# Effect of Formulation and Process Variables on the Properties of Cyclosporine Ophthalmic Ointments

**Yixuan Dong[1], Haiou Qu[1], Naresh Pavurala[1], Jiang Wang[1], Marilyn Martinez[2], Raafat Fahmy[2], Muhammad Ashraf[1], Celia Cruz[1] and Xiaoming Xu[1]**

1. FDA/CDER/OPQ/OTR/DRPQ, Silver Spring, MD 20993; 2. FDA/OFVM/CVM/ONADE, Silver Spring, MD 20993

## Purpose

The aim of the present study was to investigate the relationship between the formulation/process variables and product critical quality attributes (CQAs) of cyclosporine ophthalmic ointment, and further determine value of in vitro assessment in the equivalence evaluation of complex topical drug products.

## Method

Following formulation and process variables were investigated employing a definitive screening design (DSD): drug strength, corn oil percentage, lanolin alcohol percentage, mixing temperature, mixing time and method of mixing. Fourteen cyclosporine ointment formulations were prepared (Table 1) and characterized. Drug contents, particle size, rheological behaviors, and in vitro drug release from ointments were evaluated for the product quality assessment.

**Table 1. Definitive screening design matrix of cyclosporine ointment formulation.**

| Formulation (DOE) | Cyclosporine (%) ($X_1$) | Corn Oil (%) ($X_2$) | Lanolin Alcohol (%) ($X_3$) | Mixing Temp. (˚C) ($X_4$) | Mixing Time (min) ($X_5$) | Method of Preparation ($X_6$)* |
|---|---|---|---|---|---|---|
| 1 | 0.3 | 35 | 3 | 50 | 60 | B |
| 2 | 0.1 | 35 | 1 | 70 | 37.5 | B |
| 3 | 0.1 | 45 | 3 | 70 | 15 | A |
| 4 | 0.3 | 40 | 1 | 70 | 60 | A |
| 5 | 0.1 | 45 | 1 | 50 | 60 | A |
| 6 | 0.2 | 45 | 5 | 70 | 60 | B |
| 7 | 0.2 | 40 | 3 | 60 | 37.5 | A |
| 8 | 0.3 | 45 | 1 | 60 | 15 | B |
| 9 | 0.1 | 35 | 5 | 60 | 60 | A |
| 10 | 0.3 | 45 | 5 | 50 | 37.5 | A |
| 11 | 0.3 | 35 | 5 | 70 | 15 | B |
| 12 | 0.1 | 40 | 5 | 50 | 15 | B |
| 13 | 0.2 | 35 | 1 | 50 | 15 | A |
| 14 | 0.2 | 40 | 3 | 60 | 37.5 | B |

* Method A: cyclosporine was dissolved in corn oil first before adding into mixture of lanolin alcohol and ointment base; Method B: cyclosporine was added into mixture of lanolin alcohol and ointment base before adding into corn oil.

## Results

The mixing time and percent of corn oil were found to have a relatively higher negative effect on drug assay while the preparation method was found to affect content uniformity of the ointment. The in vitro drug release from ointments exhibited square root of time dependence. The content of API and percent of corn oil significantly influenced the drug release rates. The corn oil percentage was also found to significantly impact the viscosity under low shear rate. Processing variables were found to impact insignificantly various responses of the cyclosporine ointments.

## Results

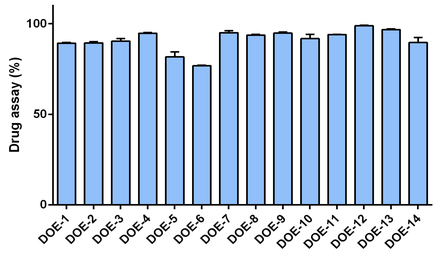


**Figure 1. Drug assay for DoE formulations (n=6).**

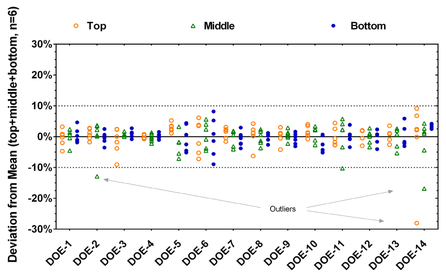


**Figure 2. Deviation from mean assay for DoE formulations (top, middle, and bottom portions, n = 6).**

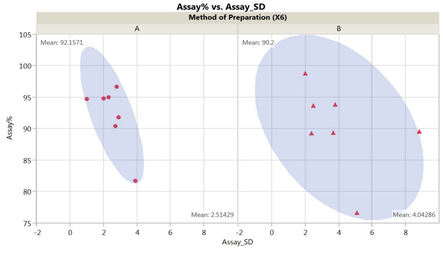


**Figure 3. The effect of method of preparation on drug assay and content uniformity of fourteen DoE formulations (Left: Method A in corn oil; Right: Method B in petrolatum/lanolin mixture).**

