Cyclosporine & Difluprednate Ophthalmic Emulsions

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 4: Noteworthy Complex Generic Drug Approvals: Multiphase Systems

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Learning Objectives

- Describe differences between two Cyclosporine (CsA) Ophthalmic Emulsions in Globule Size Distribution (GSD) study.
- Tell how to select the membrane in the in vitro release test (IVRT) for Cyclosporine and Difluprednate Ophthalmic Emulsions.
- Tell how long IVRT be evaluated.
- Describe the discriminative IVRT.

Background

Draft Product-Specific Guidance (PSG) for Cyclosporine and Difluprednate Ophthalmic Emulsions provide In Vitro option for Bioequivalence (BE), which recommends

- Q1(qualitative)/ Q2(quantitative)/ Q3(physicochemical)
- Acceptable comparative GSD
- Acceptable comparative IVRT

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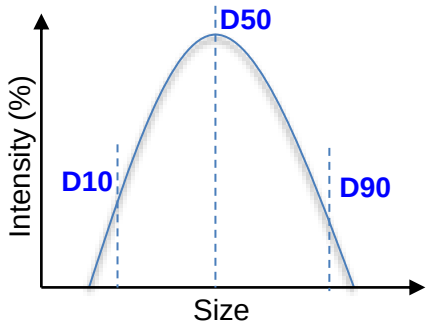
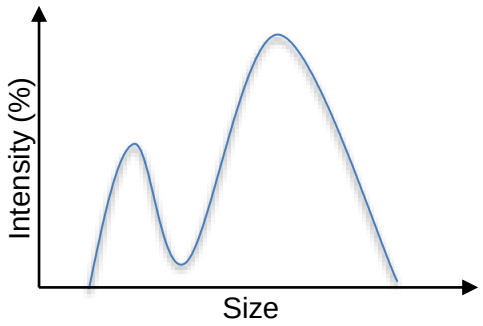
GSD for CsA Ophthalmic Emulsion

Why GSD study methods are different in two CsA Ophthalmic Emulsions?

Draft PSG	CsA Opht. Emulsion 0.1% NDA214965, PSG recommended Aug. 2022	CsA Opht. Emulsion 0.05% NDA050790, PSG revised Oct. 2016
BE based on **GSD D50 and SPAN***	✓	
BE based on **Earth Mover's Distance** or other appropriate metrics		✓
GSD		

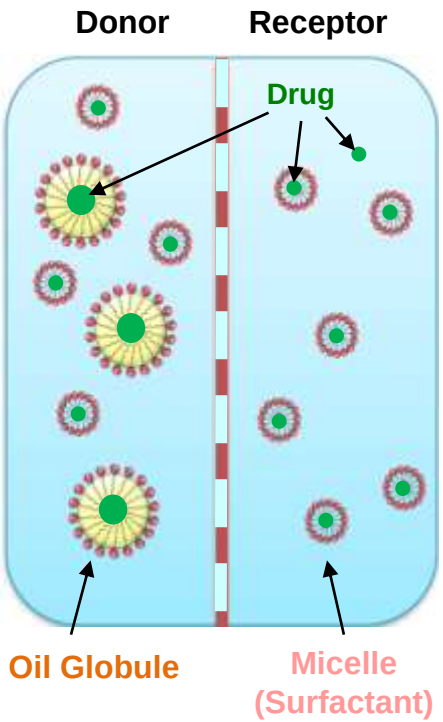
*Alternatively, Z-average and Polydispersity Index.

IVRT for Ophthalmic Emulsions

General Recommendations

How to select membranes in IVRT for ophthalmic emulsions?

- Evaluate **different types of membranes** with **replicates** (e.g., n=6).
  - Membrane significantly affects drug release kinetics.
  - Identify the reproducibility.
- **Pore size** and **inertness.**
  - Pore size smaller than the globule size and larger than micelles.
  - Minimize the membrane adsorption.
- **Mass-Balance** study verifies the selected membrane/IVRT method.
  - Evaluate drug(%), surfactant(%) and oil(%) in donor and receptor compartments throughout the study duration.



