U.S. FOOD & DRUG ADMINISTRATION

Theoretical Principles and Best Practices In Vitro Release Testing (IVRT)

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

Day 2, Session 3: (Topical Products Pt.2)

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Disclaimer

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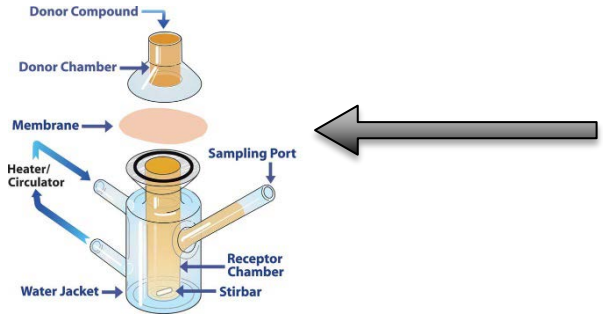
Learning Objectives

- Describe considerations for IVRT study design when used as a component of characterization-based bioequivalence (BE) approaches
- Describe considerations and the current thinking related to
  - IVRT method development
  - IVRT method validation

IVRT

- IVRT is a performance test to study the arrangement of matter.



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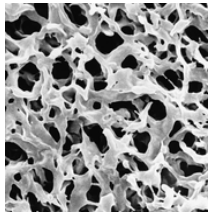

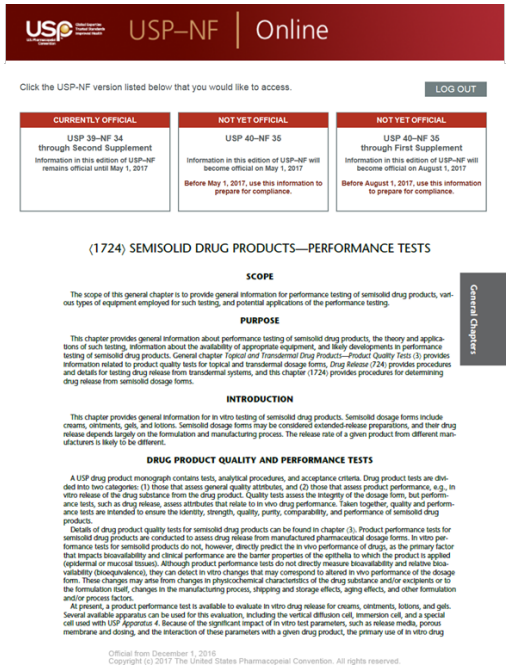
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⟨1724⟩ SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

General Chapters

SCOPE

The scope of this general chapter is to provide general information for performance testing of semisolid drug products, various types of equipment employed for such testing, and potential applications of the performance testing.

PURPOSE

This chapter provides general information about performance testing of semisolid drug products, the theory and applications of such testing, information about the availability of appropriate equipment, and likely developments in performance testing of semisolid drug products. General chapter *Topical and Transdermal Drug Products—Product Quality Tests* ⟨3⟩ provides information related to product quality tests for topical and transdermal dosage forms, *Drug Release* ⟨724⟩ provides procedures and details for testing drug release from transdermal systems, and this chapter ⟨1724⟩ provides procedures for determining drug release from semisolid dosage forms.

INTRODUCTION

This chapter provides general information for in vitro testing of semisolid drug products. Semisolid dosage forms include creams, ointments, gels, and lotions. Semisolid dosage forms may be considered extended-release preparations, and their drug release depends largely on the formulation and manufacturing process. The release rate of a given product from different manufacturers is likely to be different.

DRUG PRODUCT QUALITY AND PERFORMANCE TESTS

A USP drug product monograph contains tests, analytical procedures, and acceptance criteria. Drug product tests are divided into two categories: (1) those that assess general quality attributes, and (2) those that assess product performance, e.g., in vitro release of the drug substance from the drug product. Quality tests assess the integrity of the dosage form, but performance tests, such as drug release, assess attributes that relate to in vivo drug performance. Taken together, quality and performance tests are intended to ensure the identity, strength, quality, purity, comparability, and performance of semisolid drug products.

Details of drug product quality tests for semisolid drug products can be found in chapter ⟨3⟩. Product performance tests for semisolid drug products are conducted to assess drug release from manufactured pharmaceutical dosage forms. In vitro performance tests for semisolid products do not, however, directly predict the in vivo performance of drugs, as the primary factor that impacts bioavailability and clinical performance are the barrier properties of the epithelia to which the product is applied (epidermal or mucosal tissues). Although product performance tests do not directly measure bioavailability and relative bioavailability (bioequivalence), they can detect in vitro changes that may correspond to altered in vivo performance of the dosage form. These changes may arise from changes in physicochemical characteristics of the drug substance and/or excipients or to the formulation itself, changes in the manufacturing process, shipping and storage effects, aging effects, and other formulation and/or process factors.

