In Vitro Drug Release Testing for Complex Generics: A Bioequivalence Perspective

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 1: Method Development/Validation for Non-traditional Analytical Methods

Topic 3: Development and Validation Considerations for Drug Release and Permeation Testing of Complex Dosage Forms

Yan Wang, PhD

Pharmacologist, Acting Team Lead

Division of Therapeutic Performance, Office of Research and Standards

Office of Generic Drugs | CDER | U.S. FDA

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Disclaimer

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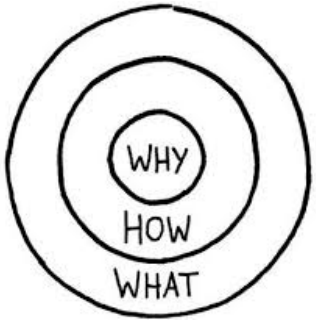
Learning objectives

- **WHY**
  - Recognize the role of in vitro release testing (IVRT)
- **HOW**
  - Employ IVRT method development and validation
- **WHAT**
  - Manage current challenges for IVRT of complex drugs
  - Describe key considerations
  - Recognize IVRT expectations



Why: purpose of an IVRT

- Product development (formulation screening)
- Quality control (batch-to-batch consistency)
- In lieu of in vivo test (in vitro in vivo correlation (IVIVC), Post-approval changes)
- Bioequivalence (BE) (sameness in drug release)

Why: role of IVRT for bioequivalence

- A performance test evaluating sameness in the rate and extent of drug release between test and reference products
- One component of a totality of evidence approach
  - Part of an in vitro approach
    - Detect variations in formulation (Q1/Q2 sameness, ± 5%)
    - Detect variations in physicochemical characteristics (Q3)
  - In conjunction with in vivo BE studies
    - Detect differences that may not be captured by in vivo BE studies

Example recommendations: in vitro approach

- Ointments
  - Ophthalmic
  - Topical
- Emulsions
  - Ophthalmic
  - Parenteral
- Suspensions
  - Ophthalmic
  - Injectable

Active Ingredient: Difluprednate

Dosage Form; Route: Emulsion; ophthalmic

Strength: 0.05%

Recommended Study: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product, the following criteria should be met.

i. The test and Reference Listed Drug (RLD) formulations are qualitatively[1] and quantitatively[2] the same (Q1/Q2)

ii. Acceptable comparative physicochemical characterization of the test and RLD formulations. The comparative study should be performed on at least three exhibit lots of both test and reference products.[3]

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality, and surface tension. Sponsors should also submit information on the drug distribution in different phases within the formulation.

Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) based on D_{50} and SPAN (alternatively harmonic intensity-weighted average particle diameter and polydispersity index derived from cumulant analysis of the intensity size distribution) for the globule size distribution only (the other parameters do not require PBE analysis). The applicants should provide no less than 10 datasets from 3 batches each of the Test and Reference products to be used in the PBE analysis. Sponsors should compare the size parameter upon serial dilution (if applicable) of the Test and Reference products, and provide histograms of size distribution data of each diluted sample.

iii. Acceptable comparative in vitro drug release rate tests of difluprednate from the test and Reference formulations. The methodology used for in vitro drug release testing

Example recommendations: in vitro in vivo combination

- Example product: **Risperdal® Consta®** (Risperidone PLGA microspheres)
  - Indicated for schizophrenia, bipolar I disorder
  - Every **2 weeks** via IM
  - Multi-phasic in vitro and in vivo release profiles

Active Ingredient:		Risperidone
Dosage Form; Route:		Injectable; intramuscular
Recommended Studies:		Two studies: in vitro and in vivo
1.	Type of study:	In vitro drug release
	Strength:	25 mg/vial
	Medium:	Dissolution medium (pH 7.4) prepared as indicated below
	Volume:	400 mL (200 mL for each temperature)
	Apparatus:	Cylinder bottle
	Temperature:	37 °C and 45 °C (water bath)
	Sampling Times:	Day 1 and Day 21 for 37 °C Multiple time points from Days 0 to 8 for 45 °C. Two sampling time points, that bracket $T_{50\%}$ (which is defined as the time of 50% drug release), are to be linearly interpolated to determine $T_{50\%}$.

2. Type of study: In vivo, two-period, crossover steady-state
Strength: 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial
Subjects: Male and nonpregnant female patients with schizophrenia or bipolar I disorder who are already receiving a stable regimen of risperidone long-acting injection via the intramuscular route. Patients who are receiving any dosage regimen of risperidone long-acting injection every two weeks would be eligible to participate in the study by continuing their established maintenance dose.
Additional comments: FDA recommends that studies not be conducted using healthy subjects or patients on a different antipsychotic treatment. All strengths of the test product need to be from the same bulk in order for all strengths of the Test to be administered in the PK BE study.

