Session III:
Novel In Vitro Release Testing for Complex Formulations

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Outline

- Current thinking of IVRT for complex products
  - The role that IVRT plays in supporting BE determination
  - Expectations in the development of an IVRT method
  - Current challenges in IVRT development
  - New technologies and IVRT methods
  - The role of GDUFA funded IVRT research

Role of IVRT

- In general, IVRT for bioequivalence (BE) determination is one component of a totality of evidence approach.
  - IVRT can be recommended as part of in vitro testing to demonstrate sameness between two products with highly similar formulations.
  - IVRT can be recommended in conjunction with in vivo tests to demonstrate sameness between formulations with known differences.
- Once validated, IVRT can also be used as a specification to control product quality and/or acceptability of post-approval manufacturing changes.

IVRT for assessing complex formulations

- Confirmation that a proposed generic product has a comparable release rate to that of the RLD can help ensure that the proposed generic product will deliver drug in a manner comparable to that of the RLD.
  - IVRT is not intended to mimic the in vivo administration environment or predict the therapeutic effect of the drug.
  - An in vivo in vitro correlation (IVIVC) does not need to be established to justify an IVRT method or assessment

IVRT for assessing complex formulations

- Assessing an IVRT profile is intended to enable a sensitive determination of any potential formulation and/or manufacture differences.
  - An IVRT method can be adjusted to provide a sensitive evaluation of two highly similar formulations compared to in vivo and/or IVIVC testing.
  - GDUFA research has focused on methods to optimize IVRT sensitivity for formulation assessment:
    - Prof. Sailor: *"In vitro drug release testing of ophthalmic suspensions"* Grant: 1U01FD005173-01
    - Dr. Bellantone: "Pulsatile microdialysis of suspension and emulsion products" Contract: HHSF223201610105C

IVRT: Product properties

- An in vitro release rate reflects the combined effect of several physical and chemical properties in both the drug substance and the drug product.
  - Polymorphic form, aggregate/co-aggregate structure, local environment
  - Excipient grade and/or source

- Manufacturing methods and processes may change formulation attributes, thereby affecting the rate of drug release and the drug's bioavailability.
  - Location and/or structural arrangement of formulation components
  - Particle size, viscosity, non-equilibrated higher energy states

IVRT expectations

- An IVRT method should be capable of discriminating the effect of process variability in the production of the test formulation.

- IVRT should be conducted with drug products manufactured under target conditions and compared to drug products that are intentionally manufactured with meaningful variations in formulation and manufacturing parameters:
  - particle size, drug loading, types and/or amounts of excipients.

Assessing manufacture differences

- A design of experiments approach can be taken to assess critical process variables and their corresponding affect on the critical quality attributes (physicochemical properties) of the drug product.
  - Demonstrating which product properties are impacted by the manufacture process helps direct IVRT method development.
  - GDUFA research has focused on better understanding of variability of complex drugs due to differences in manufacturing:
    - Dr. Nivorozhkin *"Liposomal Formulations of Amphotericin B"* Contract: HHSF223201610093C

IVRT expectations

- Ideally, the dissolution/in vitro release method should be able to discriminate batches that are not bioequivalent.

- Drug release profiles should be complete; reach a plateau* and achieve at least 85 percent release. If not complete, additional information to explain the reasons for incomplete release should be provided.

* no significant increase over three consecutive time points

IVRT challenges for complex dosage forms

- Complex dosage forms present a number of IVRT development challenge as:
  - Compedial dissolution/IVRT methods (e.g. USP I and II) may not easily distinguish between released drug and drug still in the formulation.
  - Low solubility of the drug in the release media compared to formulation gives rise to exceptionally slow / incomplete drug release
  - IVRT components can be rate limiting step, reducing sensitivity
- These challenges do not preclude the development or review of a proposed IVRT method

Role of GDUFA research

- GDUFA funded research ensures the Agency is abreast of :
  - the latest IVRT technologies and methods
  - Potential challenges associated with developing a particular IVRT method and/or with a particular type of formulation.
  - GDUFA research also aid industry's IVRT development programs, but it does not constrain them to the GDUFA researched IVRT methods.
    - Ultimately, it is the responsibility of the drug sponsor to develop, justify and validate their IVRT method.