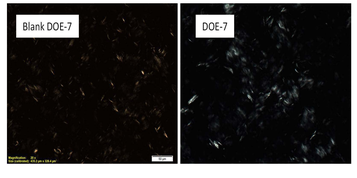


**Figure 4. Representative microscopic images of the ointments including Blank DoE-7 and cyclosporine DoE-7. The bright regions are likely result of different refractive index among components of the ointment base.**

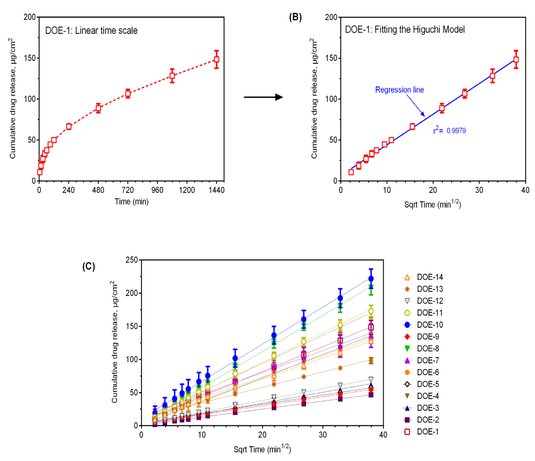


**Figure 5. *In vitro* drug release from various cyclosporine ointments (n=6): (A) Cumulative amount of drug released per unit area in linear time scale for DoE-1; (B) Cumulative amount of drug released per unit area fitted with Higuchi model for DoE-1; and (C) Cumulative amount of drug released per unit area fitted with Higuchi model for all DoE formulations.**

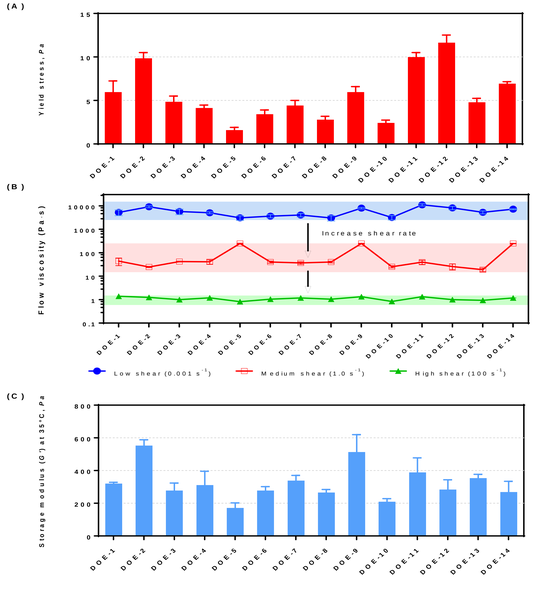


**Figure 6. Rheological characteristics of various DoE ointments. (A): Yield stress; (B): Viscosity at low (0.001 $s^{-1}$), medium (1 $s^{-1}$), and high (100 $s^{-1}$) shear rate; (C): Storage modulus at 35°C.**

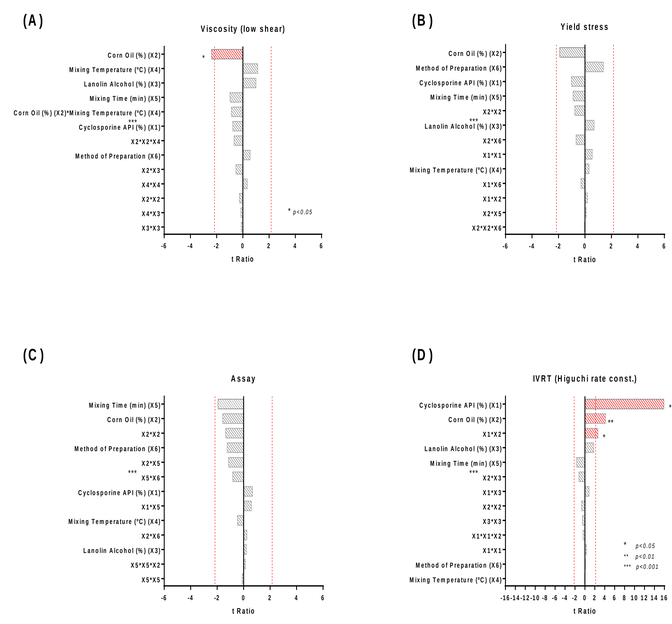


**Figure 7. Sorted parameter estimates based on t-Ratio (high to low) for various formulation and process parameters on (A) shear viscosity; (B) yield stress; (C) drug assay; (D) *in vitro* release rate (Higuchi model).**

## Conclusions

In the current study, the *in vitro* methods were shown to be discriminatory against changes in formulation and process variables. These methods may be utilized as quality control tools to ensure consistent product quality and potentially facilitate the determination of equivalence between different products.

## Acknowledgements

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## Disclaimer

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