Practical Considerations for IVRT Studies with Topical Drug Products Submitted in ANDAs

Best Practices for Topical Generic Product Development and ANDA Submission

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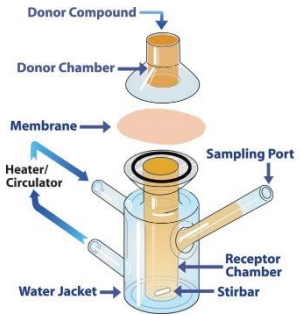
Learning Objectives

- Describe considerations for IVRT study design and validation when used as a component of characterization-based bioequivalence (BE) approaches
- Provide clarifications related to IVRT best practices and common questions

IVRT

- IVRT is a performance test to study the arrangement of matter.
- In characterization-based approach, IVRT is considered an in vitro BE study.



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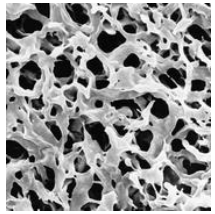


Major IVRT Study Phases:

- IVRT method development
- IVRT method validation
- IVRT pivotal study

IVRT Method Development

- Exploratory in nature
- Report which IVRT studies were done using a validated analytical method
- Sequence of selecting method parameters:
  - Equipment
  - Receptor solution
  - Membrane
  - Others (e.g., product dose amount, sampling times, stirring/agitation rate, etc)

IVRT Method validation

Equipment Qualification

- Empirical measurements along with manufacturer information (e.g., dimensions of the orifice, volume of the receptor compartment) of the diffusion cells.
- The equipment should control the diffusion cell thermoregulation.
- Membrane surface temperature is verified to be stable before dosing (e.g., at 32°C ± 1°C).

Qualification of the Receptor Solution

- Empirical solubility of the drug in the receptor solution: drug solubility exceeds the highest sample concentration in the IVRT, ideally by an order of magnitude
- Stability of the drug in the receptor solution
- Acceptable linearity and precision of the resulting drug release rate in an IVRT (**r^2 value of ≥ 0.97)**

Membrane Qualification

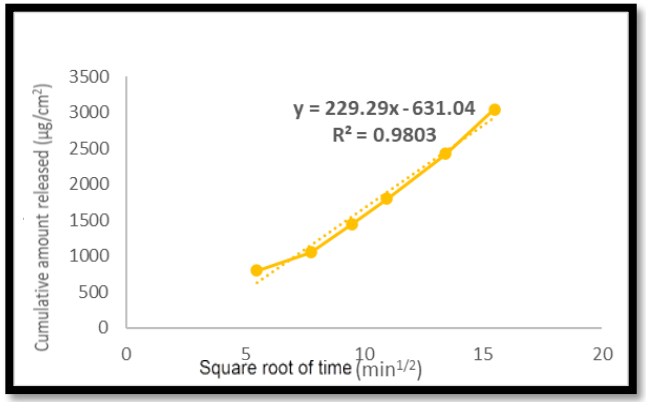
- Membrane's effective pore size (**e.g., 0.45 µm**)
- Membrane inertness in relation to membrane binding of the drug in the receptor solution at a concentration relevant to the range of drug concentrations in the receptor solution during the IVRT
- Chemical compatibility with the receptor solution
- Acceptable precision and linearity (**r^2 value of ≥ 0.97)**

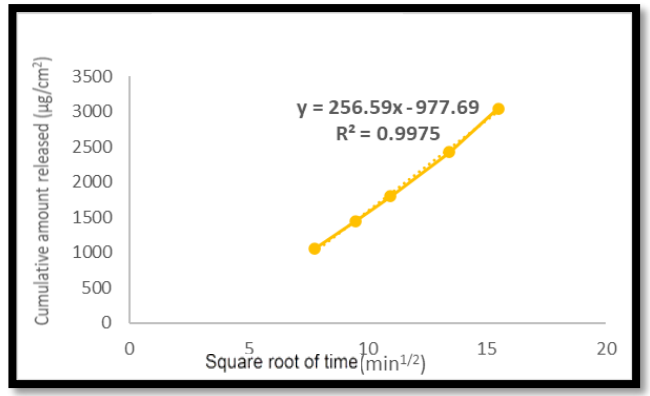
Receptor Solution Sampling Qualification

