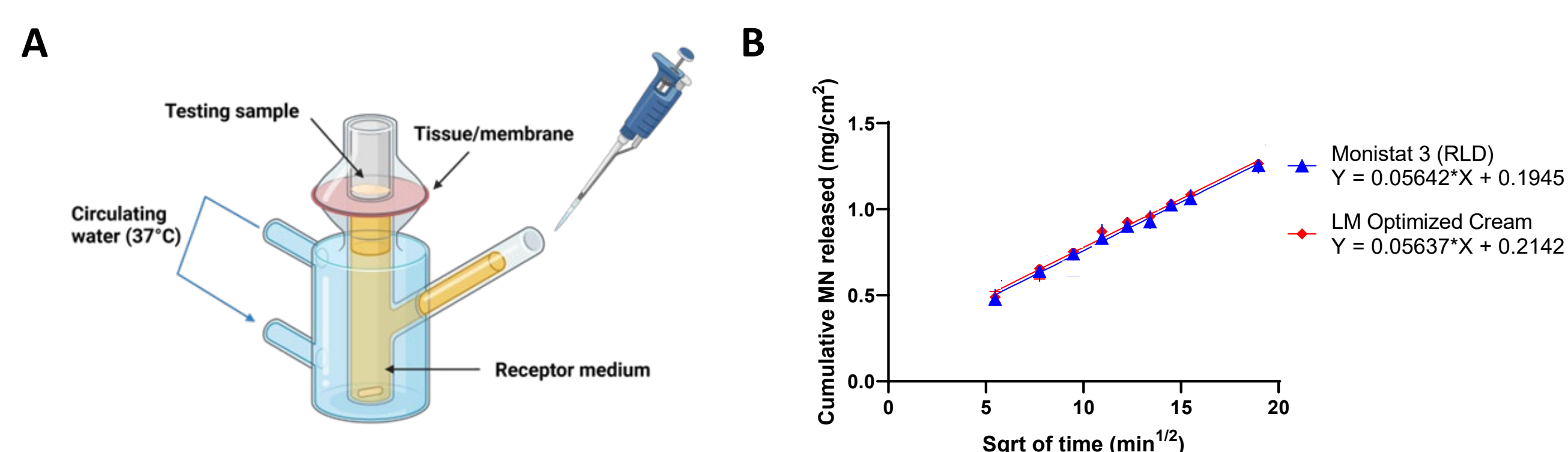


Figure 4. (A) VDC setup used in the IVRT study. (B) Cumulative MN released per area versus square root of time (0.5-6 hours) of the Monistat® 3 RLD cream and DoE optimized cream, obtained using the VDC method (n=6, Mean $\pm$ SD).

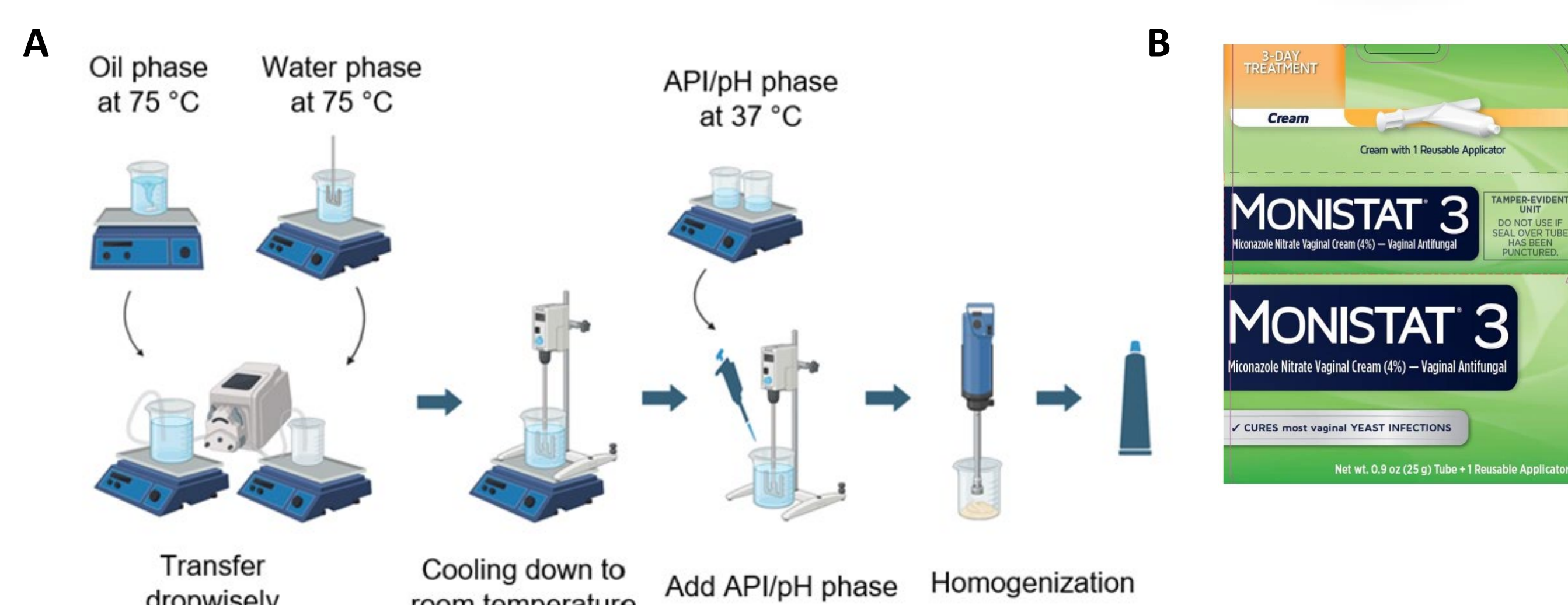


Figure 1. (A) Preparation procedure of LM MN vaginal creams. (B) RLD cream product. (Reference: <https://dailymed.nlm.nih.gov>)

