Importance of comparative unit dose concentration in the evaluation of complex ophthalmic suspension product quality

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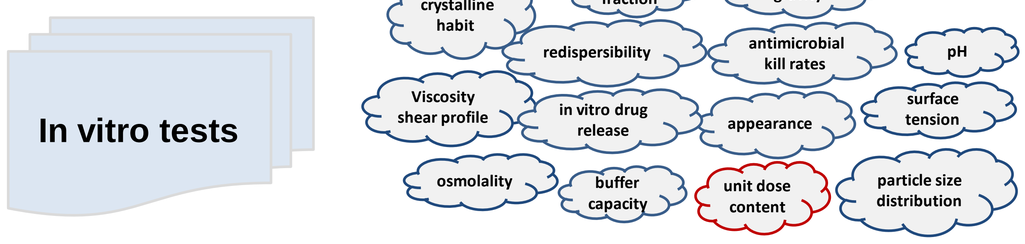
INTRODUCTION

- Drug products, such as ophthalmic suspension products, are expected to deliver a labeled amount of drug (per dose) that is consistent with the claimed strength from lot-to-lot and throughout its shelf-life and patient's usage.
- In vitro testing methods can detect potential differences in a product due to changes in formulation and/or the manufacturing process. The in vitro tests depend upon the critical quality attributes (CQA) of the formulation. In vitro testing to demonstrate CQA sameness can be used to support lot-to-lot or brand name-to-generic product quality determination.



- A CQA of particular interest is the unit dose concentration of multi-dose ophthalmic suspension drug products, as dispersion instability can give rise to a changing unit dose concentration depending on its usage state, i.e. beginning, middle, or end of the bottle.
  - Currently only resuspendability is evaluated via a qualitative visual inspection of resuspension time.
  - The purpose of this study is to investigate a quantitative measure of ophthalmic suspension stability via dose uniformity.
    - The uniformity of unit dose content can be demonstrated by measuring comparative unit dose concentration throughout the expected usage lifespan of the drug product (e.g., beginning, middle, and end), among containers, and among different batches.
    - A similar quality test is recommended for nasal spray products*.

*Recommendation for nasal spray products regarding spray content uniformity (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm070575.pdf)

OBJECTIVES

1. Evaluate and compare the unit dose concentration of the drug product to the labeled strength throughout the usage lifespan
2. Assess the effects of instability of the suspension on dose uniformity
3. Correlate the changes of unit dose content with other physicochemical properties

MATERIAL AND METHODS

MATERIALS:

- Model drug: A commercial Tobramycin Dexamethasone Ophthalmic Suspension *USP, 0.3% / 0.1%*
- Simulated flocculated suspension: 50 µL of 15% sodium dodecyl sulfate (SDS) was added to the 5 mL container of the commercial Tobramycin Dexamethasone Ophthalmic Suspension to induce drug particle flocculation.

METHODS:

- Unit dose concentration was determined by drop-to-drop comparison at the beginning (Zone 1), middle (Zone 2), and end (Zone 3) of the lifespan of a single unit 5 mL bottle.
- For each zone, the bottle was shaken gently and then ten individual drops(doses) were collected. The concentration of dexamethasone (DEX) per drop mass (n=10) was measured using high performance liquid chromatography.
- Optical microscopy was performed to characterize the particle morphology and tendency of flocculation.
- Dosing error may occur due to instability of the suspension, which manifests through particle flocculation, caking, or poor redispersibility of the drug product suspensions which may not be fully captured by particle size measurements and /or other stability tests.
- Differences in the unit dose content uniformity of the original and flocculated suspensions were statistically compared using the population bioequivalence (PBE) procedure.

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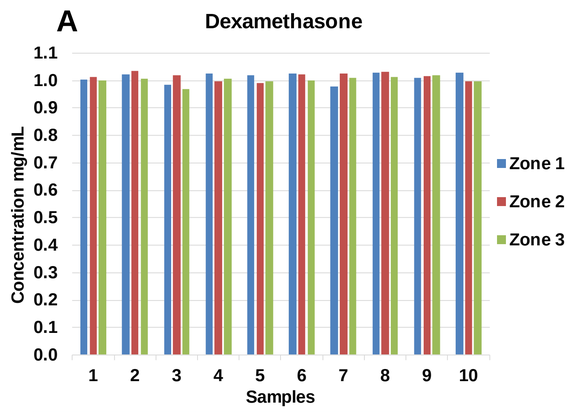
DISCLAIMER

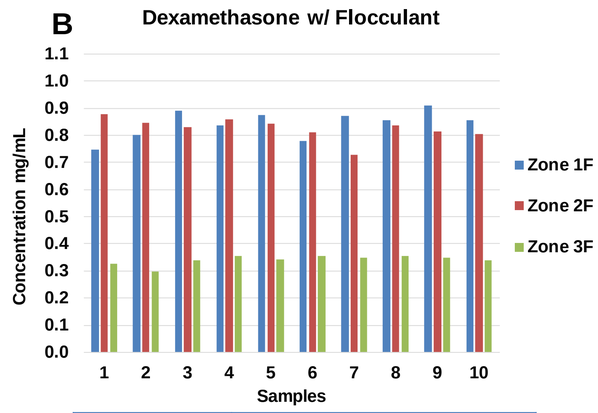
The views expressed in this poster do not necessarily reflect the official policies of the U.S Food and Drug Administration; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

