

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.

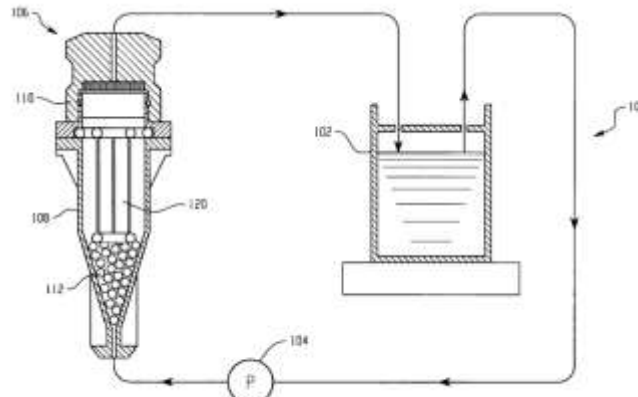
Developing IVRT methods

Example of the Range of dialysis based IVRT methodologies

Large volume
'float-analyzer' dialysis

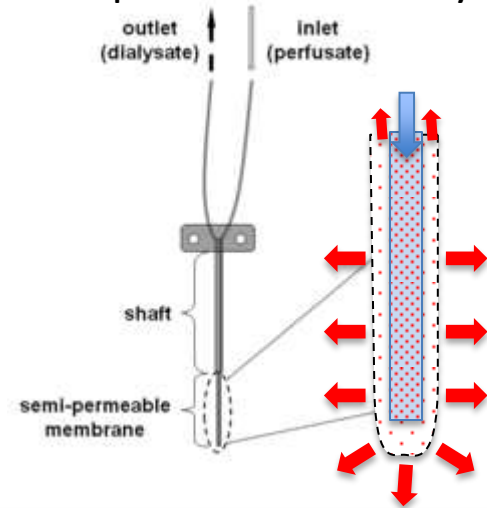


Membranes for modified USP



Dialysis (USP IV adapter) US 8318506 B2

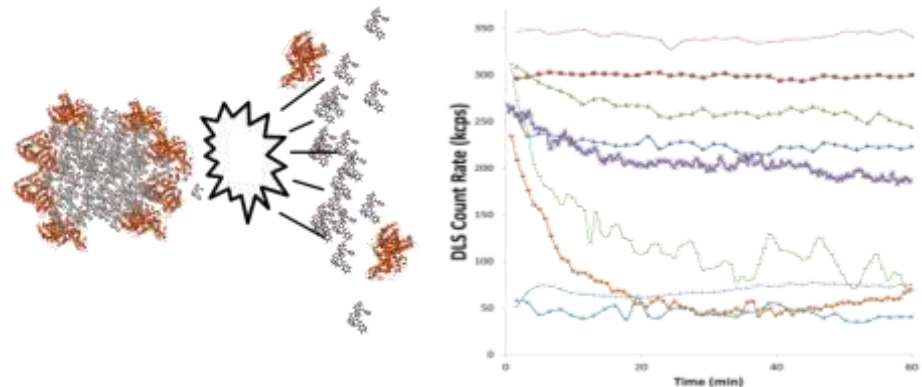
Low volume microdialysis
and pulsatile microdialysis



Custom built IVRT devices

Each flow cell has three chambers to accommodate multiple samples for better statistics and faster experimental turnover rate. The interior of the flow cell accommodates the volume of the rabbit vitreous (1.5mL) and has is sealed with O-rings to prevent leakage and maintain the pressure.

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.