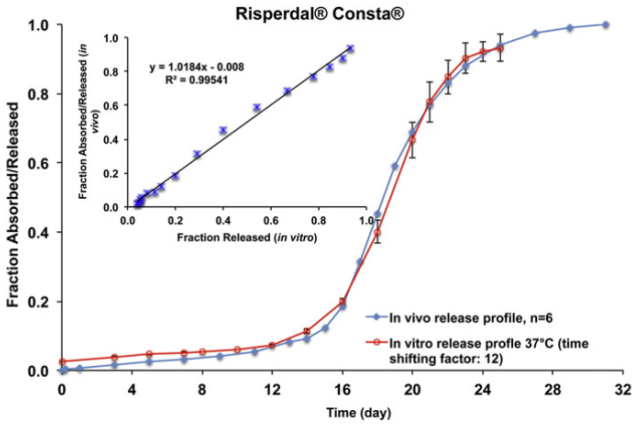


Fig. 6. *In vivo* absorption/release and *in vitro* release (time shifting factor: 12) profiles in 10 mM PBS (pH 7.4) at 37 °C of Risperdal® Consta®. Inserted figure shows linear correlation between fractions released *in vitro* (37 °C) and fraction absorbed/released *in vivo*.

In vitro release testing is included to assess equivalence of the initial release phase and the lag phase.

www.fda.gov

Shen J, et al. In vitro-in vivo correlation of parenteral risperidone polymeric microspheres. 2015 Journal of Controlled Release

How: method development and validation

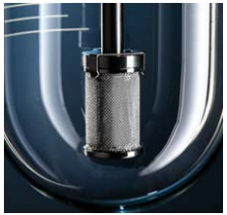
1. What are available IVRT methods?

2. What are the parameters to consider for method development?

3. How should the IVRT method be validated?

In vitro release test (IVRT) methods

USP Apparatus 1

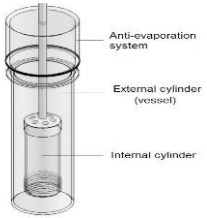


Basket

USP Apparatus 2

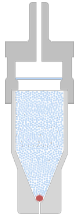
Paddle

USP Apparatus 3



Reciprocating Cylinder

USP Apparatus 4



Flow-through Cell

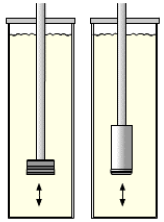
USP Apparatus 5

Paddle over Disk

USP Apparatus 6

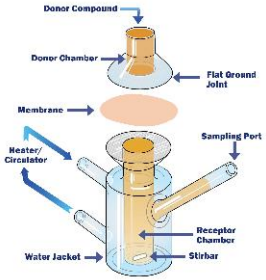
Rotating Cylinder

USP Apparatus 7

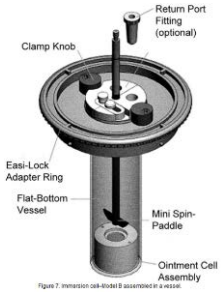


Reciprocating Holder

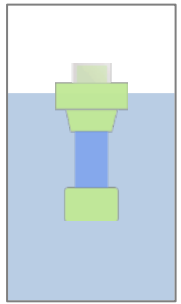
Vertical Diffusion Cell



USP 2 Immersion Cell



Dialysis



Bottle-shaking

Sample-and-separate

Others

- Pulsatile Microdialysis (PMD)
- Miniatured flow-through cell
- MicroDiss^{TM}
- MicroFLUX^{TM}
- Scissor^{TM} (sub-cutaneous)