RESULTS

Unit Dose Concentration



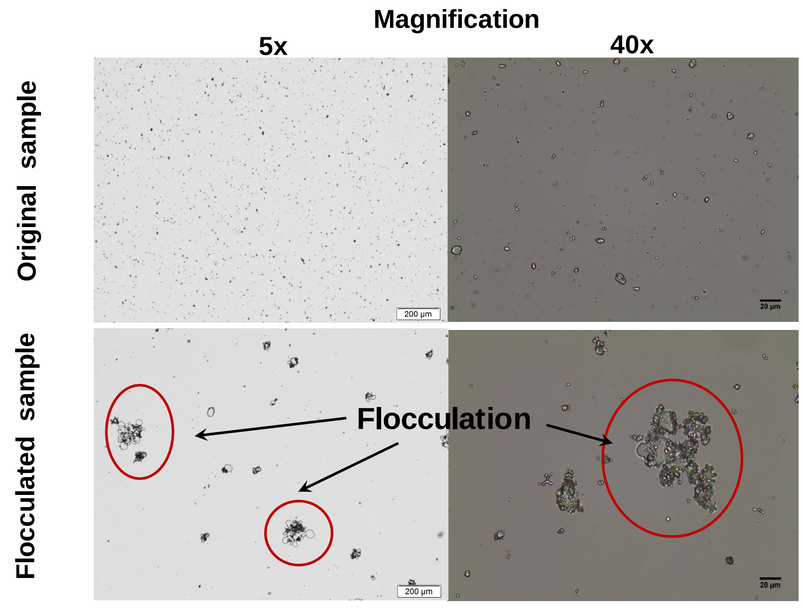
Zone 1	1.012 ± 0.018 mg/mL
Zone 2	1.015 ± 0.015 mg/mL
Zone 3	1.002 ± 0.013 mg/mL



Zone 1F	0.842 ± 0.051 mg/mL
Zone 2F	0.825 ± 0.040 mg/mL
Zone 3F	0.314 ± 0.017 mg/mL

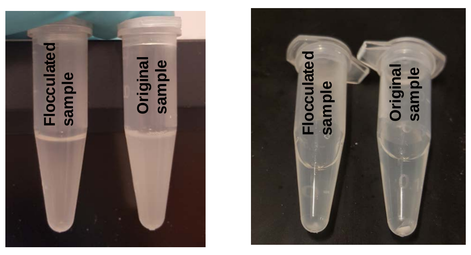
- ***A :*** **The unit dose concentration of DEX from the beginning, middle and the end of the original product (n=10) was consistent to the labeled strength 1 mg/mL**
- ***B:*** **The unit dose concentration of DEX in the flocculated product (n=10) decreased from the beginning to the end of the product (Zone 1F, 84% recovery; Zone 2F, 82.5% recovery; Zone 3F, 31.4% recovery)**

Optical Imaging



- **Optical imaging confirmed the flocculation was caused by adding SDS to the sample.**

Particle Sedimentation



- **Particle sedimentation was observed in both original and flocculated samples over time.**

Population Bioequivalence Statistical Test

Reference-scaled:	**Point estimate:**	**0.5117**
	Confidence Interval	**1.1527**
	Pass/Fail:	**Fail**
Constant-scaled:	**Point estimate:**	**0.4923**
	Confidence interval	**1.1334**
	Pass/Fail:	**Fail**
Overall Test Outcome	**Pass/Fail:**	**Fail**

- **All criteria showed "fail" which indicated original formulation and flocculated formulation are not equivalent.**

DISCUSSION

- **The unit dose concentration of DEX in the original Tobramycin Dexamethasone Ophthalmic Suspension was highly consistent in yielding the label claimed strength (concentration) of 1 mg/mL in each zone.**
- **In contrast, the unit dose concentration of DEX in the bottle flocculated with SDS was lower than the original bottle. It also decreased to less than 1/3 of the labeled concentration in Zone 3.**
- **Population bioequivalence statistical test using a 95% upper confidence bound interval (CI) confirmed that the unit dose concentration delivered in the original bottle and the flocculated bottle were not equivalent.**

CONCLUSIONS

- **An unstable suspension was successfully simulated by controlling the degree of SDS added and was confirmed with optical imaging.**
- **The comparative unit dose concentration test sampled from the beginning, middle, and the end of a container is a potential sensitive quantitative measurement for dose content uniformity of ophthalmic suspension products.**
- **This test may be used, along with other in vitro and/or in vivo tests to ensure product quality.**

FUTURE PLANS

- **Replicate analysis using more lots of Tobramycin Dexamethasone Ophthalmic Suspension.**
- **Comparative measure of size from the original and flocculated bottle over three zones.**
- **Evaluate the effect of dosing error on other complementary tests such as particle size measurement.**

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