Advancing IVRT

- Since 2012, 24 GDUFA funded research projects have focused on developing and evaluating new IVRT methods for complex products.
  - Seven on ophthalmic dosage forms: topical suspensions, emulsion and ointments as well as inserts.
  - Five on parenteral microsphere products
  - Three on liposomal products
  - Three on periodontal inserts
  - Three on topical dosage forms: ointments, creams, and gels
  - Two on orally inhaled drug products
  - One on long-acting intrauterine device

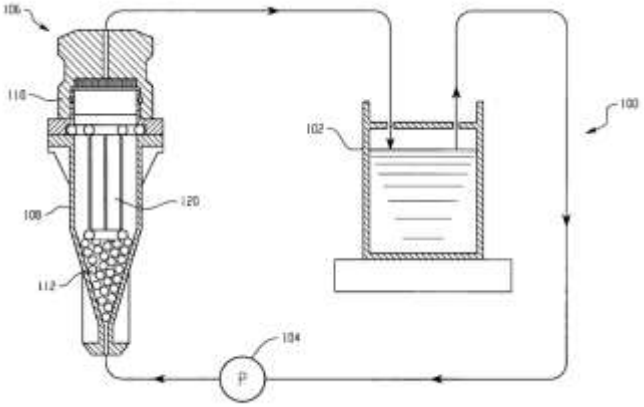
- This research has helped FDA identify promising technologies, current challenges and limitations in IVRT development, and better understand the critical quality attributes of complex products and regulatory review.
- These findings are publically disseminated through workshops, presentations, and academic publications.

Developing IVRT methods

Example of the Range of dialysis based IVRT methodologies

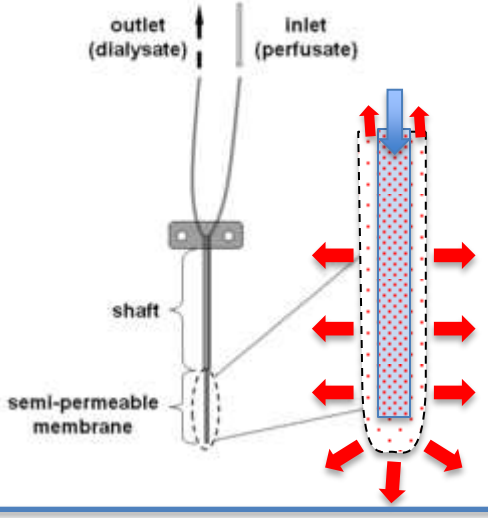
Large volume 'float-alyzer' dialysis

Membranes for modified USP

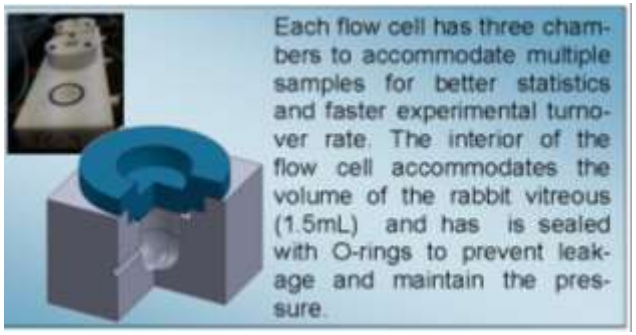


Dialysis (USP IV adapter) US 8318506 B2

Low volume microdialysis and pulsatile micodialysis

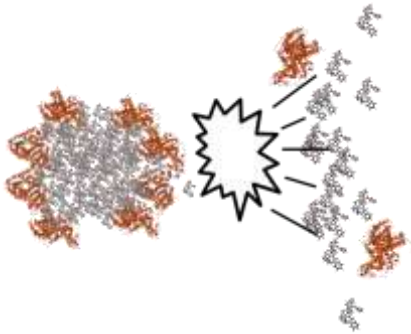


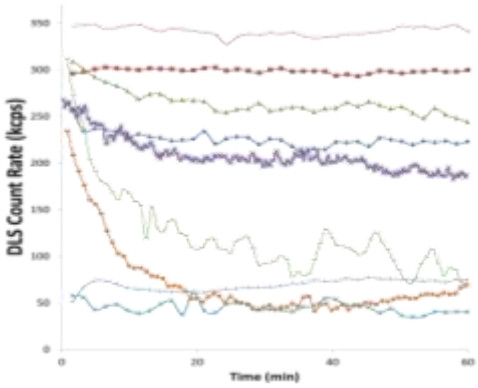
Custom built IVRT devices



Dr. Sailor Grant# 1U01FD005173

Novel indirect measurements





Session III Speakers

1:30 – 2:00 pm ***"In vitro drug release testing of ophthalmic suspensions"***
Michael J. Sailor, PhD
University of California, San Diego

2:00 – 2:30 pm ***"Pulsatile microdialysis of suspension and emulsion products"***
Robert Bellantone, PhD
Physical Pharmaceutica, LLC.

2:30 – 3:00 pm ***"Liposomal Formulations of Amphotericin B"***
Alex Nivorozhkin, PhD
Neo-Advent Technologies, LLC.