Injectable Suspensions: Tools and Methods Bridging The In Vivo and In Vitro Gap

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 3: (Complex Injectables, Ophthalmic and Otic Products Pt. 1)

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Learning Objectives

- Describe bioequivalence (BE) approaches for injectable suspensions
- Identify pathways to discuss alternative BE approaches
- Summarize impact of particle flocculating on the dissolution and bioavailability of injectable suspensions: GDUFA research highlight.

Injectable Suspension

- Consists of nano- and/or micro-sized solid drug particles suspended in aqueous vehicle
- Used for a variety of parenteral routes of administration, e.g., intramuscular, subcutaneous
- Supplied as powders for injection or ready-to-use suspension
- Offers various levels of sustained release, which is controlled by the water solubility and the particle size of the drug substance

Demonstrating Equivalence of Injectable Suspension to RLD

- Same active ingredient(s), strength, dosage form, and route of administration, condition of use, labeling
- Qualitatively (Q1) and quantitatively (Q2) the same inactive ingredients as the reference listed drug[1]
- Bioequivalence (BE)
  - In vivo BE studies
  - In vitro BE studies

1. Differences in preservative, buffer, or antioxidant are permissible, per 21 CFR 314.94(a)(9)

BE Approaches of Injectable Suspension

- BE study needs to be sensitive, accurate and reproducible
- In general, a BE study with pharmacokinetic (PK) endpoints is recommended by FDA in product-specific guidance (PSG)[2] for systemically acting injectable suspension products including suspensions for short term use (e.g., triamcinolone acetonide, penicillin G benzathine) and long-acting injectable (LAI) suspensions for chronic use (e.g., paliperidone palmitate)
- In addition to FDA's recommended in vivo BE study approach, FDA has recommended in vitro BE option for some injectable suspensions for short term use

2. https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

In Vitro BE Approaches for LAI Suspensions

- From formulation perspective, injectable suspensions are similar, e.g., drug substance is the only insoluble component; drug release is driven by dissolution of drug substance particle.
- However, the prolonged in vivo application duration and the indication of the long-acting suspensions (e.g., paliperidone palmitate for antipsychotic) present a higher risk compared to injectable suspensions for short term use (e.g., triamcinolone acetonide)

In Vitro BE Approaches for LAI Suspensions (cont.)

- Need to understand which factors cause in vivo PK variability
  - Contributions from physiological factors VS. contributions from formulation factors
- Need to conduct failure mode analysis to better understand key parameters that are responsible for product performance, e.g., potential dose dumping if applicable
- Need to demonstrate how the proposed physicochemical characterization studies correlate with critical quality attributes and in vitro/in vivo drug release of the drug product, such as information on the design space of the critical quality attributes
- In vivo in vitro correlation (IVIVC) can be helpful to support in vitro only approach but establishing IVIVC may not be less challenging than the current PSG recommended study (e.g., steady state BE study in patients)

Proposing an Alternative BE Approach to a PSG Recommendation

- OGD is open to novel alternative approaches for assessing BE
- Engage with OGD early and provide sufficient information/data to support your proposal
- Pathways to discuss an alternative BE approach:
  - Controlled correspondences[3]
  - Pre-ANDA meeting requests[4]

3. Guidance for Industry *Controlled Correspondence Related to Generic Drug Development* (Dec 2020)
4. Guidance For Industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Nov 2020)

GDUFA Research on Injectable Suspensions

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Impact of particle flocculation on the dissolution and bioavailability of injectable suspensions

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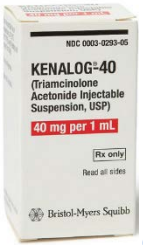
ABSTRACT

Injectable suspensions occasionally exhibit variations in dissolution and bioavailability, which may impact the clinical outcome of the drug product. Here, variation in the injection method (*i.e.*, applied shear) for triamcinolone acetonide (TA) injectable suspension (40 mg/mL) altered the flocculation state of the particles and subsequently their dissolution. Notably, TA suspensions contained primary particles of approximately 2 μm and secondary flocculates of tens of microns. The conversion between flocculated and deflocculated particles was rapid, reversible and highly shear dependent. As such, changing shear rates during laser diffraction (LD) measurement like stirring rate, sonication, and sample introduction method (micropipette vs 25-gauge needle) may result in variability in particle size distributions (PSD) that have the potential to alter drug dissolution. Furthermore, a non-sink, discriminatory *in vitro* release testing (IVRT) method was developed, which combined *in-situ* fiber optic UV with LD to simultaneously monitor the dissolution and changing PSD of the suspension. The simultaneously measured dissolution and PSD data showed that flocculated and deflocculated particles followed different dissolution pathways. Importantly, deflocculated particles dissolved up to six times faster than the flocculated particles. Similar shear-induced changes during injection could occur in a clinical setting and have implications for drug bioavailability.