At present, a product performance test is available to evaluate in vitro drug release for creams, ointments, lotions, and gels. Several available apparatus can be used for this evaluation, including the vertical diffusion cell, immersion cell, and a special cell used with USP *Apparatus 4*. Because of the significant impact of in vitro test parameters, such as release media, porous membrane and dosing, and the interaction of these parameters with a given drug product, the primary use of in vitro drug

Official from December 1, 2016

- Major IVRT Study Phases
  - IVRT method development
  - IVRT method validation
  - IVRT pivotal study

IVRT Method Development

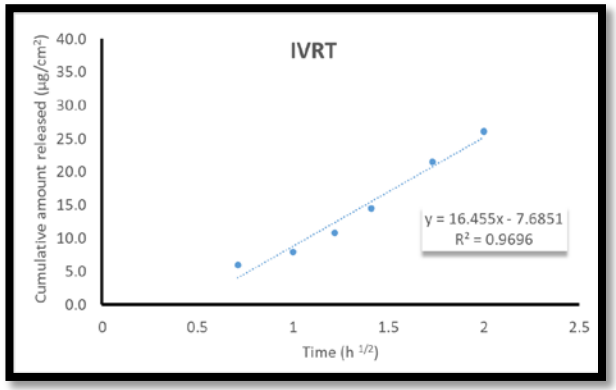
- Exploratory in nature
- May not be performed using a validated analytical method
- Sequence of selecting method parameters:
  - Apparatus
  - Receptor solution
  - Membrane

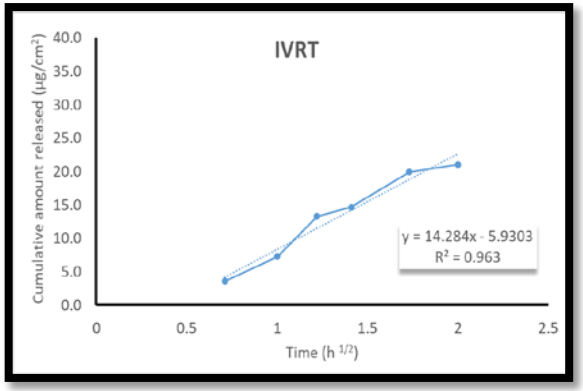
Qualification of the Receptor Solution

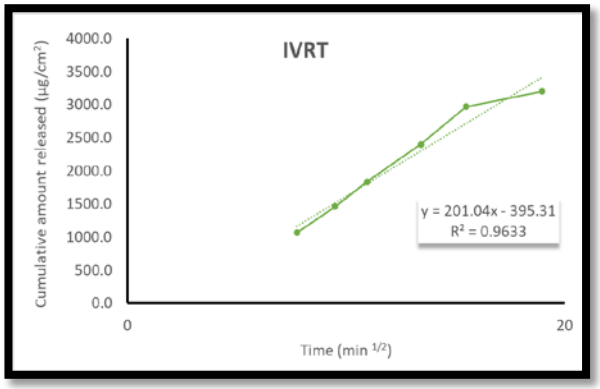
- Empirical solubility of the drug in the receptor solution
- Stability of the drug in the receptor solution
- Acceptable linearity and precision of the resulting drug release rate in an IVRT

Acceptable Linearity

- The linearity of the drug release across all time points should ideally have an r^2 value of ≥ 0.97.







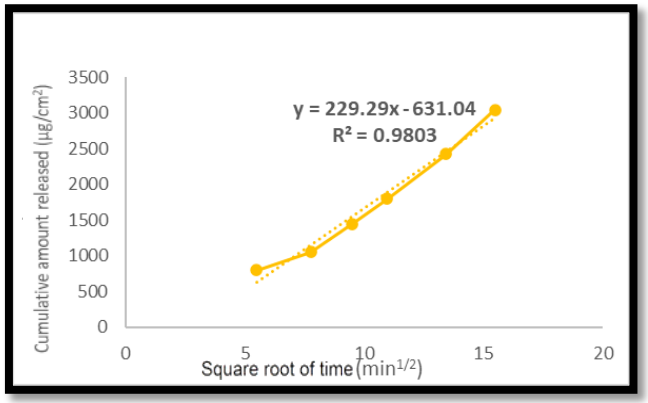
- For well-developed and suitably controlled IVRT methods, it is routinely observed that the r^2 value ≥ 0.99