How to develop an IVRT method

1. Physical form, e.g., tablets, capsules, powder, semisolids (ointment and cream), transdermal patches

2. Need to separate the released drug, e.g., liposomes, emulsions, protein-drug complexes, suspensions

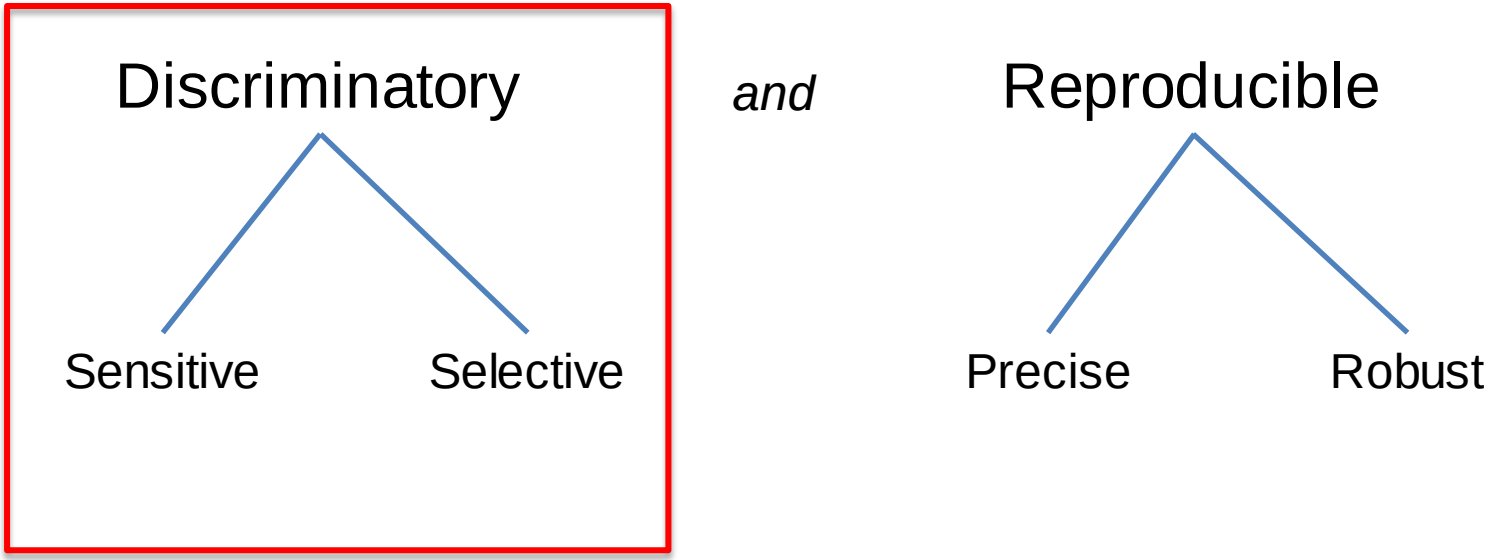
3. Other constraints, e.g., time (rapid- or slow- release), volume, multi-phasic, degradation, adsorption, bio-/physiologically relevant

Common experimental parameters

- Media composition (components, pH)
- Media volume (sink condition vs non sink condition)
- Temperature
- Membrane selection (inertness, non-specific binding)
- Dose amount
- Stirring rate
- Sampling volume
- Sampling schedule

