Product Quality Testing for Topical Ophthalmic Suspension Products

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Presentation Outline

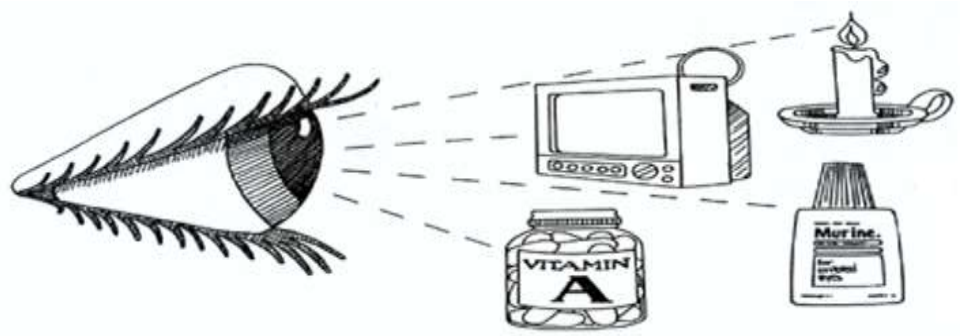
- Introduction
- Formulation Development Considerations
- Manufacturing Considerations (In-Process Tests)
- Product Quality Tests for Release and Stability
- Stability Study Conditions {ICH Q1A(R2)}

Presentation Goal

- To highlight some of the critical studies that should be performed during product development and some of the critical quality attributes of the drug product that should be evaluated during in-process, release and stability to ensure quality of the final ophthalmic suspension drug product.

Introduction

- The human eye is a very precious and very sensitive organ.
  - Hence, to maintain or improve eye health, drug products introduced into the eye must be of high quality, safe and efficacious.



Eyescare.org: If your eyes are functioning up to par they will bring you clear images of the world around you.

Introduction

- Ophthalmic suspensions:
  - Sterile dosage forms in which the drug substance is insoluble in the formulation and stays suspended in the vehicle.

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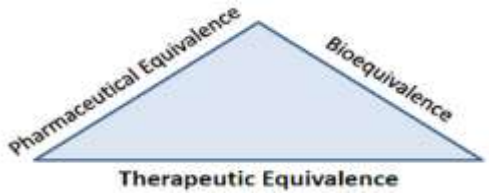
  - Pose problems with physical instability of the formulation (e.g., particle size growth over time, or difficulties with resuspension after storage for a period of time).

Introduction

- Regulatory Requirements for Ophthalmic Suspension Drug Products
  - Q1/Q2 (Qualitatively and Quantitatively same) with RLD (21 CFR 314.94(a)(9)(iv))



- Quality Tests for Ophthalmic Suspension Drug Products
  - USP <771> Ophthalmic Products – Quality Tests
- Ophthalmic suspension products must meet all regulatory requirements and applicable quality standards prior to approval

Formulation Development Considerations

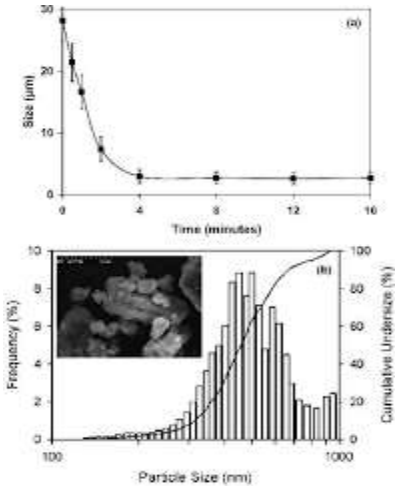
- Development Studies (Formulation and Process)
  - Demonstrate product understanding, understanding of the risks to product quality and risk to patient
  - Provide supporting data to demonstrate that the risks have been adequately mitigated

Risk to Product Quality ⟷ Risk to Patient



Formulation Development Considerations

- RLD Characterization and Comparable Physicochemical Testing of RLD and Proposed Generic
- Evaluation of Drug Substance (DS) Critical Attributes
  - API quality has a direct impact upon drug product formulation development and manufacturing
  - DS Particle Size
    - Is your DS micronized or unmicronized?
    - Recommend 3-tier particle size limits in DS specification

