Assessment of Complex Drug Product – Physicochemical Characteristics to Support In-Vitro Bioequivalence Studies

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 1: Method Development/Validation for Non-traditional Analytical Methods

Topic 3: Development and Validation Considerations for Drug Release and Permeation Testing of Complex Dosage Forms

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Background

Product-Specific Guidance for Ophthalmic Emulsions provides for In Vitro option for Bioequivalence (BE) including

- Test and Reference products to be Q1/Q2
- Comparative physicochemical characteristics (Q3) including drug distribution in different phases
- Acceptable comparative in vitro drug release rate

Learning Objectives

1) Highlight role of comparative physicochemical characteristics

2) Provide expectation on validation requirements for drug distribution study

Complex Ophthalmic Drug Products

As defined in the GDUFA II Commitment Letter, complex products are:

- Products with complex active ingredients (e.g., peptides, polymeric compounds, complex mixtures of [active pharmaceutical ingredients], naturally sourced ingredients);
- Complex formulations (e.g., liposomes, colloids);
- Complex routes of delivery (e.g., locally acting drugs such as dermatological products and *complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions, or gels*);
- or Complex dosage forms (e.g., transdermals, metered dose inhalers, extended-release injectables)

Draft Guidance on Difluprednate

To qualify for the in vitro option for this drug product, the following criteria should be met.

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

ii. Acceptable comparative physicochemical characterization of the test and RLD formulations. The comparative study should be performed on at least three exhibit lots of both test and reference products.[3]

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality, and surface tension. Sponsors should also submit information on the drug distribution in different phases within the formulation.

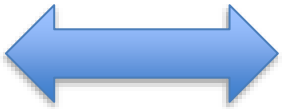
iii. Acceptable comparative in vitro drug release rate tests of difluprednate from the test and Reference formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

Physicochemical Characteristics

Reference

1. Globule size distribution
2. Viscosity @ diff. shear rates
3. pH
4. Zeta Potential
5. Osmolality
6. Surface Tension

In Vitro Bioequivalence



Test

1. Globule size distribution
2. Viscosity @ diff. shear rates
3. pH
4. Zeta Potential
5. Osmolality
6. Surface Tension

Retention

Irritation

Stability

Drug Release

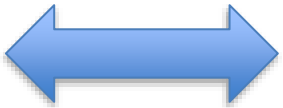
Clinical

Physicochemical Characteristics

Reference

1. Globule size distribution
2. Viscosity @ diff. shear rates
3. pH
4. Zeta Potential
5. Osmolality
6. Surface Tension

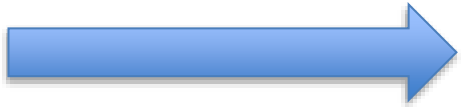
In Vitro Bioequivalence



Test

1. Globule size distribution
2. Viscosity @ diff. shear rates
3. pH
4. Zeta Potential
5. Osmolality
6. Surface Tension

Help Establish Specifications for Release and Stability

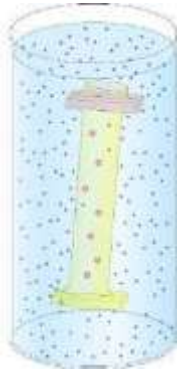


Product Quality for Lifecycle

- Drug distribution in different phases?