- Accuracy and precision of receptor sample collection
- Sampling technique can reliably collect a consistent volume of the sample from the well-mixed volume of the receptor compartment
- Submit manufacturer's specification for the accuracy and precision of receptor solution sampling

Receptor Solution Sampling

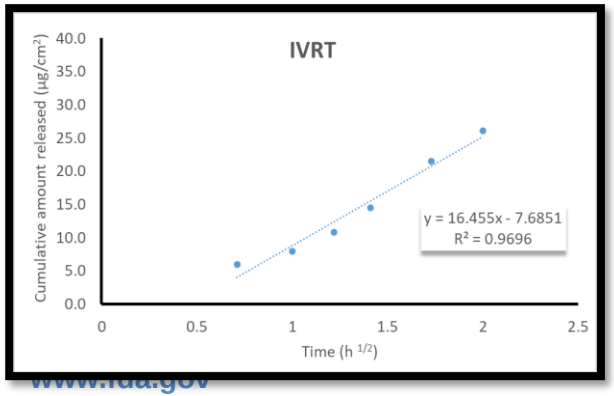
- Sampling frequency
- Number of sampling timepoints

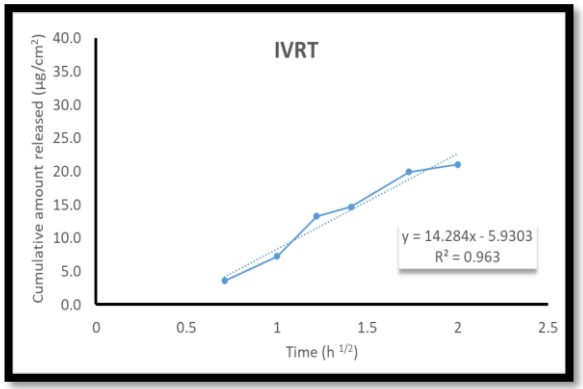


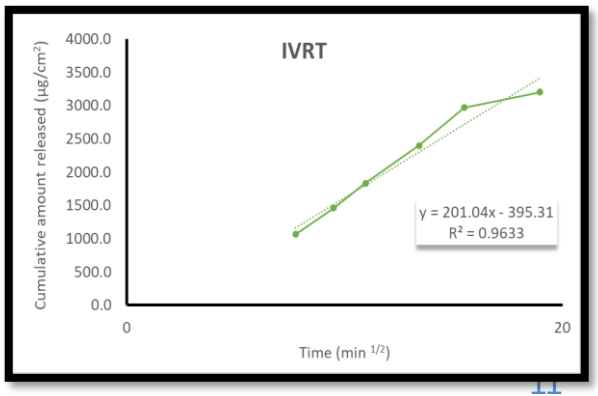


Acceptable Linearity

- The linearity of the drug release across all time points should be calculated and reported for each diffusion cell and compared within and across all IVRT runs.
- For the release rate to be considered suitably linear, it should have an **r^2 value ≥ 0.97** across IVRT study duration.







Duration of the IVRT Study

- IVRT duration (e.g., 4-6 hours)
- Duration of < 4 hours may be insufficient to assess whether the release rates represent the steady state drug release kinetics
- Duration of < 4 hours (which is not recommended) may be justified by compelling experimental data

Dosing

- Dose amount (pseudo-infinite dose)
- Dosing procedure for a selected apparatus
- Dose application method and its impact on product's microstructure
- The applied dose should be occluded during the IVRT study.