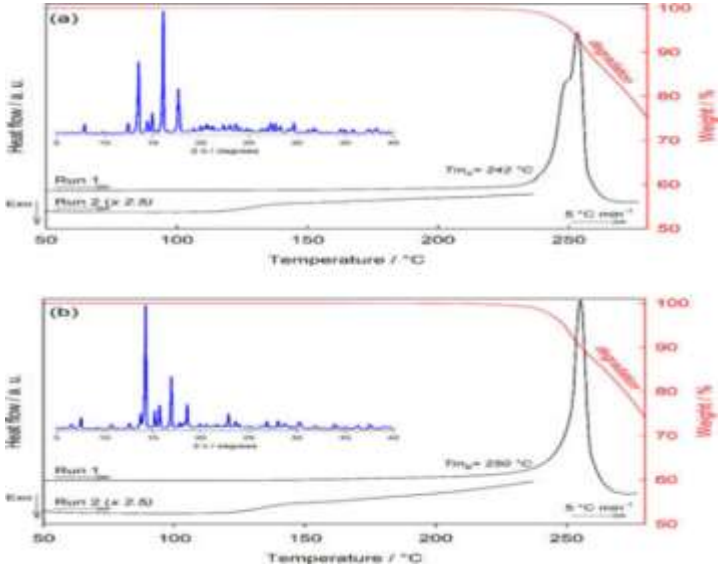


https://www.ncbi.nlm.nih.gov/pubmed/15906179
Pharm Res. 2005 May;22(5):826-35. Epub 2005 May 17.

Formulation Development Considerations

- Evaluation of Drug Substance (DS) Critical Attributes - continued
  - DS Morphology (Polymorphism)
    - Does your drug substance exhibit polymorphism?
    - Is your DS polymorphic form consistent with that of RLD or is it different?
    - Is there form transformation during drug product manufacture and storage?

- DSC scan (5 °C/min), TGA scan (5 °C/min), and PXRD pattern of the initial materials: (a) DEX Form A, (b) DEX Form B.



Cryst. Growth Des. 2018, 18, 1748−1757; pubs.acs.org/crystal

Formulation Development Considerations

- Typical Studies during Product Development:
  - Comparable Physicochemical Testing of RLD and Proposed Generic (e.g., Appearance, Particle Size Distribution, viscosity/viscosity profile, Assay, Impurities, pH, Osmolality, redispersibility/resuspendability, etc.)
  - Studies on Excipient grade and Critical excipient properties*
  - Excipient Compatibility study
  - Contact Material 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)

- Typical Studies during Product Development (Continued):
  - Antimicrobial Effectiveness study on lowest levels of preservative
  - Antioxidant level justification (if applicable)
  - Elemental Impurities (ICH Q3D/USP <232>)
  - Stability studies
    - Photostability
    - Freeze-Thaw/Thermal Cycling
  - Container Closure System (CCS) Characterization and Qualification Studies
    - CCS Design (including tamper-evident features)
    - Cap Color (per AAO recommendation)
    - Drop size/weight study (one-time study)
    - USP<87>/<88>, USP <661>, USP<671>
    - CCS Integrity Study
    - Extractables/Leachables study (per USP <1663> and <1664>)

Formulation Development Considerations

- Excipient Studies
  - Studies on Excipient Grade
    - Example: Viscosity modifiers (e.g., Guar gum, Hydroxyethylcellulose, Carbomer) – different grades may impact product viscosity
  - Studies on Critical Excipient Properties
    - Examples:
      - Preservatives: Any interaction with other components (e.g., Surfactants, thickening agents, CCS, etc.)?
      - Multi-component excipients, e,g., Benzalkonium chloride (BAC)
        - » C12/C14/C16 ratio may impact preservative effectiveness
  - Anhydrous versus Hydrate form, e.g., Edetate Disodium (EDTA)
  - Demonstrate differences in excipient grade and excipient properties between suppliers will not impact product quality and performance.
    - Excipient specifications should include those critical quality attributes of the material that could impact drug product quality and/or performance.

Manufacturing Considerations (In-Process Tests)

- Typical In-process Tests
  - Appearance
  - Assay - API, Preservatives, Antioxidants (as applicable)
  - pH
  - Viscosity (as applicable)
  - Density
  - Fill volume/range

- Typical In-process Tests (Continued)
  - Bulk and Packaged Product homogeneity (top, middle, bottom of the tank and during filling operation)*
  - Particle Size distribution*
  - Bioburden
  - Seal integrity/leak test
  - Filter integrity

Manufacturing Considerations (In-Process Tests)

- Though DP is Q1/Q2 with RLD, process parameters can impact quality or performance of the final product.
- Bulk and Packaged Product homogeneity
  - Demonstrate homogeneity of the bulk suspension from top, middle and bottom of the tank and beginning, middle and end of the filling operation.
- Particle size Distribution (as applicable)
  - Reduce particle size of the drug product (most particles should be < 10 um) to minimize excessive lacrimation and eye irritation.
  - At least 3-tier particle size limits recommended.

