U.S. FOOD & DRUG ADMINISTRATION

IVRT Method Development, Validation, and Transfer

Theoretical Principles and Practical Challenges

2021 CRCG IVRT/IVPT Workshop

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Apparatus Selection

- Apparatus to be compatible with the conceptual design in USP General Chapter <1724>:
  - Vertical diffusion cell
  - Immersion cell
  - A flow-through cell used with USP Apparatus 4
- Considerations related to the dosage form

Apparatus Qualification

- Sampling
- Stirring rate
- Temperature control
- Donor and receptor chambers diameters
- Receptor volume
- Satisfactory performance verification

Receptor Solution

- Qualification:
  - Maintaining sink conditions (adequate solubility)
  - Drug stability
  - Acceptable release profile
- Considerations when using volatile solvents
- Two drugs in the formulation

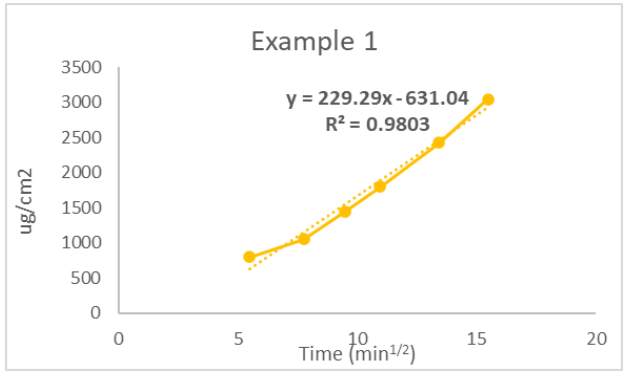
Membrane

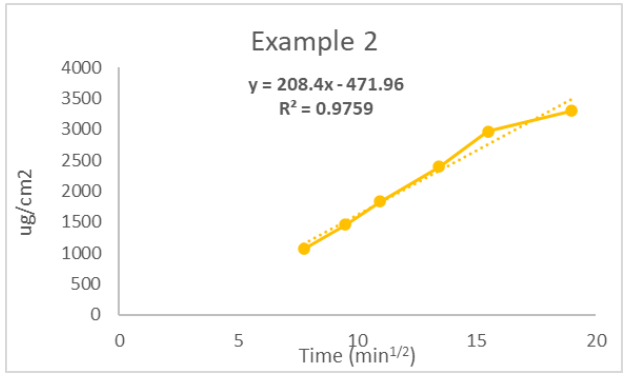
- Membrane Inertness with respect to the drug, dosage form, receptor solution, and analytical method
- Porosity (e.g., 0.45 µm)
- Objective criteria for method parameter selection
- Equilibration duration
- Membrane reproducibility and quality control (QC) between different lots, and availability

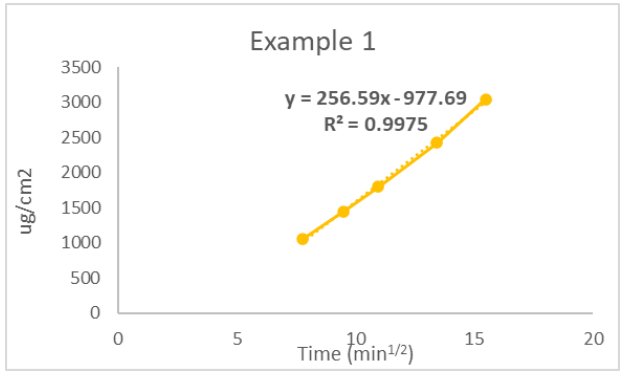
IVRT Design: Duration and Linearity

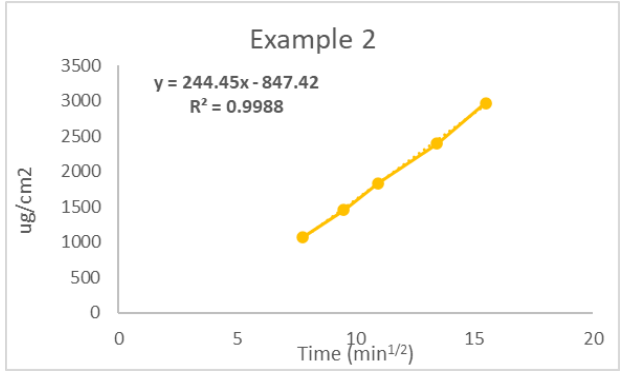
- Suitably linear steady state release: r^2 value ≥ 0.97
- Recommended IVRT study duration of 4–6 hours
- Dose depletion and loss of steady state
- Sampling time points

IVRT Design: Duration and Linearity









IVRT Design: Dosing

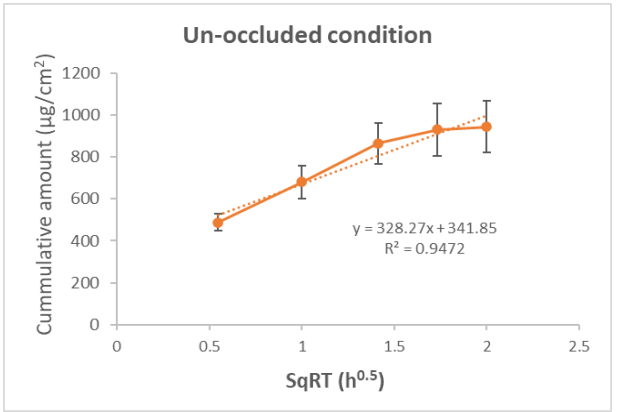
- Dose amount
- Dosing procedure for a selected apparatus
  - Dosing inside or outside the apparatus?
  - Dosing technique and accuracy

