

Challenges in the Approval of Complex Otic and Ophthalmic Generic Products: Quality Perspectives

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval
Day 1, Session 3: (Complex Injectable, Ophthalmic and Otic Products Pt. 2)

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Learning Objective



- Highlight the role of comparative physicochemical characterization from quality perspective to support in vitro BE studies
- Discuss some of the critical studies that should be performed during product development for complex Otic suspension and Ophthalmic Gel drug products to ensure quality of the final drug products

Complex 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., transdermal, metered dose inhalers, extended-release injectables)

Background- Otic Suspensions

- Sterile dosage forms in which the drug substance is insoluble in the formulation and stays suspended in the vehicle
- Drug Product (DP) is instilled into the ear with a dropper, to treat or prevent ear infections, especially infections of the outer ear and ear canal
- Pose problems with physical instability of the formulation (e.g., particle size growth over time, or difficulties with resuspension after storage for a period of time)

Case 1- Otic Suspension


I. In Vitro Studies:

To qualify for the in vitro option for ciprofloxacin; dexamethasone otic suspension (0.3%; 0.1%) pursuant to 21 CFR 320.24 (b)(6), under which “any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence” may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:

- i. The test and reference listed drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).
- ii. Acceptable comparative physicochemical characterizations of the test and RLD formulations. The characterization study should be performed on at least three exhibit batches of both the test and RLD products and should include:
 - Comparative crystalline habit of dexamethasone
 - Comparative appearance, pH, specific gravity, osmolality, and viscosity
 - Comparative re-dispersibility (time required to re-disperse the formulation)
 - Comparative soluble fraction of dexamethasone in the final drug product
 - Comparative unit dose content (four drops per unit dose, for both APIs). Provide data for the amount of unit dose (four drops) with assay for both APIs from a minimum of 10 units from three batches each of the test and reference products. The unit dose content should be compared using population BE (95% upper confidence bound).
 - Comparative drug particle and particle size distribution. The particle size distribution should be compared using population BE (95% upper confidence bound) based on D50 and SPAN (D90-D10)/D50 or polydispersity index. The applicant should provide no fewer than ten data sets from three different batches each of the test and reference products for the population BE analysis. Full profiles of the particle size distributions should also be submitted for all samples tested.
- iii. Acceptable comparative in vitro drug release of dexamethasone from the test and RLD formulations. The abbreviated new drug application (ANDA) applicant should develop an in vitro dissolution method using U.S. Pharmacopoeia (USP) Apparatus Type IV or other appropriate apparatus.
- iv. Acceptable comparative in vitro antimicrobial kill rates of the test and RLD formulations. Refer to the dexamethasone/tobramycin ophthalmic suspension guidance for details on this study.



Q1/Q2 Required



**Comparable
Physicochemical
Characteristics**



**In Vitro Drug
Release**



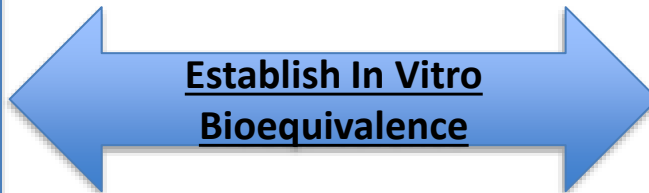
**In Vitro Antimicrobial
Kill Rate**

Comparative Physicochemical Characterization



Reference Product

1. Crystalline Habit of Insoluble APIs
2. Appearance, pH, Specific Gravity, Osmolality and Viscosity
3. Redispersibility
4. Soluble Fraction of Insoluble APIs
5. Unit Dose Content of all APIs
6. 3-tier Particle Size



Test Product

1. Crystalline Habit of Insoluble APIs
2. Appearance, pH, Specific Gravity, Osmolality and Viscosity
3. Redispersibility
4. Soluble Fraction of Insoluble APIs
5. Unit Dose Content of all APIs
6. 3-tier Particle Size

Retention, Irritation, Stability, Drug Release, Clinical performance

- Sterile dosage forms in which the drug substance (API) is soluble, insoluble, or somewhere in between in the drug product formulation?