Key:
Sufficient justification should be included in the development report

IVRT method validation

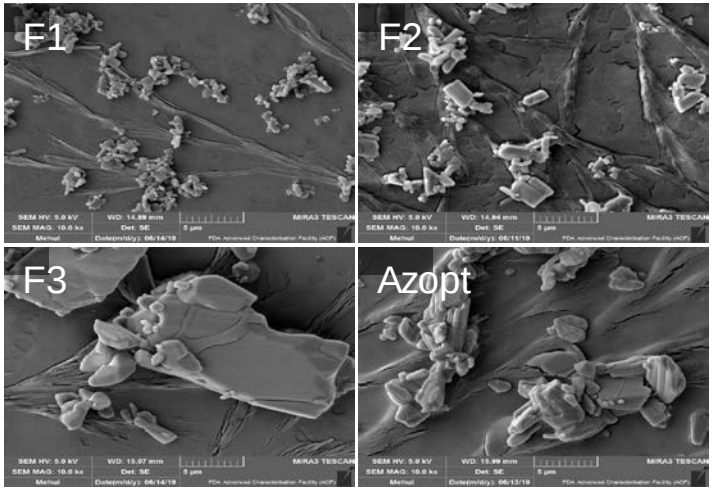


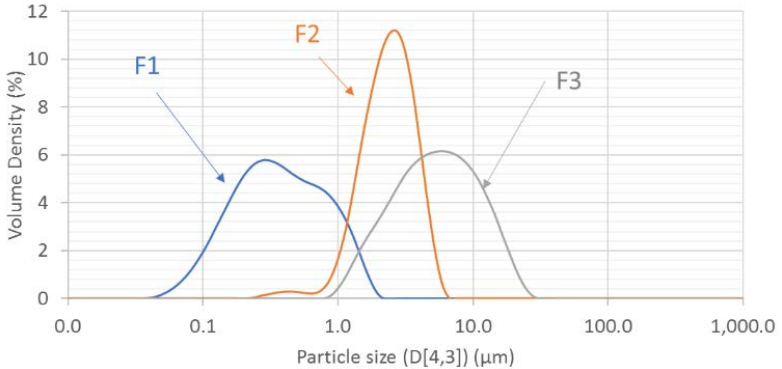
IVRT validation: product properties

- The combined effect of several physicochemical properties in both the drug substance and the drug product
  - Polymorphic form, aggregation/co-aggregation structure
  - Excipient grade and/or source
- Formulation attributes affected by manufacturing methods and processes
  - Location and/or structural arrangement of formulation components
  - Particle size, viscosity

Case 1: suspensions

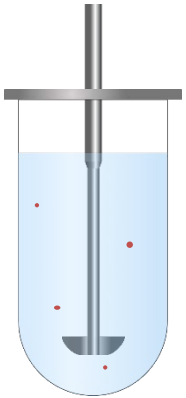
- Critical quality attributes for drug release:
  - Particle size distribution (PSD)
  - Viscosity
- Expected to have different dissolution rates
- Prepared in-house with varying PSDs (relative to the reference listed drug (RLD))
- Validation of IVRT to be discriminatory in terms of PSD

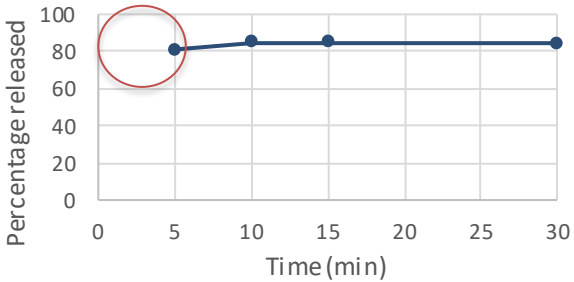




How to improve discrimination?

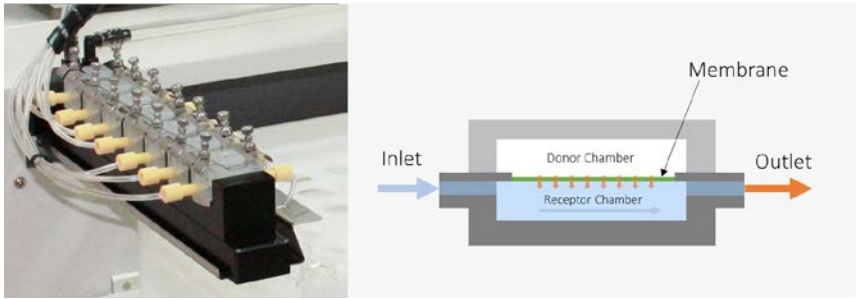
Option 1: USP 2 (900 mL)

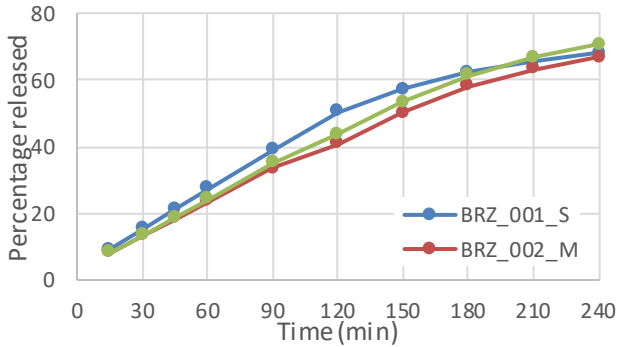




Release too fast, all formulation dissolves nearly identically

Option 2: VDC (0.45 um membrane)

