Investigating the Effect of Formulation and Process Factors on the Properties of Cyclosporine Ointment using Design of Experiments (DoE)

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Purpose
The aim of the present research work was to investigate the relationship between the formulation/process variables and product critical quality attributes (CQAs) of cyclosporine ophthalmic ointment and further explore the feasibility of in vitro approaches for assessing product sameness.

Methods
A definitive screening design (DSD), which is capable of distinguishing the potential two-way interactions, was selected to evaluate the impact of various factors. The evaluated formulation factors included drug strength, corn oil percentage, and lanolin alcohol percentage while the process factors included mixing temperature, mixing time and method of preparation. Fourteen different cyclosporine ophthalmic ointment formulations were prepared and characterized in terms of drug assay, drug content uniformity, storage modulus, viscosity, and in vitro drug release. A bi-phase extraction method was developed and verified for the drug assay and content uniformity determination. Rheological behaviors of ointments were evaluated using a stress-controlled hybrid rheometer equipped with a step-peltier stage and a 25 mm sandblasted parallel plate. A modified USP Apparatus 2 equipped with 200 mL flat bottom vessels and mini paddles were used for drug release studies.

Results
The drug assay was found to vary from 76.75% to 98.82% for all fourteen formulations. Mixing time and corn oil percentage were found to have relatively higher negative effects in drug assay and variation of content uniformity (Figure 1). With yield stress ranging between 2 and 12 Pa and viscosity considerably higher than the viscosity of tear fluid at all shear rate ranges, all of the investigated ophthalmic ointments would be considered easily spreadable and having longer retention at the ocular surface. Corn oil percentage significantly impacted the viscosity under low shear rate. The release profiles of cyclosporine from all DoE formulations were found to follow classical Higuchi release (Figure 2). The rate of drug release was significantly influenced by drug strength and corn oil percentage. Processing had minor impact on all investigated responses of the cyclosporine ointments.

Conclusion
A definitive screening design successfully identified the effect of various formulation and process parameters on the product quality and performance. The results demonstrated that the in vitro methodologies can detect critical formulation and process changes, and could potentially serve as tools to assess product sameness.

![Figure 1](image1.png)  ![Figure 2](image2.png)

Figure 1. Sorted parameter estimates based on Rate: (A) Drug assay, (B) yield stress, (C) storage viscosity, (D) in vitro release constant (Higuchi model).

Figure 2. In vitro drug release from various cyclosporine ophthalmic ointment formulations: (A) Cumulative amount of drug released per unit area in linear time scale for DoE-1, (B) Cumulative amount of drug released per unit area fitted with Higuchi model for DoE-1, and (C) Cumulative amount of drug released per unit area fitted with Higuchi model for all DoE formulations.