API Soluble in DP

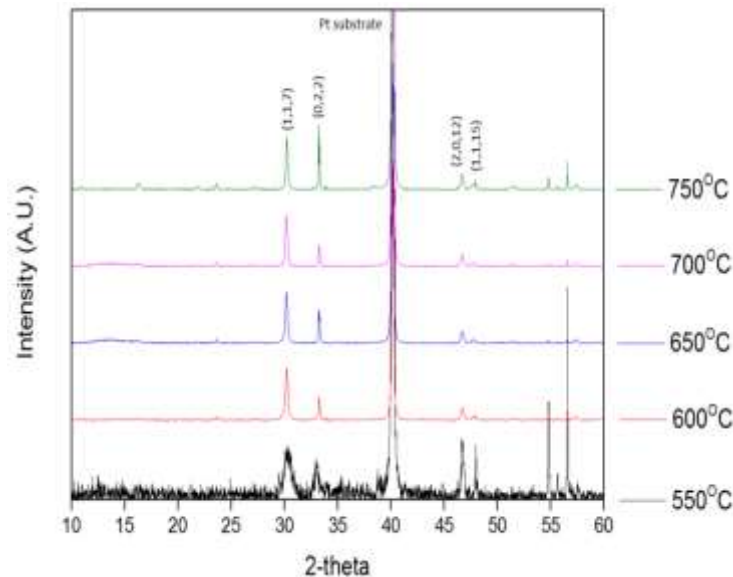
- Solubility of API as a function of pH and temperature?
- Evidence that DS will remain fully solubilized in DP over time?

API Insoluble in DP

- Insoluble in the formulation and stays suspended in the vehicle.
- Polymorphic form?
- Comparative XRD data to support?
- DS micronized or unmicronized - 3-tier particle size limits in DS specifications

Crystalline habit of insoluble API (e.g., Dexamethasone):

- Dexamethasone is suspended in the formulation and exhibits two crystalline forms (A and B) with distinct X-ray diffraction (XRD) patterns
- Comparative XRD testing of the test product and RLD to confirm sameness of crystalline form of dexamethasone



Otic Suspension Formulation Development Considerations



- Excipient compatibility study (e.g., studies on excipient grade, critical excipient properties etc.)
- Material contact equipment study (Extractables, compatibility, adsorptive loss)
- Order of addition (DS and Excipients)
- Mixing speed/time and process temperature
- Bulk hold time study
- Oxygen sensitivity study (if needed)
- Antimicrobial Effectiveness study on lowest levels of preservative
- Antioxidant level justification (if applicable)
- Stability studies (Photostability, Freeze/Thaw/Thermal Cycling and water loss/weight loss)
- Risk Assessment for Elemental Impurities (per ICH Q3D/USP <232>)
- Container Closure System (CCS) characterization and Qualification studies (CCS design, Cap color, *Drop size*, USP <87/<88>, USP <661> and <671>, CCS integrity and Extractable/Leachable study (USP <1663> and <1664>)

Otic Suspension Formulation Development Considerations

➤ Comparable Physicochemical Testing of RLD and Test Product (from at least 3 lots)

- Crystalline habit of insoluble APIs
- Appearance (Color and Uniformity of the suspension)
- pH (USP<791>)
- Specific Gravity
- Osmolality (USP<785>)
- Viscosity
- Redispersibility (time required to re-disperse)
- Soluble Fraction of Insoluble API
- Unit Dose Content of all APIs
- 3-tier Particle Size (USP<429>)

➤ Additional Tests from Quality Perspective such as Assay, Impurities etc.