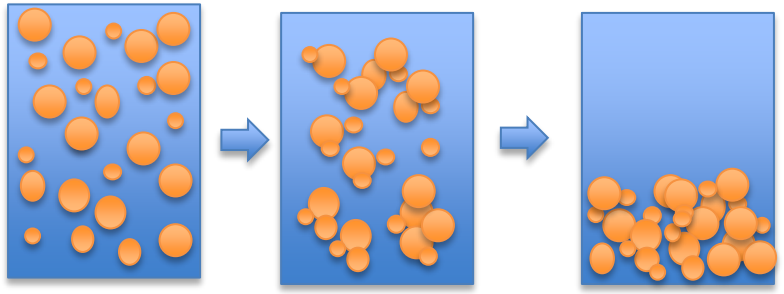
- Triamcinolone acetonide (TA) injectable suspension for intramuscular displayed high variability in PK profiles[5]
- The variability is not likely due to the deposition of TA itself
- This research explored the potential cause of in vivo PK variability from formulation physicochemical property perspective.

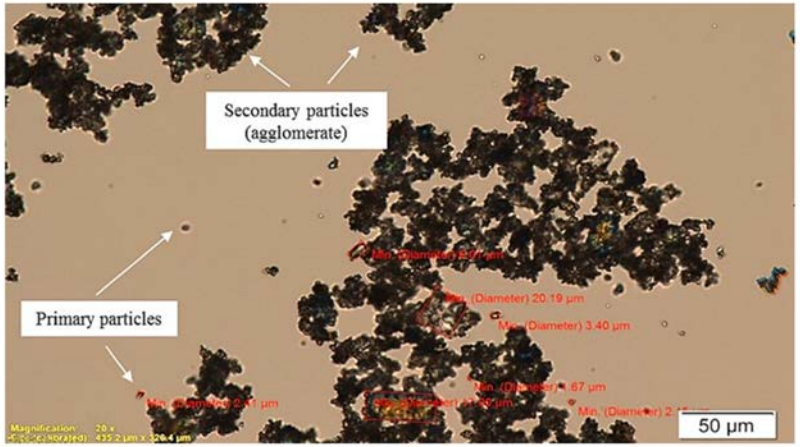


5. Sergi Coll, et al. Steroids, 2019, 151, 108464

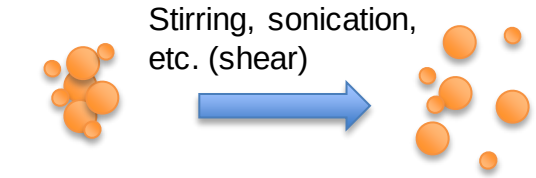
Flocculated Suspensions

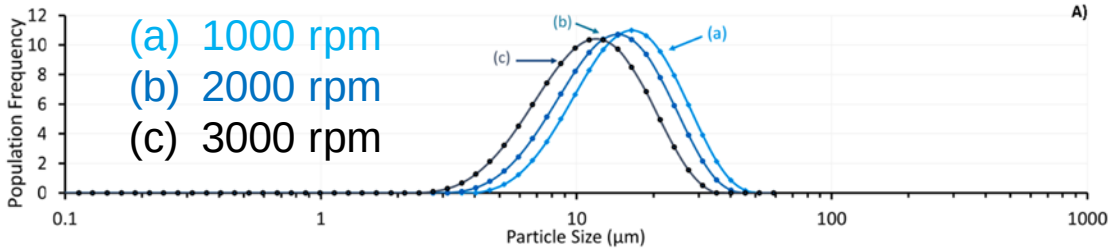
- Injectable suspensions are often designed to be an easily reversible flocculated suspension to maintain physical stability
- Loose networks of flocculates maintains particle-particle distance in the sediment to prevent irreversible particle aggregation
- TA injectable suspension is a flocculated suspension formulation. It contains primary particles of 1-4 µm and secondary flocculates of tens of microns.

