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

- Highlights of new draft PSG on Cyclosporine (August 2022)
- Nuclear Magnetic Resonance (NMR) method for quantifying the Drug Distribution of Difluprednate in different phases

Background

Product-Specific Guidances for Ophthalmic Emulsions provide In Vitro option for Bioequivalence (BE) including:

- The test and RLD formulations to be qualitatively (Q1) and quantitatively (Q2) the same
- Acceptable comparative physicochemical characterization (Q3) including drug distribution in different phases
- Acceptable comparative globule size distribution (in vitro BE study 1) and in vitro drug release rate (in vitro BE study 2)

What's New in Current Draft PSG for Cyclosporine Ophthalmic Emulsion?

Recommended Aug 2022

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Cyclosporine

August 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic cyclosporine.

1. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).[3]

2. Acceptable comparative physicochemical characterization of the test and Reference Standard (RS) products. The comparative study should be performed on at least three batches of both the test and RS products.[4]

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[1] Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[2] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.
[3] For ophthalmic drug products, FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD, even in inactive ingredients listed in 21 CFR 314.94(a)(9)(iv), should be accompanied by an appropriate in vivo BE study or studies. *ANDA Submissions – Refuse-to-Receive Standards: Guidance for Industry*.
[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches. All 3 exhibit batches should be at least 1/10 the size of the commercial batch.

1. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).[3]

2. Acceptable comparative physicochemical characterization of the test and Reference Standard (RS) products. The comparative study should be performed on at least three batches of both the test and RS products.[4]

Parameters to measure: Zeta potential, viscosity profile as a function of applied shear, pH, osmolality, surface tension and cyclosporine distribution in different phases within the formulation.

In vitro bioequivalence study 1:
Comparative globule size distribution of test and RS products

Further reading: Product Quality Research for Developing and Assessing Regulatory Submissions for Generic Cyclosporine Ophthalmic Emulsions | SpringerLink

Additional information:

Device:
The reference listed drug (RLD) product is presented in a single-dose vial with a dropper tip. The vial with dropper tip is the device constituent.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the test device.

User Interface Assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[b]

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NMR Method for Quantifying the Drug Distribution of Difluprednate in Different Phases

Researched by D. Wang, JH Park, J. Zheng, B. Cai,
DA Keire & K. Chen, OTR/OPQ/CDER/FDA