Unit dose content data:

- Quantitative test/Acceptance Criteria for dose accuracy
- Test product should deliver the amount of drug as per label claim
- Shaking per labeling instructions
- Assay of samples (top, middle and bottom) from the container after shaking per label instructions to ensure dose homogeneity within the container through out the drug product shelf life

Product Quality Tests for Release and Stability: Case-1 (Otic Suspensions)

- *Description/Appearance*
- *Quantitative Color Test (as applicable)*
- *Identification (Chromatographic/Spectroscopic)- Release only*
- *Foreign and particulate matter/Visible Particulates*
- *Assay API, Preservative and Antioxidant*
- *Impurities/Degradants*
- *Minimum Fill volume*
- *Elemental Impurities (USP <232>) - Release only*
- *Residual Solvents (USP<467>) - Release only*
- *pH (USP<791>)*
- *Osmolality (USP<785>)*
- *Viscosity (if viscosity enhancer is present)*
- *Specific Gravity*
- *Container Content (Minimum Fill, USP<755>) - Release only*
- *Leachables (if applicable)*
- *Container-Closure Integrity/Package Integrity test*
- *Particle size*
- *Unit Dose Content/Dose Uniformity*
- *Dissolution*
- *Resuspendability/Redispersibility*
- *Antimicrobial Effectiveness Test (AET) (USP<51>)*
- *Sterility (USP<71>)*
- *Bacterial Endotoxin (USP<85>)*
- *Water loss/Weight Loss- Stability only*

Background- Ophthalmic Gels

- Sterile products meant for instillation into the eye in the space between eye lid and eyeball
- Ophthalmic Gels are semisolid preparations in which API may be in solubilized/and or suspended form
- USP<771> ophthalmic products- quality tests
- Product specific Guidance for Ophthalmic drug products for in vitro support for establishing Bioequivalence (BE)

Case 2- Ophthalmic Gels


I. In vitro option:

To qualify for the in vitro option for this drug product all of the following criteria should be met:

- i. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)¹ and quantitatively (Q2)² the same (Q1/Q2).³
- ii. Acceptable comparative physicochemical characterizations of the test and Reference Standard (RS) products. The comparative study should be performed on at least three exhibit batches of both the test and RS products and should include:⁴
 - Comparative crystalline habit of loteprednol etabonate.
 - Comparative appearance, pH, specific gravity, and osmolality.
 - Comparative soluble fraction of loteprednol etabonate in the final drug product.
 - Comparable rheological properties including yield stress and viscosity. The applicant should characterize viscosity over a range of shear rates.
 - Comparative drug particle size distribution. The particle size distribution should be compared using PBE (95% upper confidence bound) based on D_{50} and SPAN [i.e. $(D_{90}-D_{10})/D_{50}$]. The applicant should provide no fewer than ten data sets from three different batches of both the test and reference products for PBE analysis.
- iii. Acceptable comparative in vitro drug release of loteprednol etabonate from the test and RS formulations.



Q1/Q2 required



**Comparable
Physicochemical
Characteristics**



**In Vitro Drug
Release**

Comparative Physicochemical Characterization

Reference Product

1. Crystalline Habit of Insoluble APIs
2. Appearance, pH, Specific Gravity, Osmolality and Viscosity
3. Soluble Fraction of Insoluble APIs
4. Rheological Properties including Yield Stress and Viscosity
5. 3-tier Particle Size

Establish In Vitro
Bioequivalence

Test Product

1. Crystalline Habit of Insoluble APIs
2. Appearance, pH, Specific Gravity, Osmolality and Viscosity
3. Soluble Fraction of Insoluble APIs
4. Rheological Properties including Yield Stress and Viscosity
5. 3-tier Particle Size

Retention, Irritation, Stability, Drug Release, Clinical performance

Ophthalmic Gel Formulation Development Considerations

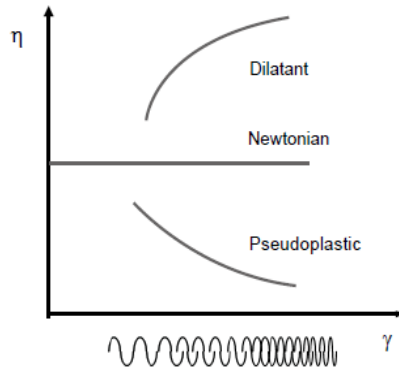
➤ Comparable Physicochemical Testing of RLD and Test Product (from at least 3 lots)