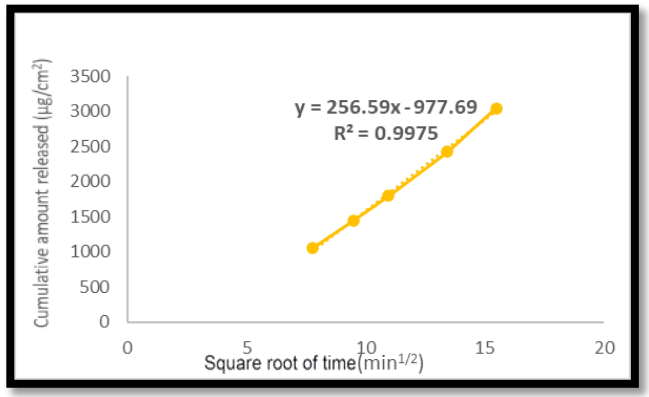
IVRT Membrane

- Pore size (~0.5µm ± 0.3µm is often suitable)
- Inertness to binding the drug
- Chemical compatibility
- Membrane equilibration prior to dosing
- Maintain the membrane temperature at 32°C ± 1°C

Receptor Solution Sampling

- Sampling duration (e.g., 4-6 hours)
- Sampling frequency and number of sampling timepoints





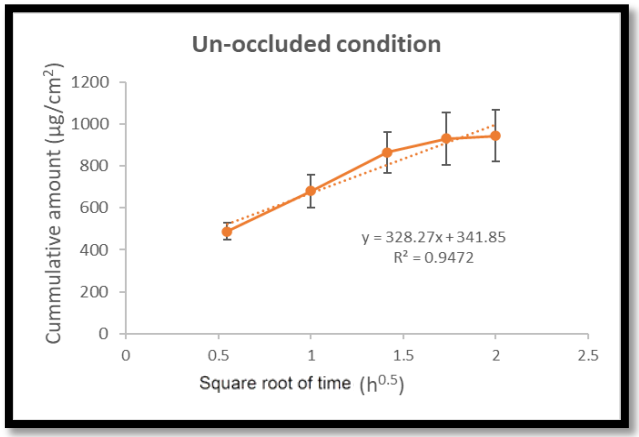
- Sampling procedure qualification

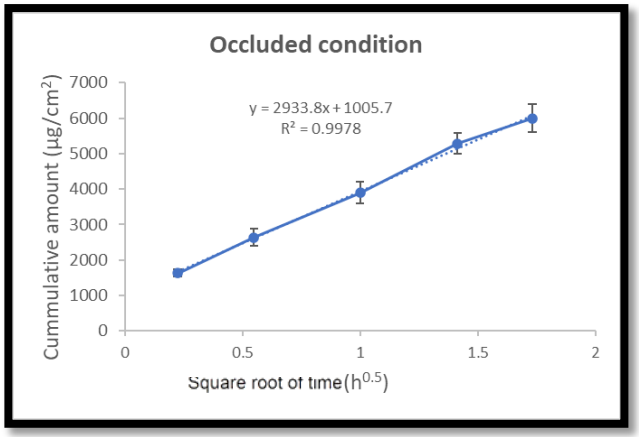
Dosing

- Dose amount (infinite dose)
- Dosing procedure for a selected apparatus
- Dose application method and its impact on product's microstructure

Occlusion

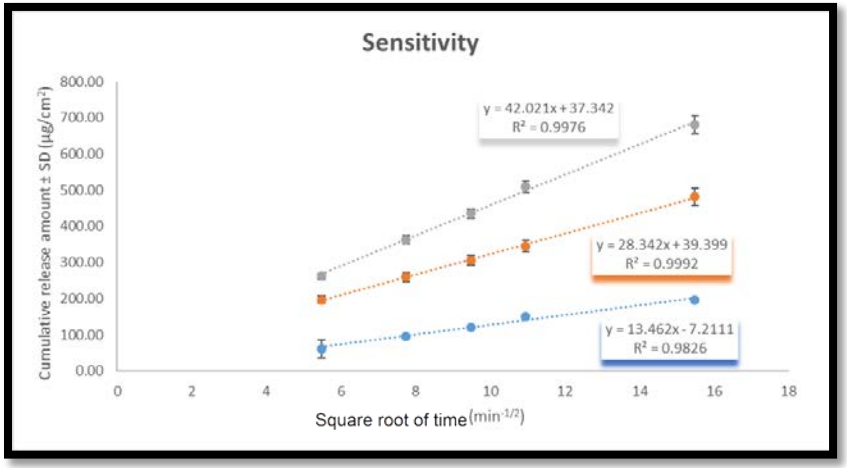
- The donor chamber should be occluded during the IVRT study.
- Per the Higuchi kinetics, a steady state drug release is not expected when the dose is un-occluded and undergoing metamorphosis.