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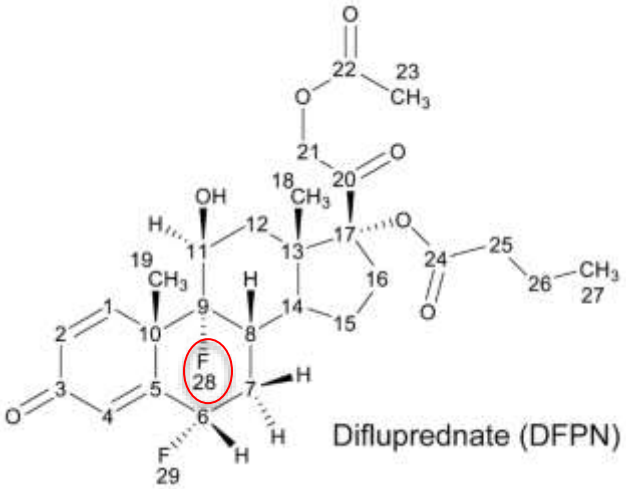
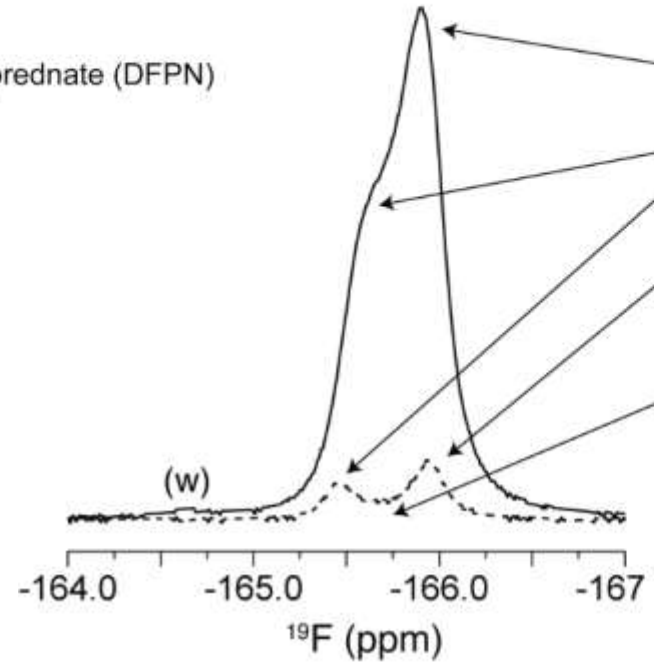
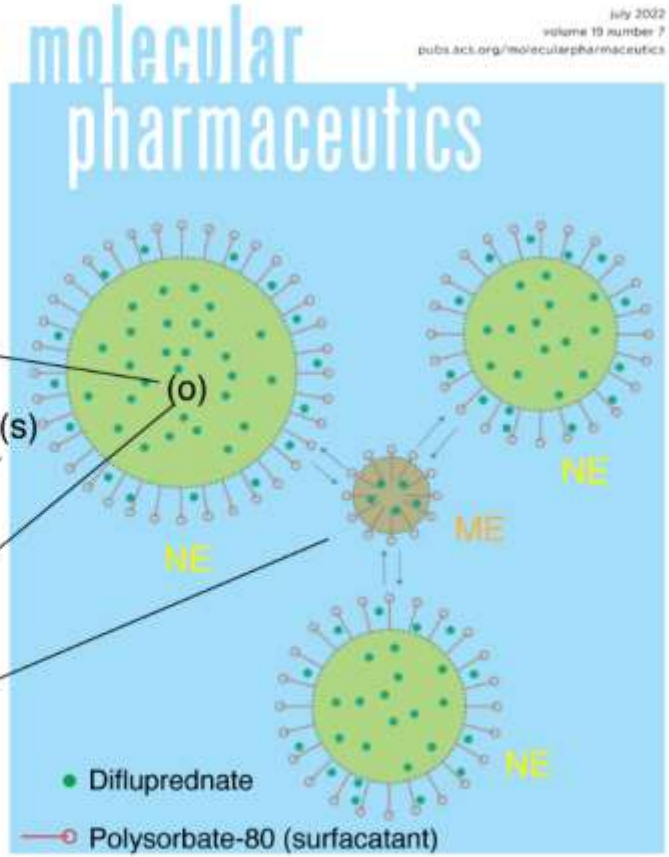
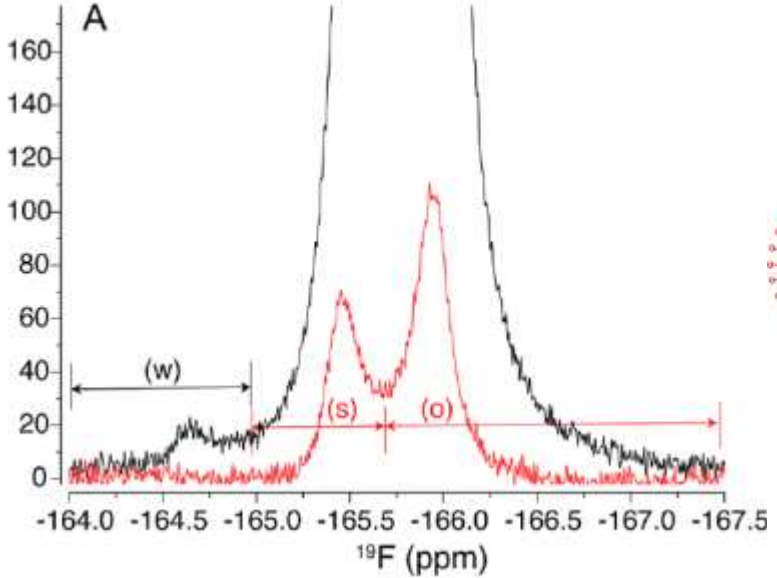
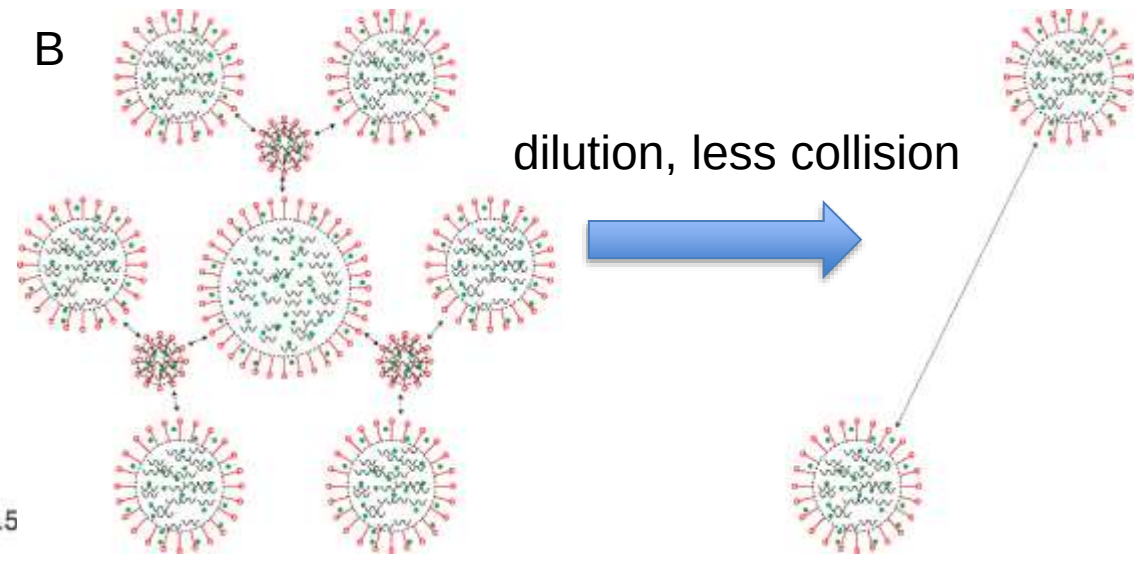

