U.S. FOOD & DRUG ADMINISTRATION

Considerations and Expectations for In Vitro Release Testing of Complex Formulations

Complex Generic Drug Product Development Workshop

Session 3: Complex Formulations/Dosage Forms

September 12, 2018

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Outline

- The role of in vitro release testing (IVRT) for complex generics
- Expectations in IVRT method development and validation
- Take home messages

Role of IVRT

In general,

- Dissolution and drug release tests are in vitro tests that measure the rate and extent of dissolution or release of the drug substance from a drug product under a specific condition
- IVRT can be a sensitive and discriminating method that is responsive to physicochemical changes in drug products
  - Polymorphic form, aggregate/co-aggregate structure, local environment
  - Excipient grade and/or source
- IVRT is an important quality control tool used for monitoring drug product stability and manufacturing process
  - Location and/or structural arrangement of formulation components
  - Particle size, viscosity, non-equilibrated higher energy states

IVRT for Complex Generic Drugs

- IVRT serves as a valuable tool for demonstrating comparative in vitro drug release rates/profiles between the test and reference products

- IVRT for bioequivalence (BE) determination is one component of a totality of evidence approach and is not expected to correlate with or be predictive of in vivo bioavailability

IVRT for BE Determination (Example 1)

- IVRT can be recommended as part of in vitro testing only approach to demonstrate BE

Active Ingredient: Dexamethasone; Tobramycin

Dosage Form; Route: Suspension; ophthalmic

Recommended Study: Two options

I. Option One: In vitro studies

To qualify for the in vitro option for this drug product (dexamethasone; tobramycin 0.05%; 0.3%), all of 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 characterizations of the test and RLD formulations. The characterization study should be performed on at least three exhibit batches of both the test and RLD products[3] and should include:

iii. Acceptable comparative in vitro drug release rate tests of cyclosporine from the test and RLD formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

IVRT for BE Determination (Example 2)

- IVRT can be recommended in conjunction with in vivo tests to demonstrate BE

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 $T_{50\%}$.

Parameters to measure: Cumulative drug release at Days 1 and 21 at 37 °C, cumulative drug release at Day 8 at 45 °C, and $T_{50\%}$ at 45 °C.

Bioequivalence based on (90% CI): $T_{50\%}$. The 90% confidence interval of the test/reference ratio of $T_{50\%}$ should be within 80-125%.

These data are to be submitted in addition to the method specified in the Dissolution Methods Database (see below), which is to be used for stability and quality control testing.

IVRT Expectations

What should be submitted for evaluation?

- ✓ IVRT method development report
- ✓ IVRT method validation report
- ✓ IVRT pivotal study report

IVRT Method Development

Method parameters:

- Product dose amount
- Agitation/stirring rate
- Sampling time points
- IVRT apparatus
- Dissolution media composition, volume, pH, temperature
- Drug solubility in the release media
- Membrane inertness (if applicable)

IVRT Method Validation

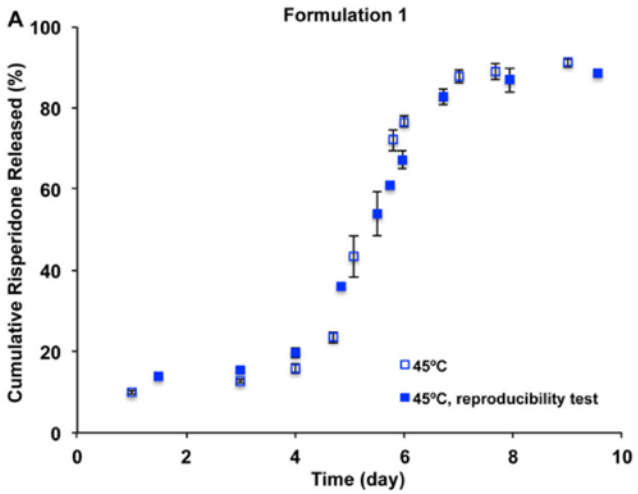
Validation components:

- Linearity and Range
- Accuracy/Precision and Reproducibility
- Sensitivity and Specificity
- Selectivity
- Robustness
- Solution Solubility/Stability

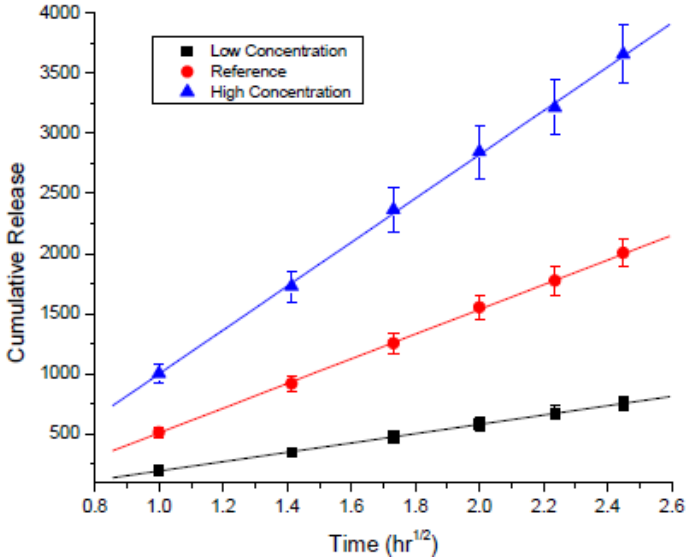
IVRT Method Validation

Validation components:

Reproducibility



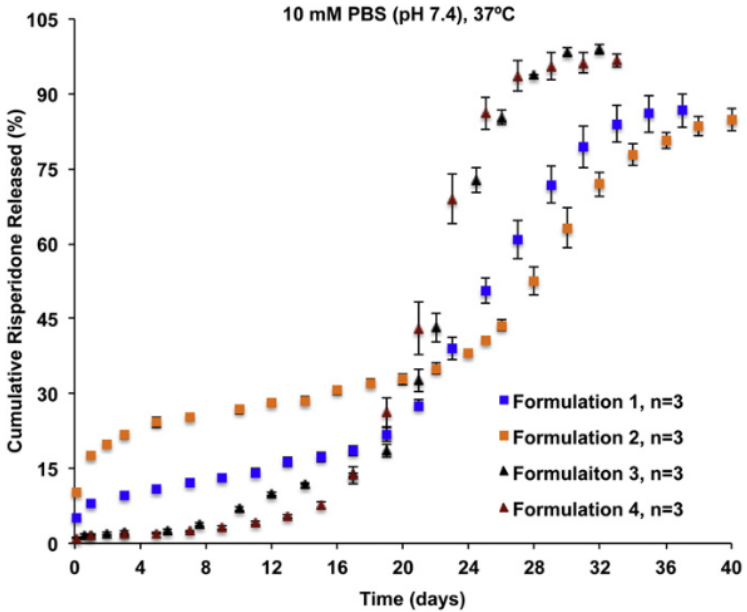
Sensitivity



IVRT Method Validation

Validation components:

Selectivity/ Discriminatory Ability



Ability to discriminate the effect of process variability in the production of the test formulation.

Take Home Messages

- The IVRT for BE determination should be able to discriminate batches that are not bioequivalent.
- 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.

Take Home Messages (cont.)

- 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

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