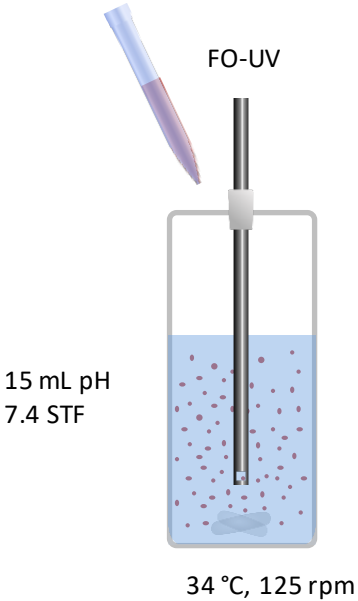




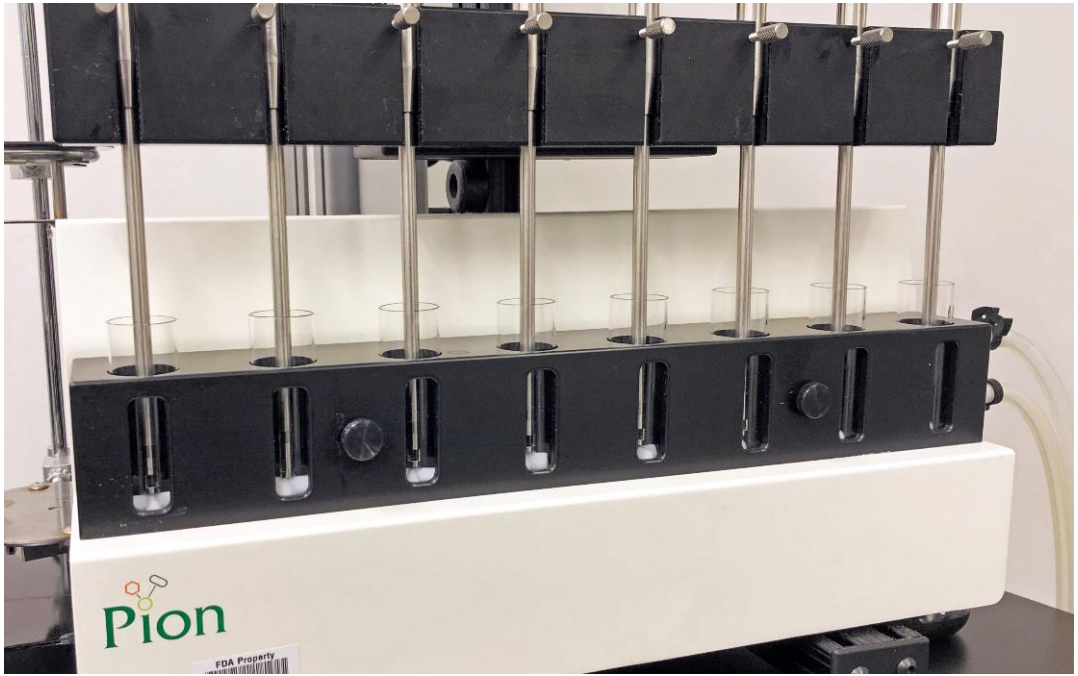
Release slowed down (by membrane), but no discrimination either

Slide courtesy of Xiaoming Xu

How to improve discrimination? (cont.)



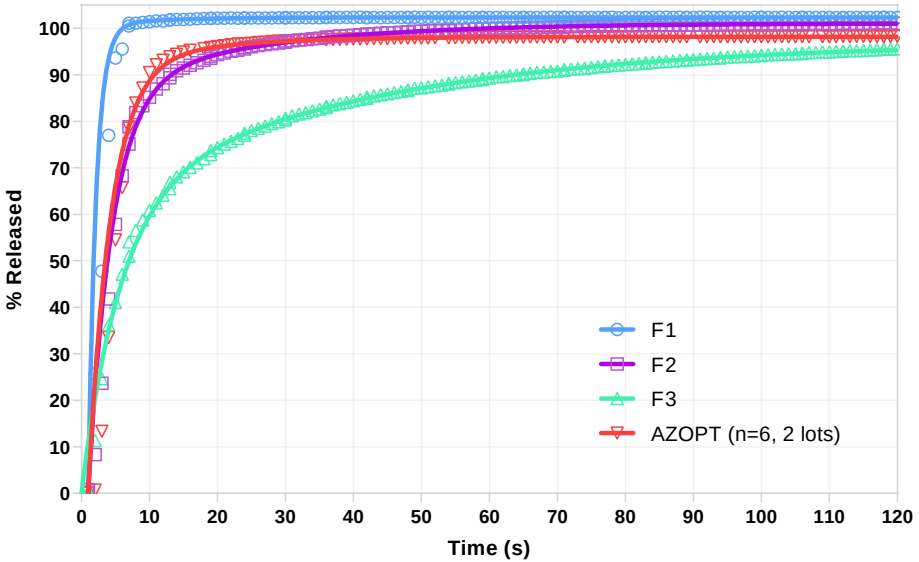
❶ non-sink condition (just like in the eye)