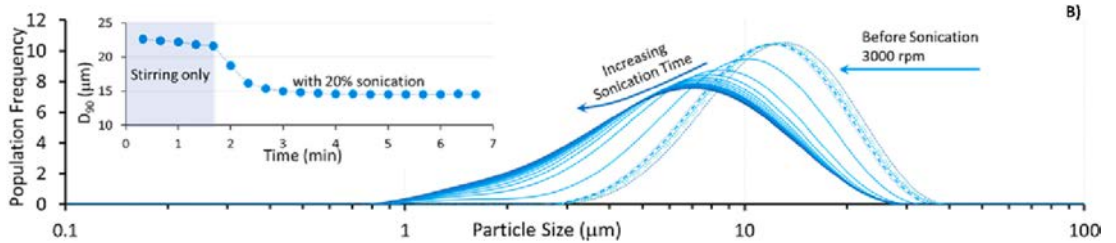


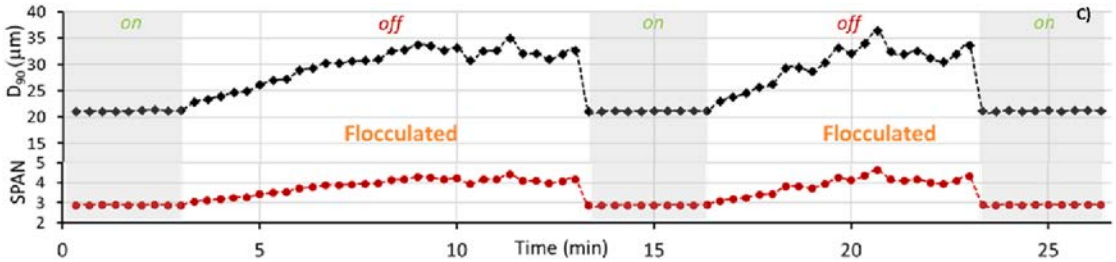


Impact of Shear on Particle Size Distribution of Flocculated Suspensions









- Conversion between flocculated and deflocculated particles was reversible and shear-dependent.

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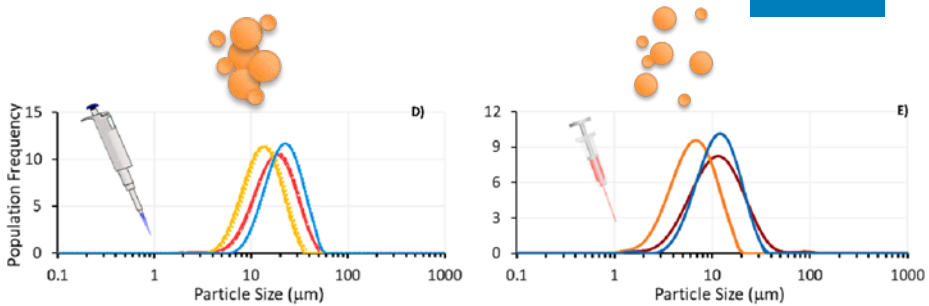
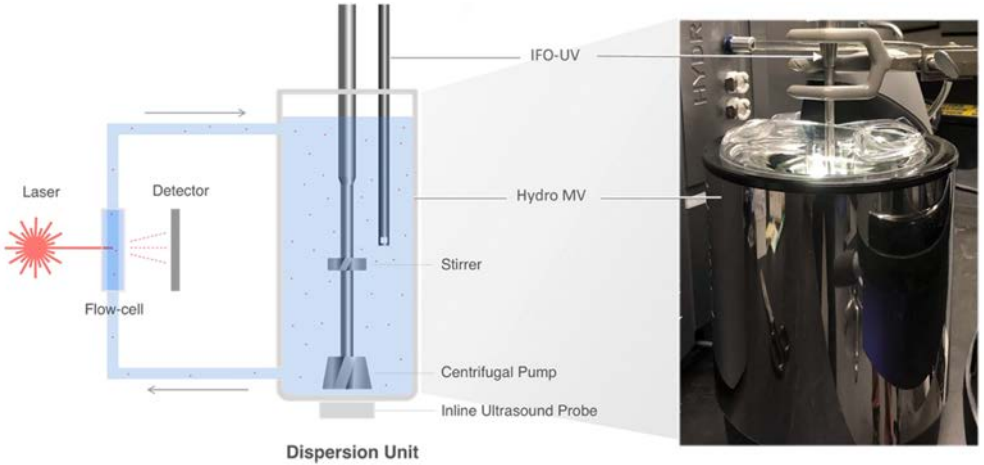
Dissolution Setup

- Sample introduction method:
  - 25 G syringe (high shear)
  - Micropipette (low shear)
- Non-sink condition
- Combined in situ fiber optic UV with laser diffraction