Dose Depletion (DD)

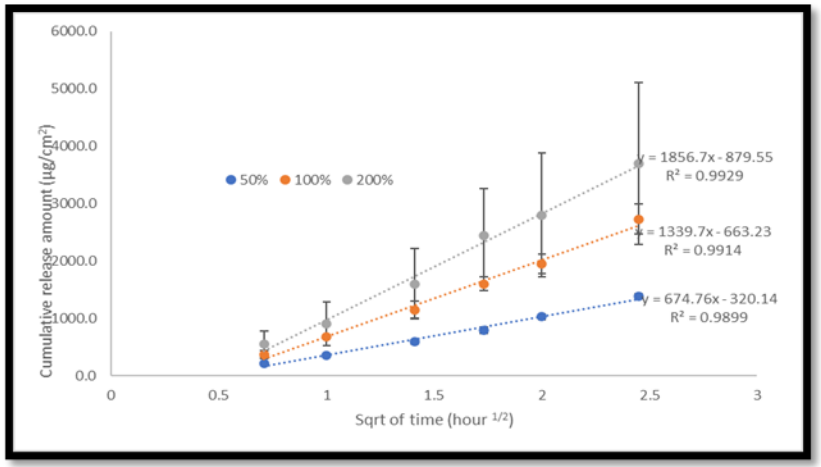
- DD is expressed as a percentage of the amount of drug in the applied dose. The average DD should be reported.
- Steady state release kinetics is assumed when DD is < 30%.
- For some topical products, steady state release kinetics may continue to be observed at higher percentage DD.
- A DD of >30% may be acceptable if the release rate remains suitably linear.

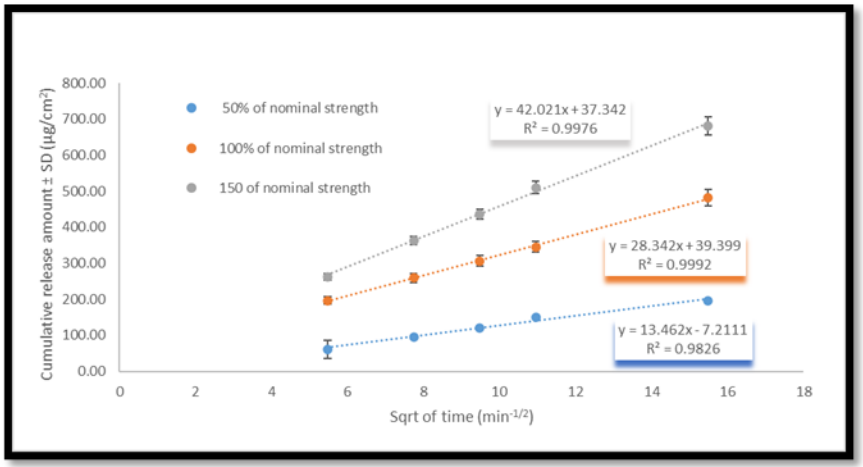
Precision and Reproducibility

- The intra-run and inter-run precision and reproducibility may be compared for the release rate calculated for each diffusion cell.
- A minimum intra-run and inter-run %CV ≤ 15% is recommended.
- A minimum of **three independent** precision and reproducibility runs is recommended.

IVRT Discrimination: Sensitivity

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





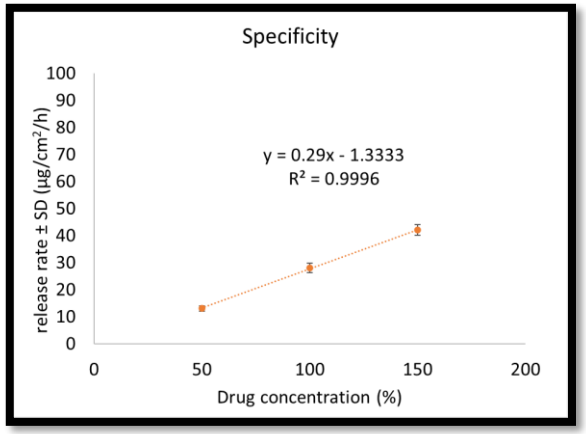
- Allowance may be made if a higher strength of test product is not feasible to formulate without substantial reformulation.