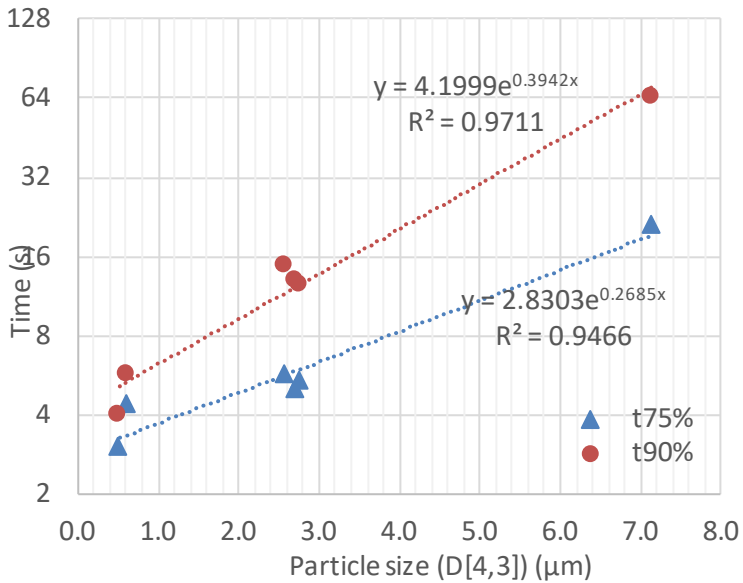


❷ Continuous monitoring

A. Vo, et al. In Vitro Physicochemical Characterization and Dissolution of Brinzolamide Ophthalmic Suspensions with Similar Composition. International Journal of Pharmaceutics, Submitted

Discriminatory IVRT for suspensions

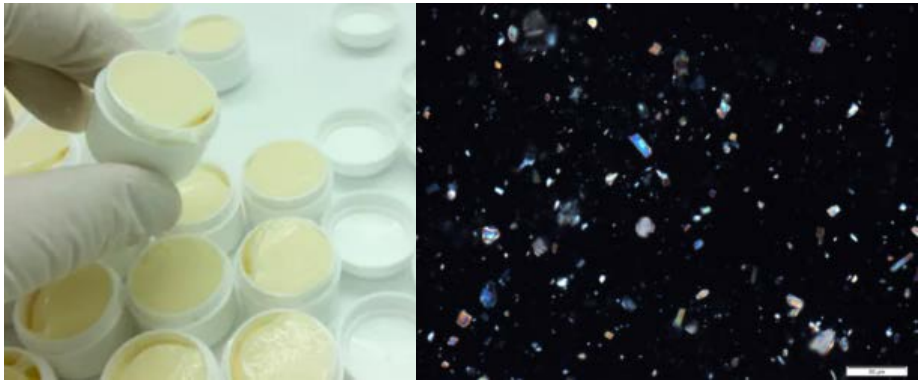




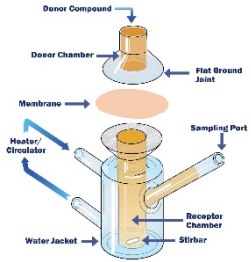
- Nanosuspensions complete dissolution within 6 seconds
- Micron suspensions dissolves in 2 min
- Good correlation (r^2>0.9) between dissolution rate and PSD

A. Vo, et al. In Vitro Physicochemical Characterization and Dissolution of Brinzolamide Ophthalmic Suspensions with Similar Composition. International Journal of Pharmaceutics, Submitted

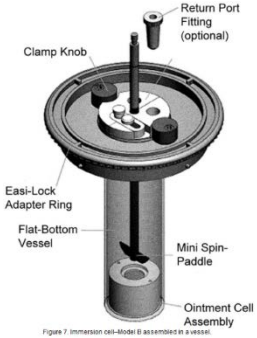
Case 2: ointments



Vertical diffusion cell (VDC) A,B,C

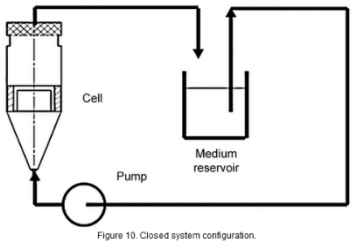


Immersion cell



- Oleaginous base (i.e., only petrolatum)
- Active ingredient remains as solid particles (not soluble in petrolatum)
- Three setups recommended by USP (for semisolids)
- Drug release is determined as "the amount of drug released (e.g., µg) per area (cm^2)", not as percentage
- Recommend to fit Higuchi release, and using T/R ratio to compare reference and test product (8^{th} and 29^{th} percentile)

USP 4 with semisolid cell



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IVRT method validation for ointments

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Research paper

A comprehensive approach to qualify and validate the essential parameters of an in vitro release test (IVRT) method for acyclovir cream, 5%