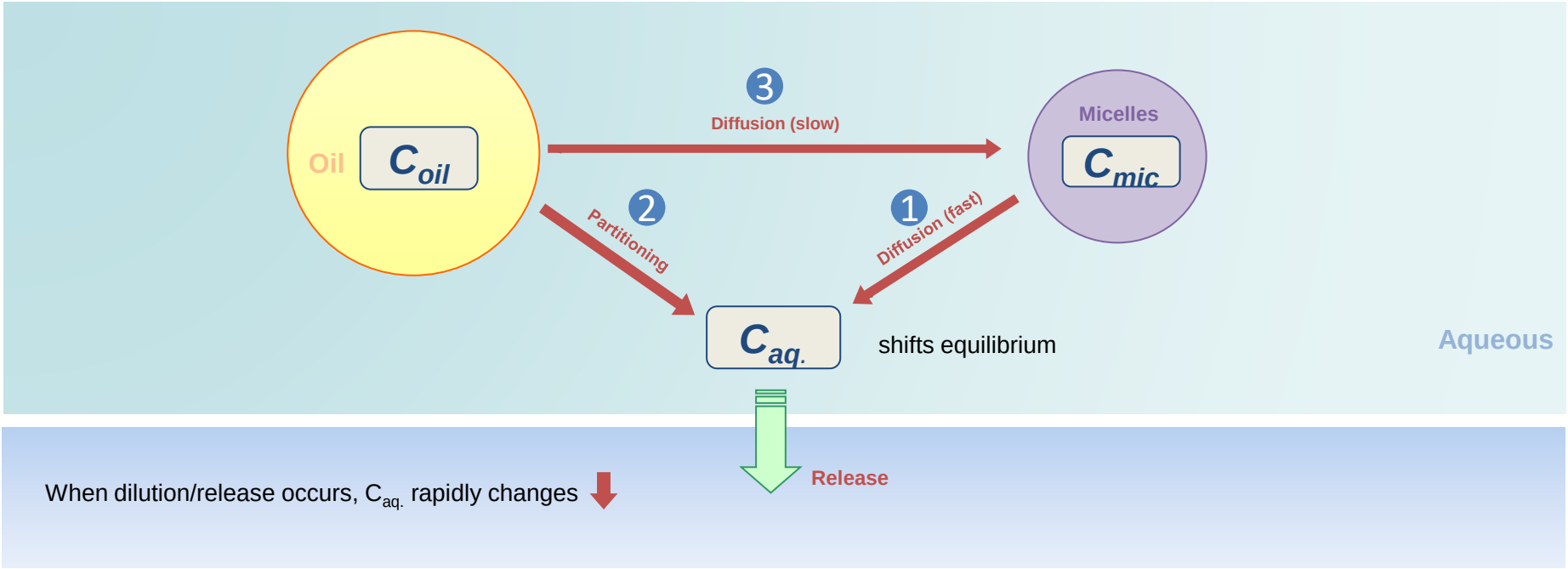
Drug Distribution in Different Phases

- One-time Study needed for In-Vitro BE
- Reported methods:
  - Ultracentrifugation
  - Phase Separation
  - Ultrafiltration
  - Dialysis



No Agency Recommended Method Yet

Three Phases in Ophthalmic Emulsions



Transfer rate of 1 is much faster compared to 2 and 3.

Y. Dong, et al., *Journal of Controlled Release* 313(2019), 96-105

Drug Distribution in Different Phases

Challenges:

- Determination of drug in different phases of the emulsion with minimal disruption due to employed method
- Adequately demonstrate validity of the methodology

Example – Ultrafiltration Method

- Most reported
- Method involves using suitable molecular weight cut-off (MWCO) membrane to separate different phases
- Gentle separation
- Need to validate method to demonstrate method's
  - Specificity
  - Accuracy
  - Suitability for intended use

Method Specificity

- The separation method and membrane should be specific to the phases in emulsion system.

- The filtrate (micellar and aqueous phases) should be measured for micelle particle size distribution (PSD) to demonstrate that the micelles present have PSD that is typical of this product.

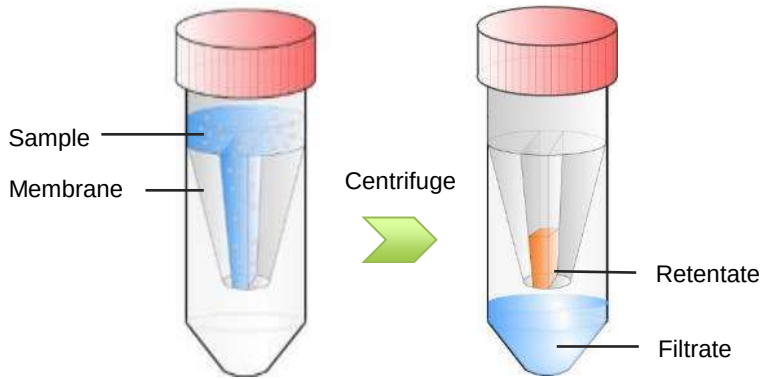
- The filtrates should also be measured for drug concentration.