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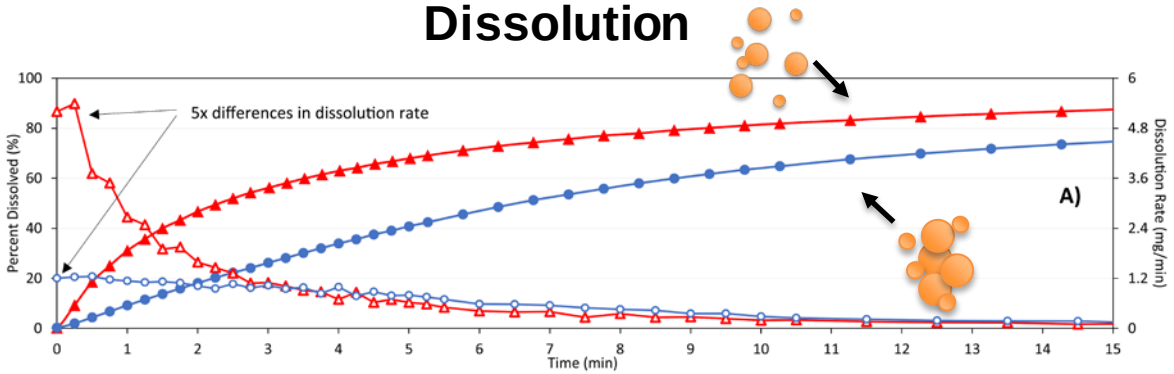
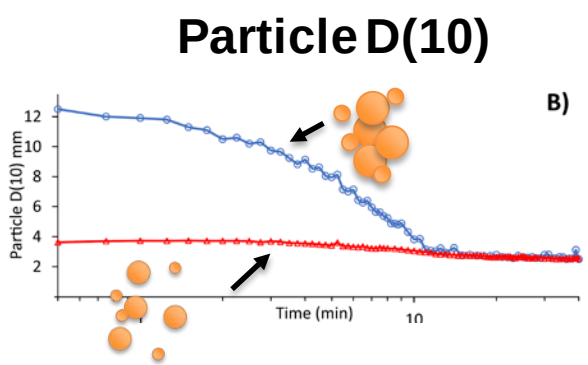
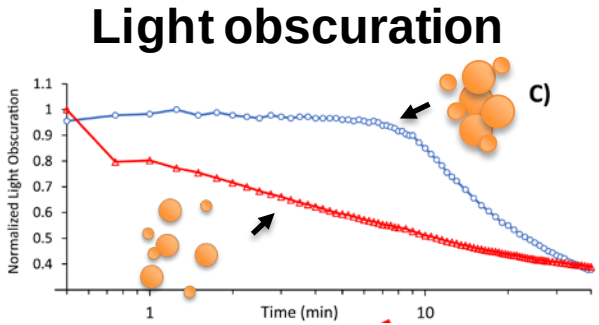
Dissolution of Flocculated vs. Deflocculated Particles

- The in vitro release testing (IVRT) method is discriminatory to TA particles introduced by low shear and high shear methods

- Flocculated and deflocculated particles display different tends of particle size and particle concentration during dissolution







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Summary of GDUFA research

- Triamcinolone acetonide injectable suspensions contain primary particles and secondary flocculates.
- Conversion between flocculated and deflocculated particles was rapid, reversible and shear dependent. Changing shear rate during laser diffraction measurement may result in variability in particle size distribution.
- A non-sink, discriminative IVRT method was developed to simultaneously monitor dissolution and change of particle size distribution.
- Shear during administration or sample introduction significantly impacted the dissolution rate of products.

Summary

- A BE approach needs to be accurate, sensitive, and reproducible.
- The prolonged duration and indication of the LAI suspensions present a higher risk of clinical failure compared to injectable suspensions for short term use.
- To develop an in vitro alternative approach for LAI suspensions, sufficient understanding on critical formulation characteristics and their impact on product in vivo performance needs to be obtained.
- GDUFA research developed tools and methods to bridge in vitro and in vivo gaps have improved the understanding on how flocculation properties of injectable suspension impact product characterization, dissolution profiles, and potential pharmacokinetic properties.

Challenge Question #1

Which of the following bioequivalence approach is currently recommended in the PSG on long-acting systemic injectable suspension that has potential safety concerns?

A. Biowaiver

B. In vitro approach

C. In vivo PK study

D. B & C

Challenge Question #2

Which of the following pathway can be used to get OGD's comment(s) on an alternative BE approach?

A. Controlled correspondence

B. Pre-ANDA product development meeting.

C. A & B.

D. Pre-IND meeting

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Questions?

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