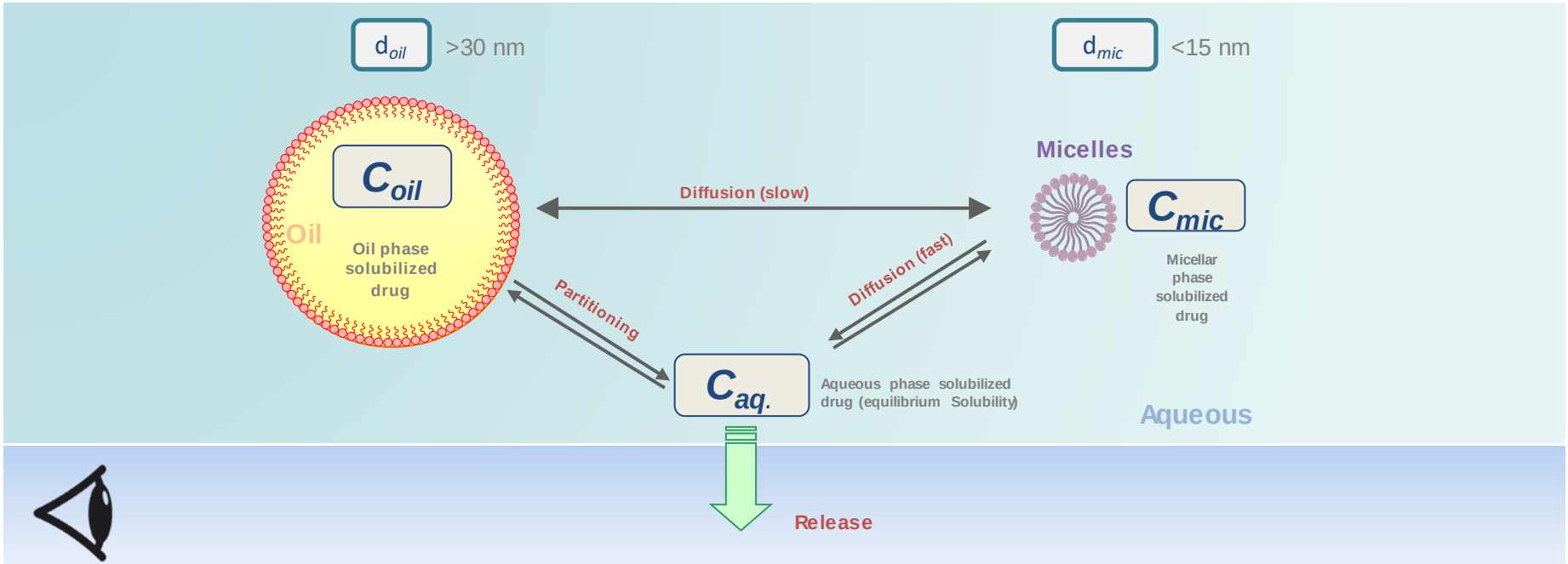
Katrin I. Tiffner[a], Isadore Kanfer[b,c,*], Thomas Augustin[a], Reingard Raml[a], Sam G. Raney[d], Frank Sinner[a]

[a] Joanneum Research Forschungsgesellschaft mbH, Health – Institute for Biomedicine and Health Sciences, Neue Stiftingtalstr. 2, 8010 Graz, Austria
[b] Rhodes University, Faculty of Pharmacy, Artillery Road, Grahamstown 6140, South Africa
[c] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada
[d] Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, U.S. FDA, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

Common issues

- Membrane inertness
- Receptor medium solubility
- Sensitivity (altered drug concentrations)
- Robustness

Case 3: emulsions



- Multi-phasic (components) and likely multi-phasic release
- Dynamic exchange

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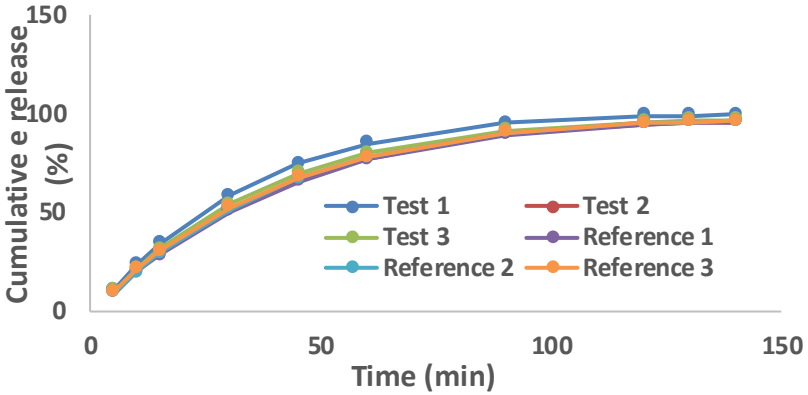
IVRT for emulsions: method development