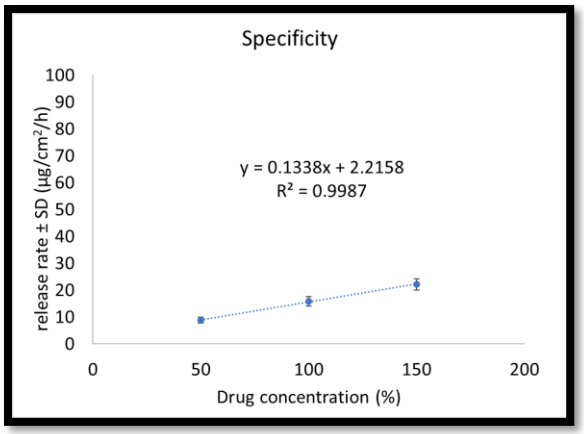
IVRT Discrimination

- Selectivity
  - Establish **non-equivalent** release rate between Test (T)/Reference standard (RS) product and altered strengths (**50% and 150% nominal strength**).
  - 6 cells of nominal strength of the RS (100%) compared with 6 cells of altered strength (50% or 150%). All 12 cells being compared should have been run in parallel on the same day.
- Supplemental selectivity
  - Using products at the same nominal strength, but altered composition and/or manufacturing process
  - The altered formulation may include changes in inactive ingredients, changes in inactive ingredient concentration(s), changes in the manufacturing processes, **or combinations thereof**. However, not all variations in a formulation will necessarily produce a difference in the release rate.

IVRT Discrimination: 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 Robustness

Robustness testing encompasses

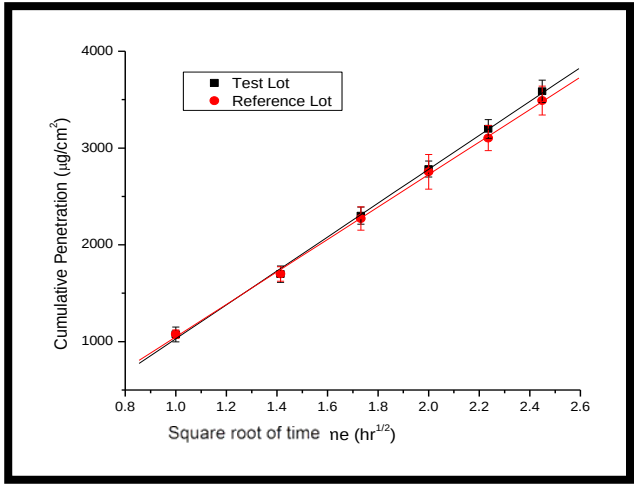
- Temperature variations (i.e., - 1°C and +1°C relative to 32°C ± 1°C)
- Dose volume variations (e.g., +10% and -10% in the dose volume)
- Receptor solution variations (e.g., change in composition and/or pH)
- Mixing rate variation (i.e., differences in stirring speed, or without stirring)

Sample Analytical Method Validation

- IVRT validation and pivotal studies should use a validated analytical method for the receptor solution sample.
- Separate and specific reports should be submitted for the sample analysis method validation and for the IVRT method validation.
- The validation should be performed using chromatography software with audit trails and should include **a multi-point calibration curve (not a single point).**

IVRT Pivotal Study

- A single batch each of a designated RS and T products are evaluated
- Blinding, dosing (alternating pattern ABABAB or BABABA), and dosing procedure
- The release rates for T and R products are compared utilizing a Wilcoxon Rank Sum/Mann-Whitney rank test



References

- The recordings and meeting materials from Virtual public workshop hosted by the FDA and the Center for Research on Complex Generics (CRCG) on August 18-20, 2021, *In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions*. Available at http://www.complexgenerics.org/IVRTIVPT/.
- USP chapter <1724>
- Other relevant FDA guidances

Acknowledgements

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Questions?

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