The Effect of Emollient Selection on the Microstructure and Release of Clotrimazole from Topical Cream Formulations
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PURPOSE
When observed under the microscope, different commercially-available, branded and generic, topical creams, containing Clotrimazole, show distinctly different API crystal morphologies. The objective of this study was to explore whether the selection of excipients (Q1) used in a topical semi-solid cream formulation, can impact the microstructural features of the formulation (Q3) and thereby key performance attributes (e.g. dermal drug delivery). We conducted a systematic evaluation using Clotrimazole creams as a model system. To test our hypothesis, we prepared four different formulations which only varied in the selection of oil that was used, all other excipients (Q1) and quantities (Q2) remained identical. Formulations were observed under the microscope and key performance attributes were measured.

RESULTS
After preparation, each of the four Clotrimazole cream variants showed good cream-like consistency. Under accelerated stability conditions, the octyldodecanol (Kollicream® OD)-and mineral oil - containing formulations showed a drop in viscosity (to a more lotion-like consistency) after two weeks. The isopropyl myristate (Kollicream® IPM)-containing formulation demonstrated a lotion-like consistency by week three and remained as such at week 4. The cocoyl caprylocaprate (Kollicream® 3C) formulations remained stable through week 4. Microscopical imaging showed that the formulations had different oil droplet sizes and size distributions. Image J software was used to evaluate the population of oil droplets in the images, determine their area (in pixels) and then plot histograms of the size distributions. Most notable was that the MO formulation showed a very wide distribution of droplet sizes, even reaching as high as approximately 500 sq. pixels, while IPM and 3C showed maxima around 10 sq. pixels and did not exceed 320 sq. pixels. Results from shear rheology measurements demonstrated that all the formulations showed a typical shear-thinning behavior and modest differences in viscosity.

CONCLUSIONS
Emollient selection had a significant effect on cream formulation microstructure as demonstrated by oil droplet sizes and Clotrimazole crystal habits. The impact of observed microstructural differences on viscous properties, as measured in shear sweep experiments (on products stored at room temperature) was minimal. However, under accelerated stability storage conditions (40°C/75% RH) the impact of emollient choice became apparent, namely Kollicream® OD and Mineral Oil being the least stable, impact of emollient choice became apparent, namely Kollicream® OD and Mineral Oil being the least stable. Emollient selection had a significant effect on Clotrimazole permeation through a skin model membrane, Strat M®. Clotrimazole has its antifungal effect on skin surfaces (e.g. vaginal mucosal membranes, etc.) so ideally the formulator might select Kollicream® 3C (cocoyl caprylocaprate) as the emollient of choice due to its good stability and retardation of Clotrimazole permeation for this particular model formulation.

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