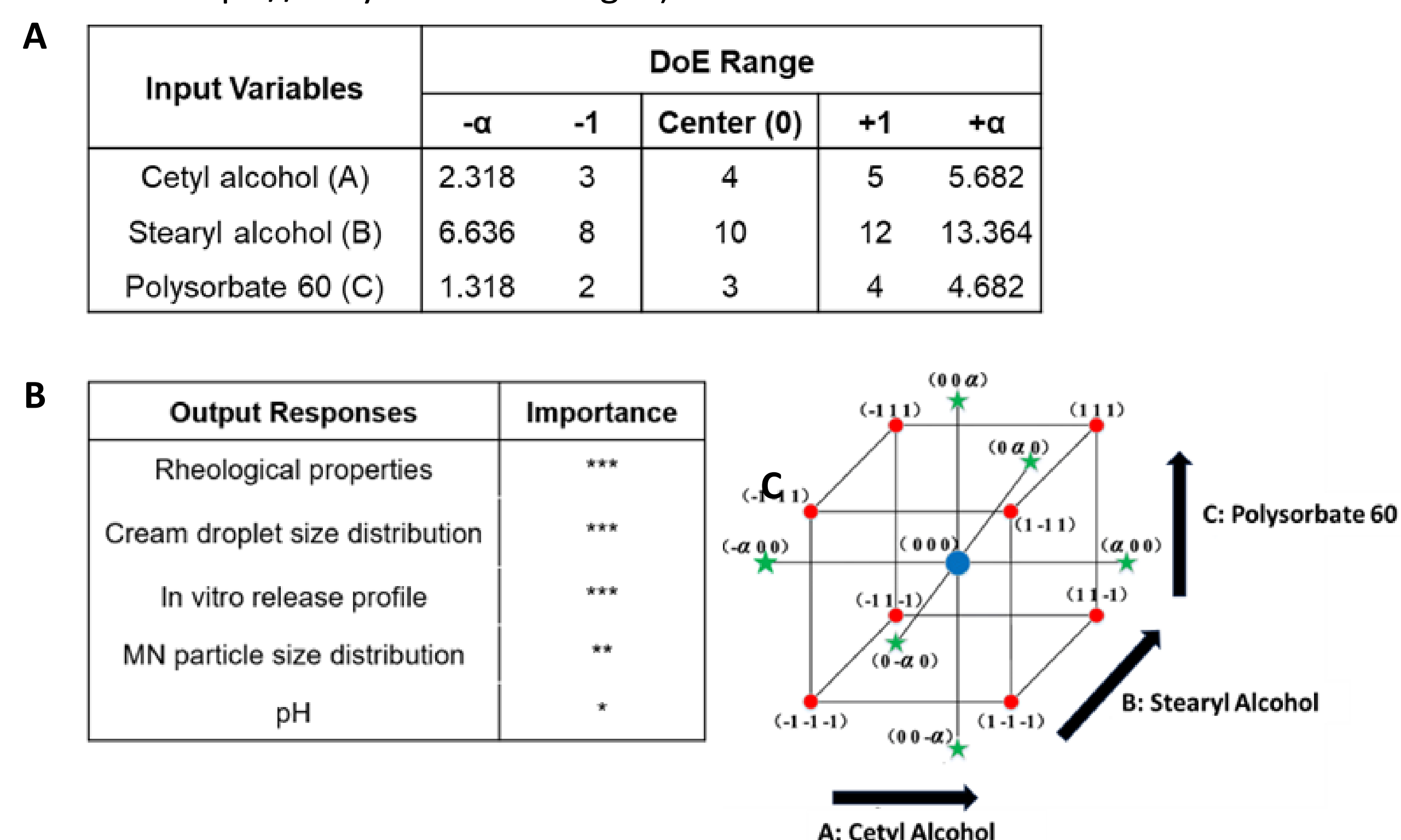


Figure 2. DoE study design. (A) Ranges of input variables used in the DoE study. (B) Relative importance of input variables for each response. (C) Schematic representation of the CCD with five levels.

RESULTS

Strong correlations were observed between the three compositional variables and key Q3 parameters, including storage modulus, viscosity, and droplet size. The LM formulation identified through DoE analysis exhibited CQAs comparable to those of the RLD cream (**Figure 3**). The predicted CQAs of the optimized cream were within $\pm 10\%$ of the experimentally observed values, indicating good predictability of the DoE models. Moreover, the DoE optimized cream showed similar in vitro MN release rate compared with the RLD cream (**Figure 4**).

CONCLUSION

This study provides insights into the impact of critical formulation components (such as cetyl alcohol, stearic acid and polysorbate 60) on the CQAs of MN vaginal creams. Quality by Design (QbD), implemented through DoE, successfully optimized the MN vaginal cream composition to achieve similar Q3 attributes and in vitro MN release kinetics compared with the RLD cream. These data illustrate the importance of understanding the impact of compositional changes on various Q3 attributes and performance during development of Q3 similar products.

ACKNOWLEDGEMENT

This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a grant (1U01FD007656) totaling \$1,000,000 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.