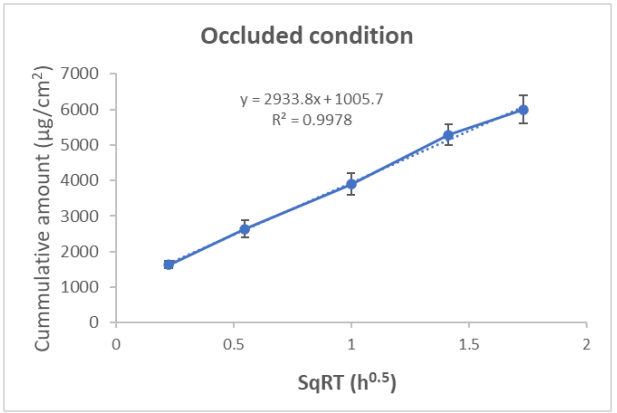
IVRT Design: Sampling

- Sampling method qualification
- Selection of the sampling tool
- Sampling calibration
- Sampling frequency

IVRT Methodology

- Temperature control
- Back-diffusion
- Stirring rate
- Occlusion





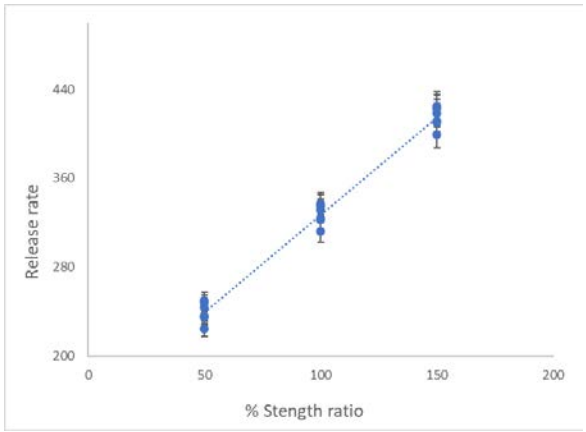
IVRT Validation

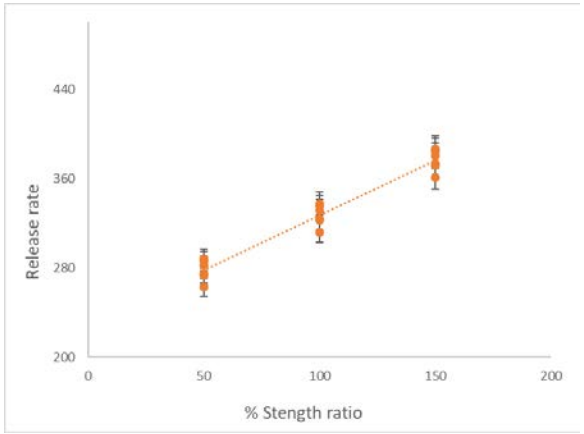
- IVRT reproducibility and precision
  - % CV
- IVRT sensitivity
  - Alerted strengths (50% and 150% strengths)
    - Bench vs. GMP batches
    - Challenges with preparation of 150% strength with some drug products

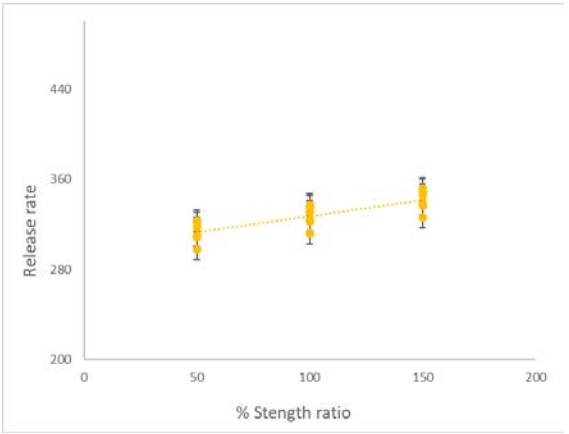
IVRT Validation

- Selectivity vs supplemental selectivity
  - Demonstrated by statistical analysis
  - Challenges with demonstrating supplemental selectivity with an “altered” formulation
- Specificity

IVRT Validation







- Choosing Test or Reference products for validation studies?

IVRT Sample Analysis

- Analytical method validation
  - Compared to bioanalytical method validation guideline
  - Compared to ICH Guideline
- Interference of excipients
- Is it analogous to dissolution method standards?
- Would single point calibration curve be acceptable?

Additional Considerations

- IVRT validation vs development
  - Validated analytical method
- Batch to batch performance of the drug product
- Age of the drug product
- Failing first stage of IVRT analysis
- IVRT method transfer
- IVRT for post-approval changes vs bioequivalence assessment

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