Difluprednate (DFPN)


(s)
(w)
-164.0
-165.0
-166.0
-167
19F (ppm)


molecular pharmaceutics
(o)
NE
ME
NE
NE
Difluprednate
Polysorbate-80 (surfacatant)

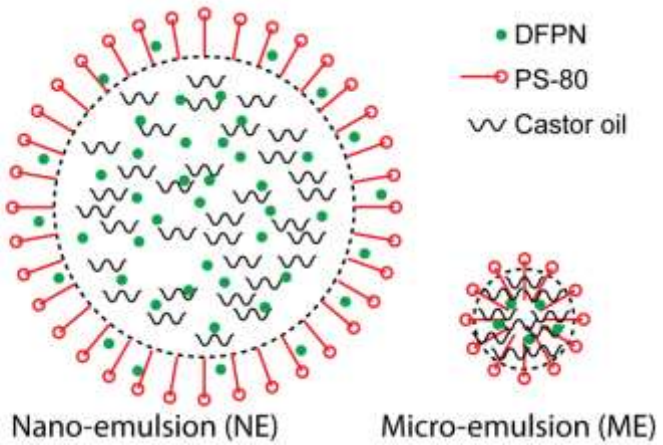




^{19}F NMR spectra of intact (black) and 10x diluted (red) drug products (DP) for phase distribution quantification (A) with the cartoon showing API distribution and globule exchange (B). The peak integration resulted in API quantity in each phases of (w), (s), and (o).

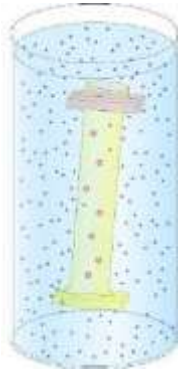
NMR Method for Drug Distribution

- Non-invasive
- Distinct peak of API in each phase in the spectra
- Direct measurement of API distribution in each phase by integration
- Mass balance
  - Water phase: 1.8 ± 0.1%
  - Surfactant phase: 35 ± 2%
  - Oil phase: 59 ± 3%
- Validation required
- Recommended one-time study



Other Reported Methods

- Ultracentrifugation
- Ultrafiltration
- Dialysis



Challenge Question

Which method for drug distribution study in different phases is non-invasive?

A. Ultracentrifugation

B. Ultrafiltration

C. NMR

D. Dialysis

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B. Ultrafiltration

C. NMR

D. Dialysis

Summary

- Highlights of new draft PSG for Cyclosporine Ophthalmic Emulsions (08/2022)
- NMR method for quantifying the drug distribution of Difluprednate in different phases non-invasively.

Acknowledgements

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SBIA Organizers