Scientific Considerations for Generic Cyclosporine Ophthalmic Emulsion In Vitro Bioequivalence Studies

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Purpose

Cyclosporine ophthalmic emulsion, 0.05% (Restasis®) is a white opaque to slightly translucent emulsion indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (KCS).[1] Currently, there is no generic cyclosporine ophthalmic emulsion product approved in the US market. On June 2013, the Office of Generic Drugs at the US Food and Drug Administration posted a product specific guidance on cyclosporine ophthalmic emulsion, which recommends two options (in vitro or in vivo) to demonstrate equivalence of the generic products to the reference listed drug (RLD). The guidance has since been revised twice, with the most recent revision in October 2016.[2]

The in vivo option recommends a clinical endpoint bioequivalence study in otherwise healthy males and females whole tear production is presumed to be suppressed due to ocular inflammation associated with KCS. According to the in vitro option, a test product should-

- Be qualitatively (Q1) and quantitatively (Q2) the same as the RLD
- Have comparative physicochemical properties
- Have acceptable comparative in vitro drug release rate using a method that is able to discriminate the effect of process variability in the production of the test formulation.

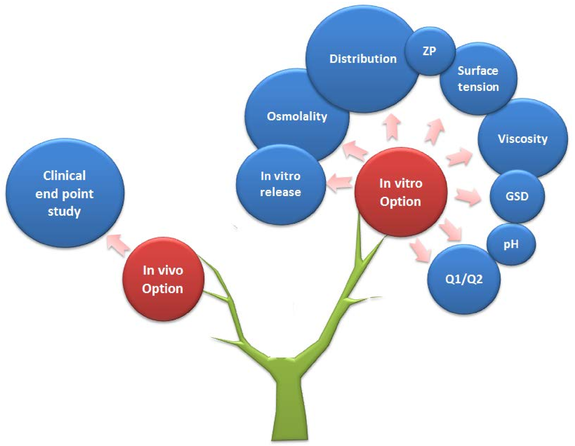

Fig. 1: Bioequivalence studies for Cyclosporine ophthalmic emulsion. ZP: Zeta potential; GSD: globule size distribution; Q1/Q2: qualitative and quantitative sameness to the RLD.

The purpose of this study is to elucidate the scientific considerations for the in vitro bioequivalence studies towards developing generic cyclosporine ophthalmic emulsion product.

Methods

Commercially available cyclosporine ophthalmic emulsion, 0.05%, was procured from US market. Globule size distribution was characterized using three dynamic light scattering instruments, i.e., Zetasizer Nano ZS (Malvern Instruments), NANO-flex nanoparticle size analyzer (Microtrac) and DynaPro plate reader II (Wyatt). For laser diffraction technique, Mastersizer 3000 with Hydro EV wet dispersion (Malvern) was used. Viscosity was measured using AR G-2 rheometer (TA instruments).

Results

Globule size distribution (GSD):

- A difference in GSD may affect ocular bioavailability of ophthalmic emulsion products due to an altered surface area to volume ratio available for diffusion and/or permeation.[3]
- GSD may influence ocular clearance.
- Drug release may be a function of GSD.

Consideration for globule size measurement

- → Shape of globule size distribution: single vs multiple peaks
- → Range in globule size: may be a few nanometers to several hundred nanometers
- → Method of measurement: DLS methods are well suited to capture small globules
- → Analysis mode: narrow analysis mode can better separate the presence of multiple peaks than the general purpose mode
- → Dilution medium and level of dilution

Comparing the GSD of the test products to the RLD also requires additional consideration.

- Commonly reported size parameters, e.g., D_{50}/SPAN or Z-average size/PdI, may not adequately represent the true mean size from a multimodal distribution profile.
- A statistical metric is preferred to assess the difference between the shapes of distribution profile.
- Earth Mover's Distance (EMD)[4] may be utilized to compare the GSD of the test and RLD products. EMD computes the minimal cost needed to transform one distribution into the other using an optimization algorithm. An average profile of all RLD samples (RLD center) can serve as the reference profile to compute the distance between RLD and test samples to the RLD center. The computed distance can be evaluated for equivalence between the test and RLD products using a statistical metric, such as the population BE test.[5]

Viscosity profile as a function of applied shear:

- Increasing viscosity of ophthalmic formulations increases contact time between the formulation and eye tissues, potentially resulting in increased ocular bioavailability.[7]
- Viscosity of cyclosporine emulsion decreases with increased shear. This can be attributed to the shear thinning property of carbomer copolymer A used in the formulation.
- Since ocular products will experience high shear originating from blinking, the test and RLD products should have a similar viscosity profile in the presence of applied shear at different shear rates.

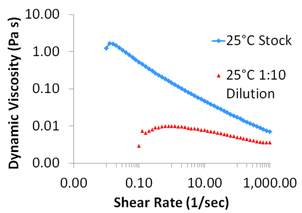

Fig. 2: Viscosity profile of cyclosporine ophthalmic emulsion with increasing shear rate.

Results

Scientific rationale for other recommended physicochemical properties

Parameters	Rationale
pH	• Irritation/drug absorption • Stability, solubility, permeability
Zeta potential	• Adhesion to cell membrane • Product stability
Osmolality	• Irritation, tissue damage • Permeability
Surface tension	• Corneal permeation • Irritation

Drug distribution in different phases within the formulation

- Within the formulation, cyclosporine can be distributed among the oil globules, micelles and the aqueous phase.
- The distribution of drug among these phases can influence the fraction of drug available for immediate absorption.
- A suitable analytical method needs to be applied to separate each phase for quantification of drug.

In vitro drug release

- The rate and extent of drug released from the emulsion can influence availability of drug for therapeutic effect.
- No validated method is currently available to test drug release from ophthalmic formulations, which necessitates developing a sensitive method.
- To account for the short ocular residence time, the method ideally should detect drug release at early time points.
- The method should be able to discriminate the effect of process variability in the production of the test formulations.

Conclusion

The recently revised draft guidance (in October 2016) on cyclosporine ophthalmic emulsion provides further essential details on the in vitro BE study parameters and the evaluation criteria.

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