- Crystalline habit of insoluble APIs
- Appearance (Color and Uniformity of the suspension)
- pH (USP<791>)
- Specific Gravity
- Osmolality (USP<785>)
- Viscosity
- Redispersibility (time required to re-disperse)
- Soluble Fraction of Insoluble API (e.g., Loteprednol in the final DP for 3 exhibit batches of the test product)
- Rheological properties including Yield Stress and Viscosity
- 3-tier Particle Size (USP<429>)

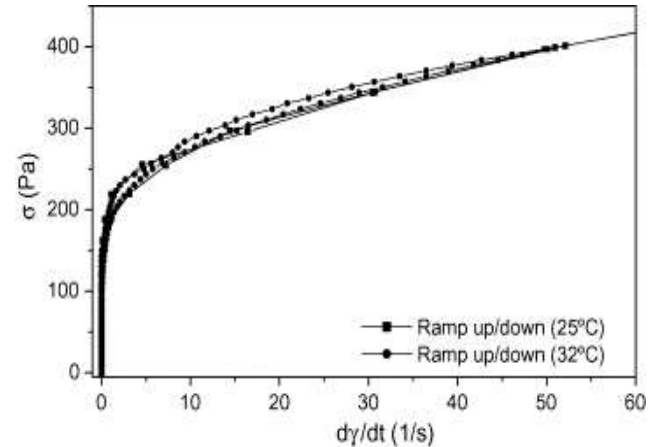
➤ Additional Tests from Quality Perspective such as Assay, Impurities etc.

Rheological properties

- Comparative Shear Rate Data
- Change in Viscosity with Stress –Thixotropic (e.g., Non-Newtonian etc.)



Viscosity change with shear rate for Newtonian and Non-Newtonian fluids



<https://www.sciencedirect.com/science/article/pii/S0378517306008027?via%3Dihub>

https://www.researchgate.net/publication/243416912_Rheological_Behavior_of_Some_Aqueous_Gels_of_Carbopol_with_Pharmaceutical_Applications

Ophthalmic Gel Formulation Development Considerations

Uniformity in Container

- Conforms USP<3>
- Sample preparation and test method validation
- Assay from beginning, middle and end of the container
- Controlled in the drug product release and stability

Unit dose content data

- Quantitative test/Acceptance Criteria
- Test product should deliver the amount of drug as per label claim

Product Quality Tests for Release and Stability: Case-2 (Ophthalmic Gels)

- *Description/Appearance*
- *Identification (Chromatographic/Spectroscopic)- Release only*
- *Foreign and particulate matter/Visible Particulates*
- *Assay API, Preservative and Antioxidant*
- *Impurities/Degradants*
- *Elemental Impurities (USP <232>) - Release only*
- *Residual Solvents (USP<467>) - Release only*
- *pH (USP<791>)*
- *Osmolality (USP<785>)*
- *Viscosity (USP<785>)*
- *Specific Gravity*
- *Container Content (Minimum Fill, USP<755>) - Release only*
- *Leachables (if applicable)*
- *Container-Closure Integrity/Package Integrity test*
- *Particle size*
- *Uniformity within the container*
- *Unit dose uniformity*
- *Dissolution*
- *Antimicrobial Effectiveness Test (AET) (USP<51>)*
- *Sterility (USP<71>)*
- *Bacterial Endotoxin (USP<85>) – DPs for Surgical Treatment*
- *Water loss/Weight Loss- Stability only*

Summary of Two Cases



- Deep understanding of drug product formulation development is the key to establish the critical quality attributes (CQA's) and ensure high quality for Otic Suspension and Ophthalmic Gel Drug Products
- Comparative physiochemical characterization testing of generic and RLD product is necessary for development and quality control of the test product and can also support invitro BE approach for the test product.

Challenge Question



Currently, the comparative physicochemical characterization of RLD and complex drug products is performed to:

- A. Demonstrate sameness of test with reference product in support of in vitro BE determination
- B. Justify critical quality attributes for drug product release and stability
- C. Assess that the test formulation is Q1/Q2 to RLD
- D. Both A and B

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