Method Specificity – Example

Test			Reference		
Oil Phase	Micelle Phase	Aqueous Phase	Oil Phase	Micelle Phase	Aqueous Phase
X%	Y%	Z%	X_1%	Y_1%	Z_1%

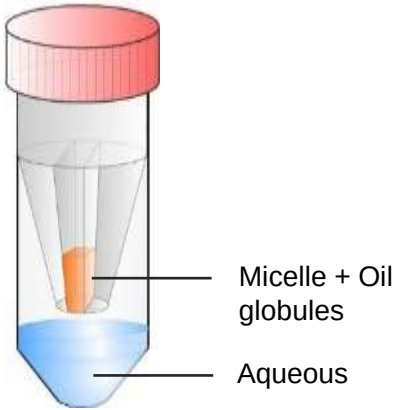
- Use of membranes with different molecular weight cut-off (MWCO)
- No further details

For method specificity, the MWCO of the membrane should be shown capable of separating the aqueous and micelle phases from the oil phase.



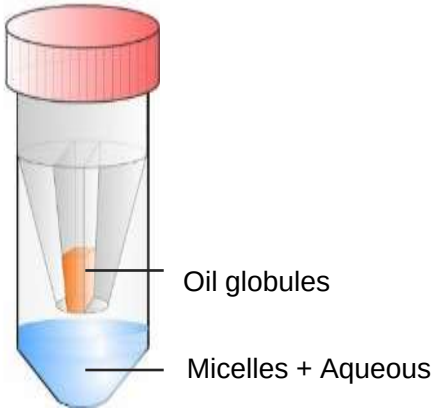
Contd' Method Specificity – Example

MWCO 1



- Absence of micelles in filtrate of aqueous phase

MWCO 2



- Absence of oil in "aqueous+micelle" phase
- Determination of micelle PSD
- Demonstration of complete "aqueous+micelle" pass through membrane, e.g., by varying centrifugation times

Method Accuracy

- Demonstrate minimal drug adsorption to the ultrafiltration membrane.
- Non-specific drug adsorption to the membrane vary depending on the properties of the drug and the chemistry of the membrane.
- Pre-saturate the membrane before use.

Method Accuracy

Aqueous	Micelle	Oil
C_{aq} <	$C_{micelle}$ <	C_{oil}

- Recovery of drug from aqueous drug solutions with known drug concentrations after passing the solutions through the membrane. **MWCO 1**
  - Practical challenges if drug concentration is too low due to adsorption

- Recovery of drug from aqueous+micelle phase with known drug concentrations after passing the solutions through the membrane. **MWCO 2**
  - Use of solution containing surfactant or placebo formulation

Method Suitability

- Manufacture batches of non-target formulations (e.g., by varying surfactant and/or drug levels).

- Capability of differentiating drug distribution of target formulation from non-quantitative equivalent formulations presumably non-bioequivalent.

Method Suitability

Non-Target Formulations

API + x%
API – x%

Surfactant + y%
Surfactant – y%

All else constant

- Significant variation in composition exhibits in drug distribution
- Drug distribution in phases within variability of the target product - ?