Updated diagram original from Xiaoming Xu, Adaptive Perfusion Method to Study Drug Release from Emulsions, CRCG Workshop, 06/29/2022

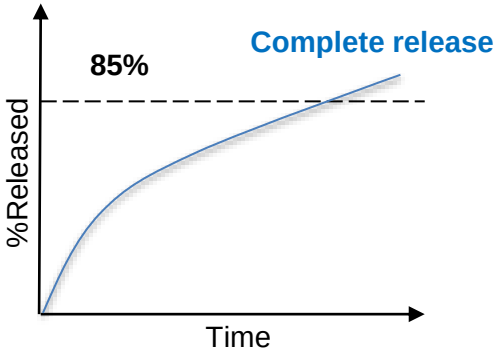
How long IVRT be tested for ophthalmic emulsions?

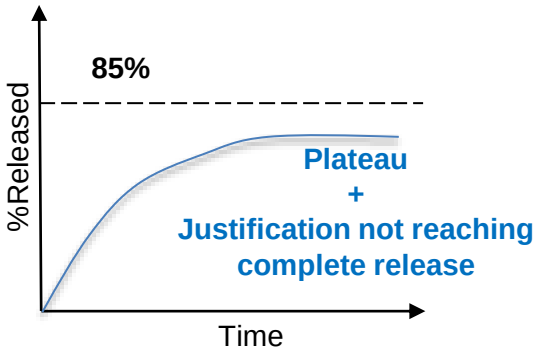
- Evaluate **entire drug release profiles**
  - Rapid drug release (aqueous/micelle phase)
  - Slow drug release (drug release from oil phase)

- **How long IVRT be tested** for ophthalmic emulsions?
  - Complete release (at least 85% drug label claim)

  or

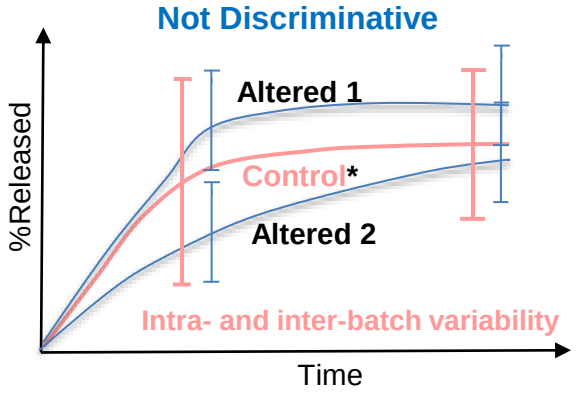
  - No significant increase over three consecutive time points (plateau)
    - If plateau < 85%, provide justification not reaching complete release.

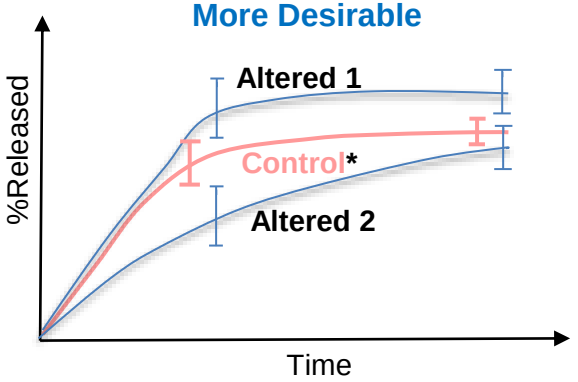




What is discriminative IVRT for ophthalmic emulsions?

- **Capture drug release profiles from the oil phase**
  - Desired but not required to mimic the physiological condition from the BE perspective.
  - Desired but not required to predict the bioavailability.
- **Discriminate batches not BE** (e.g., different globule sizes, different Q3).
  - Compare the "entire" release profiles (e.g., f2 similarity factor).
  - Adequate sensitivity.





*Test or Reference batches evaluated in the method validation and pivotal studies.

Poll Question

Which one is not needed to be evaluated in the donor and receptor compartments in the Mass-Balance Study for Ophthalmic Emulsions?

A. Active pharmaceutical ingredient

B. Oil

C. Diluent

D. Surfactant

Summary

GSD for Cyclosporine Ophthalmic Emulsions

- Different Cyclosporine Ophthalmic Emulsions may have different shape of GSD (e.g., mono-modal vs. multi-modal).

IVRT for Cyclosporine and Difluprednate Ophthalmic Emulsions

- Membrane separates drug/micelles (surfactant) from oil globules.
- Mass-balance study will help verify the selected membrane/IVRT method.
- Discriminative IVRT compares the “entire” drug release profile, not just a single time point.

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