Things to consider

- Formulation composition (i.e., the amount of oil and surfactant)
- Particle size/size distribution
- Need for separation (<10 nm vs. >100 nm)
- Mass balance: the amount of drug released vs. the amount of oil diffused through the membrane

Pivotal IVRT study for ophthalmic emulsions



Proposed test product compared with reference standard to support BE.

- **3 lots of test and reference products (12 replicates).**

Common issues

- Detailed report/data for IVRT method validation is often incomplete.
  - Robustness: temperature, RPM, flow rate, pH if solubility is pH dependent.
  - Justification for experimental conditions: pH of dissolution medium, membrane integrity, etc.
  - Data supporting the method measures API release from the formulation rather than the transfer of oil droplets across the membrane.
- Plot of the amount of drug release per unit area ($\mu g/cm^2$) against the square root of time instead of cumulative release (%) versus time.

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IVRT challenges for complex drugs

- Compendial IVRT methods (e.g., USP I and II) may not be readily applicable to complex dosage forms (i.e., emulsions, ointments, and suspensions).
- Low solubility of the drug in the release media compared to formulation gives rise to exceptionally slow/incomplete drug release.
- IVRT components (i.e., membrane) can be rate limiting step, reducing sensitivity, which need to be properly evaluated.

Key considerations

- Is it acceptable to develop an IVRT method based on a non-sink condition?
  - ➢ Yes, as long as the method is properly validated.
- Which formulations should be used for IVRT validation (test versus reference products)?
  - ➢ In-house developed formulations with meaningful variations in formulation and manufacturing parameters. Key characteristics of the target test product and the reference product are used for selecting meaningful variables.

Key considerations (Cont.)

- Is it necessary to investigate all critical quality attributes (CQAs)?
  - ➢ It is recognized that it may not be possible to develop an IVRT that can discriminate all CQAs. All CQAs should be considered and justifications should be provided to support inclusion/exclusion of CQAs. When a CQA cannot be evaluated by IVRT, a characterization testing should be developed.

IVRT expectations

- 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) is desired, but is not required.
- The IVRT should be able to discriminate batches that are not bioequivalent.
- Drug release profiles should be complete; reach a plateau (no significant increase over three consecutive time points) or achieve at least 85 percent release. If not complete, additional information to explain the reasons for incomplete release should be provided.
- Analytical method should follow the ICH or FDA bioanalytical guidance.

Take home

- Selection of an IVRT method depends on the physical form of the product.
- Complexity in IVRT generally is due to need for separation and other constraints.
- To design a good IVRT method, it starts with understanding the impact of formulation and manufacturing process parameters on drug release.
- Formulations with intentional and meaningful variations are good testing samples to verify that the IVRT method is “discriminatory” and “reproducible”.
- Understanding the mechanism of release and factors controlling release can guide the development/improvement of the IVRT method.

Acknowledgement

- Office of Generic Drugs
  - Office of Research and Standards
    - Team of complex substance and complex products
    - Darby Kozak
    - Markham Luke
    - Lei Zhang
    - Robert Lionberger
  - Office of Bioequivalence
    - Josephine E. Aimiuwu

- Office of Pharmaceutical Quality
  - Office of Testing and Research
    - Xiaoming Xu
    - An Vo

Questions?

Challenge Question #1

Which of the following statements is/are true:

A. IVIVC is required to justify the use of IVRT for supporting bioequivalence.

B. All critical quality attributes should be considered when validating an IVRT method.

C. IVRT should be able to discriminate batches that are not bioequivalent.

D. IVRT should be validated against the reference product.

Challenge Question #1

Which of the following statements are true:

A. IVIVC is required to justify the use of IVRT for supporting bioequivalence.

B. All critical quality attributes should be considered when validating an IVRT method.

C. IVRT should be able to discriminate batches that are not bioequivalent.

D. IVRT should be validated against the reference product.

Challenge Question #2

It is acceptable to develop an IVRT method based on a non-sink condition as long as the method is properly validated.

A. True

B. False

Challenge Question #2

It is acceptable to develop an IVRT method based on a non-sink condition as long as the method is properly validated.

A. True

B. False


Thank you


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