Additional Considerations

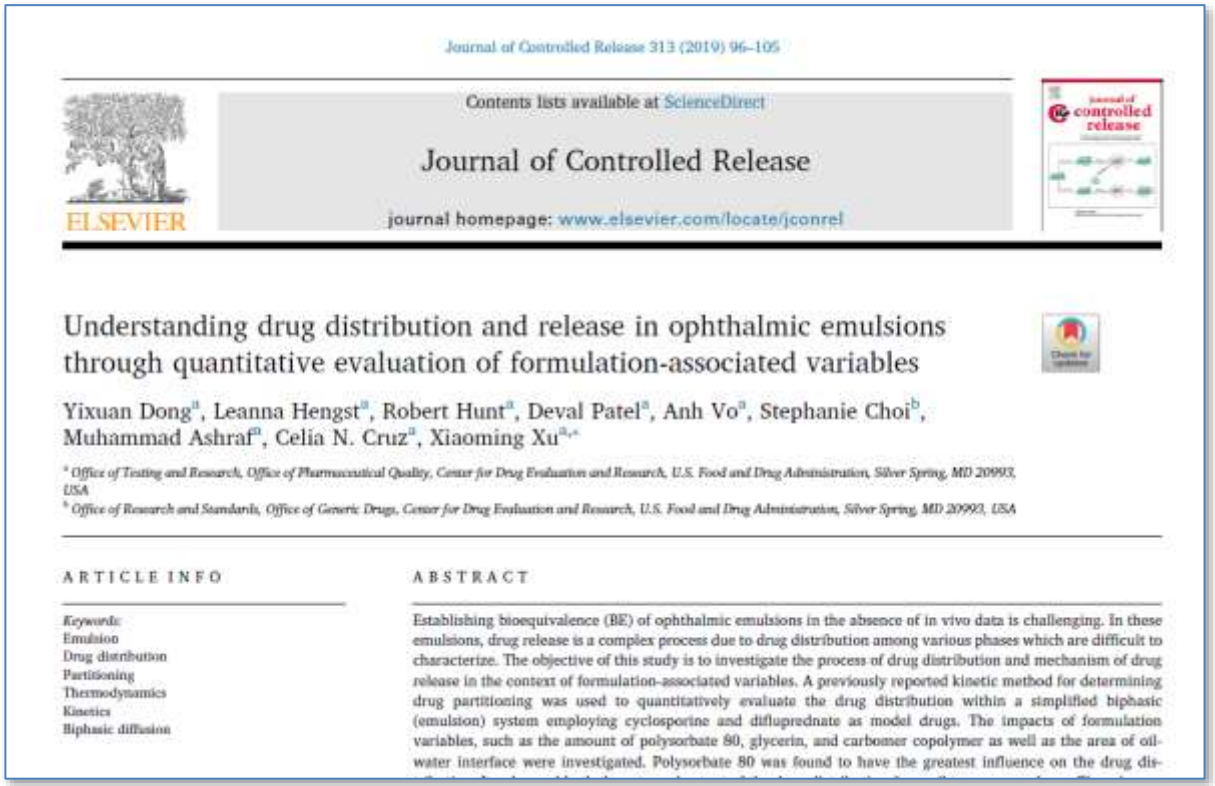
- Comparable results of drug concentrations in different phases between Test and Reference products
- Mass balance
- Three batches each of generic and RLD
- Analytical methods used to determine drug content in different phases should be adequately validated.

Data Interpretation

- Quantitative acceptance criteria not defined in PSGs
- Discussion and clinical relevance if differences are observed
- Discussion in the context of Totality of evidence (e.g., IVRT/GSD)

Importance of Fundamental Understandings

How to estimate the amount of drug in different phases of an emulsion with hypothetical composition.



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Understanding drug distribution and release in ophthalmic emulsions through quantitative evaluation of formulation-associated variables

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ABSTRACT

Establishing bioequivalence (BE) of ophthalmic emulsions in the absence of in vivo data is challenging. In these emulsions, drug release is a complex process due to drug distribution among various phases which are difficult to characterize. The objective of this study is to investigate the process of drug distribution and mechanism of drug release in the context of formulation-associated variables. A previously reported kinetic method for determining drug partitioning was used to quantitatively evaluate the drug distribution within a simplified biphasic (emulsion) system employing cyclosporine and difluprednate as model drugs. The impacts of formulation variables, such as the amount of polysorbate 80, glycerin, and carbomer copolymer as well as the area of oil-water interface were investigated. Polysorbate 80 was found to have the greatest influence on the drug dis-

Challenge Question

Drug distribution study in different phases of an ophthalmic emulsion for Test and Reference products is recommended to?

A. Establish quality attribute for drug product release and stability.

B. Justify formulation changes post approval.

C. Demonstrate sameness of Test with Reference product in support of in vitro BE determination.

D. Assess the acceptability of manufacturing site.

Summary

- Comparative physicochemical characteristics to support in vitro BE may also provide road map for product quality specification
- Method to determine drug in different phases should have minimum effect on the equilibrium distribution of the drug
- Adequate validation of the methodology is expected
- Discussion on the results should be provided

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