Product Quality Tests for Release and Stability

- Typical Quality Attributes Evaluated:
  - Description/Appearance
  - Quantitative Color Test (as applicable)
  - Identification (Chromatographic/Spectroscopic) – Release only
  - Foreign and Particulate Matter/Visible Particulates
  - Assay – API, Preservative, Antioxidant, EDTA (as applicable)*
  - Impurities/Degradants*
  - Residual Solvents (USP<467>) – Release only
  - pH (USP<791>)*
  - Osmolality (USP<785>)*
  - Viscosity (if viscosity enhancer is present)*
  - Container Content (Minimum Fill, USP<755>)* – Release only

- Typical Quality Attributes Evaluated (Continued):
  - Leachables (if applicable)
  - Particle Size and PSD (USP <429>)*
  - Drop Homogeneity/Dose Uniformity*
  - Resuspendability/Redispersability*
  - Dissolution
  - Elemental Impurities (ICH Q3D/USP <232>), (as applicable) – Release only
  - Package Integrity/Evaluation test
  - Sterility (USP<71>)
  - Antimicrobial Effectiveness Test (AET) (USP<51>)
  - Bacterial Endotoxins (USP <85>) - DPs for Surgical Treatment
  - Water loss/Weight loss – Stability only

Product Quality Tests for Release and Stability

- Acceptance criteria should be based on results of comparative testing of multiple lots of RLD near expiry.

- Assay – API, Preservatives, EDTA, Antioxidant

- pH (USP<791>) – Recommend same pH as the RLD to ensure product sameness with RLD.
  - The pH could determine:
    - Stability of the therapeutic agent
    - Ocular acceptability of the formulation
    - Absorption of the drug across cornea

Product Quality Tests for Release and Stability

- Impurities/Degradants
  - Drug product impurity limits should be similar to RLD limits, unless adequately justified (e.g., toxicity data).
    - ICH Q3B limits do not apply.
  - For USP products, the limits for specified impurities can follow USP limits (except where new safety data indicates need for tighter limits), but for unspecified/unknown impurities, the limit should be similar to RLD limit.

Product Quality Tests for Release and Stability

- Osmolality (USP<785>) – Similar limits to RLD to minimize potential for eye irritation.
- Viscosity (if viscosity enhancer is present) – Recommend similar limit to RLD to ensure similar residence time in the eye (as RLD).
  - Product development studies should evaluate viscosity as a function of applied shear.
- Particle Size Distribution (USP <429>) – Recommend similar limits to RLD to minimize potential for eye irritation and scratching of cornea.
  - Recommend at least 3-tier particle size limits (including limit for 100% of the particles)
    - Product development studies should evaluate the potential for any size changes due to Ostwald ripening or particle agglomeration.

Product Quality Tests for Release and Stability

- Container Content/Minimum Fill (USP <755>) – For release only
  - Fill volume should be similar to RLD fill volume to ensure similar number of doses through the use period.
  - Acceptance criteria should be 'NLT the labeled amount/volume'.
- Resuspendability/Redispersibility
  - Qualitative test/Acceptance criteria
  - Performed as per labeling instructions to mimic actual patient use conditions
  - Time for resuspension of drug product after storage: NMT 15 - 30 seconds.
    - Product should readily redisperse with no lumps upon shaking (per labeling instructions) after storage.

Product Quality Tests for Release and Stability

- Drop Homogeneity/Dose Uniformity
  - Quantitative test/Acceptance criteria
  - Unit dose samples should be taken from top, middle and bottom of the container after shaking per labeling instructions and tested for assay using the assay acceptance criteria to ensure drop homogeneity within the entire container through product shelf life.

- Analytical Methods
  - Validated and Suitable for the intended use

Stability Study Conditions

- Ophthalmic suspension drug products are typically packaged in semi-permeable containers, e.g., LDPE containers.
- Recommended stability conditions per ICH Q1A (R2):
  - Long-Term: 25ºC ± 2˚C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH
  - Intermediate: 30˚C ± 2˚C/65% RH ± 5% RH
  - Accelerated: 40°C ± 2˚C/NMT 25% RH
- Container Orientation - Upright and Inverted or horizontal positions

Conclusion

- Adequate product understanding is key to designing and manufacturing high quality products.
- Know the regulations and ensure your product meets all relevant regulatory requirements.
- Provide adequate supporting data in your ANDA applications to ensure smooth and timely assessment of your applications.
- Together we (FDA and Industry) can make quality products available to the American people.

Acknowledgements

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Thank you!


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