IVRT Validation: Sensitivity

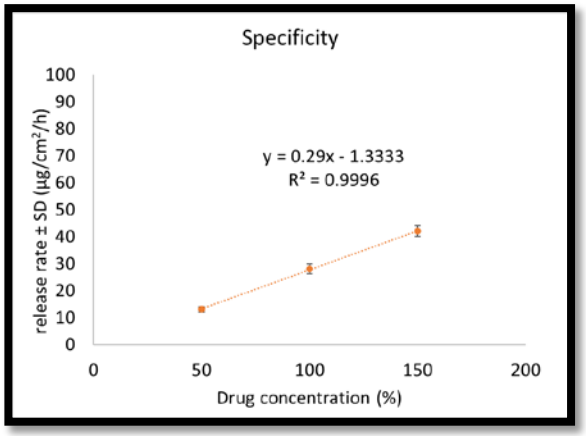
- Comparing the release rate from the test formulation with that from two comparable formulations:
  - a higher strength (150%)
  - a lower strength (50%)

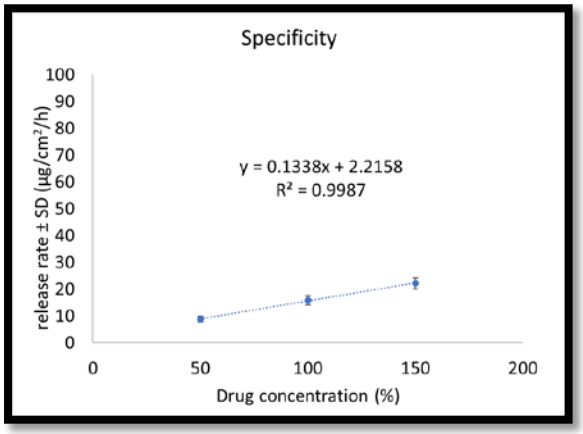


- Allowance may be made if a higher strength of test product is not feasible to formulate without substantial reformulation.

IVRT Validation: Specificity

- E.g., the IVRT method is proportionally linear in its response to differences in release rates
- A minimum r^2 value ≥ 0.95





IVRT Validation

- Selectivity
  - Establish **in-equivalent** release rate between Test (T)/Reference (R) product and altered strengths
- Supplemental selectivity
  - Using products at the same strength, but altered composition and/or manufacturing process
- Precision and Reproducibility
  - E.g., a minimum of three independent runs
  - E.g., the intra-run and inter-run percent coefficient of variation (%CV) ≤ 15%

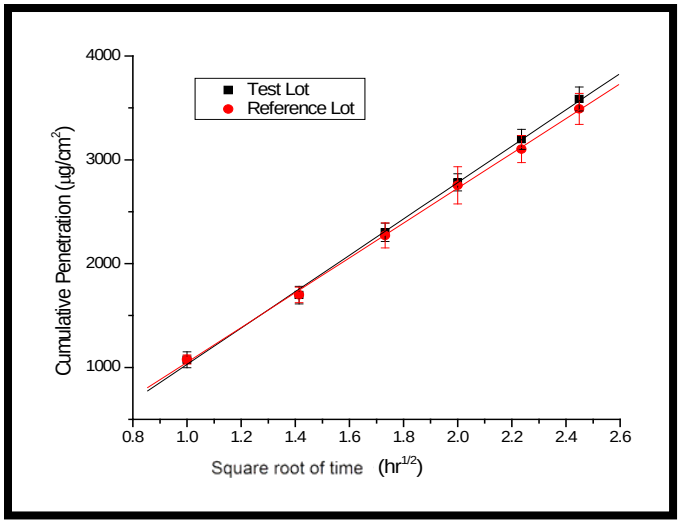
IVRT Robustness

Robustness testing encompasses

- Temperature variations (i.e., - 1°C and +1°C relative to 32°C ± 1°C)
- Dose volume variations (e.g., +10% and -10% in the dose volume)
- Receptor solution variations (e.g., change in composition and/or pH)
- Mixing rate variation (i.e., differences in stirring speed, or without stirring)

IVRT Pivotal Study

- A single batch each of a designated R and T products are evaluated
- Blinding and randomization
- The release rates for T and R products are compared utilizing a Wilcoxon Rank Sum/Mann-Whitney rank test



Summary

- Explain and justify the bases for the selection and optimization of the IVRT method parameters.
- *Draft Guidance on Acyclovir* (for topical cream, 5%) and the USP Chapter <1724> may provide a useful guide for the design, conduct, and validation of IVRT studies.

Acknowledgements

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Challenge Question

Which of the following should be established using statistical analysis?

A. IVRT sensitivity

B. IVRT selectivity

C. IVRT specificity

D. IVRT robustness

E. All of the above

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Questions?

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