Overcoming Dissolution Challenges with Low Dose Pharmaceuticals and Medical Devices

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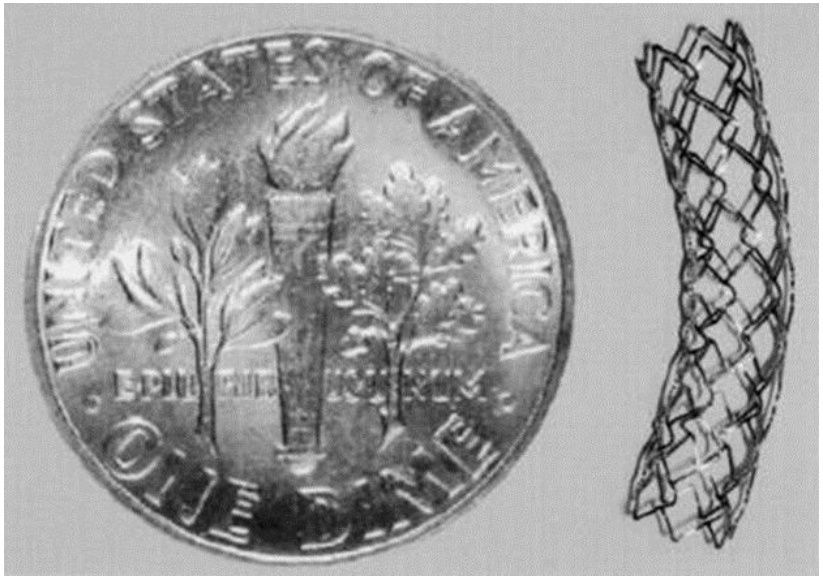
Agenda

- Low Dose Products Overview
- Requirements when Working with Low Dose Drugs
- Regulatory Concerns for Small Volume Dissolution
- Options for Small Volume Dissolution
- Case Study for a Medical Device

Low Dose Products

Low Dose Drug Products may include:

- Oral dosage units containing concentrations of analyte in the microgram or nanogram levels
- Ocular or other mucous membrane direct applications
- Transdermals
- Subcutaneous implants
- Combination devices such as drug eluting stents



Low Dose Products

Low Dose Products often require modifications to dissolution to ensure that there is an adequate concentration to analyze

- Small Volume Dissolution Conversion
- Apparatus 3, 4, and 7
- Evaporation Controls
- Changes to Sampling

Requirements when Working with Low Dose Drugs

The Concept of Small Volume Dissolution Apparatus

The Two Components of Dissolution:

- Sample preparation with the dissolution apparatus which ceases with the withdrawing and filtering of a sample
- Sample analysis with the analytical method which begins with the filtration of the sample

Requirements of Small Volume Dissolution Apparatus

Whether compendial or non-compendial, the dissolution apparatus must maintain:

- Precision
- Physical uniformity and alignment
- Temperature control
- Agitation rate
- Volume control
- Proper hydrodynamics
- Ability to sample reproducibly

Requirements of Small Volume Dissolution Apparatus

Small volume dissolution apparatus should maintain:

- Discrimination of variation from batch to batch
- Sufficient volume to be analytically quantifiable
- Ruggedness (transferable)
- Precision of design
- Calibration regimen (where practical)

The Analytical Method

For the analysis of the dissolution sample, the analytical method must maintain:

- Accuracy (sample integrity)
- Precision
- Limit of detection (LoD)
- Limit of quantitation (LoQ)
- Linearity
- Ruggedness (transferability)
- Stability of analytical solutions

Small Volume Dissolution

Whenever an adaptation is made to a Dissolution System, you must ensure you are not introducing bias and variability is kept low.

Regulatory Expectations

Regulatory Expectations

Method Considerations:

- Characterize In Vitro release early in development
- Evaluate release with various conditions: agitation media composition, pH, temp, etc.
- Establish optimum test conditions
- 80% release or asymptote
- Discriminatory as tested with critical manufacturing variable (CMV) samples – to be able to reject lots
- Specifications set to show consistent performance lot-to-lot

Regulatory Expectations

Specifications:

- Modified Release – IVIVC expectations are high
- Support controlled release and QA
- “Approvable” based on meaningful methodology and specifications
- Able to support scale up and post approval significant changes (SUPAC-MR)

Regulatory Expectations

Pharmacokinetics:

- Determine half-life (may be difficult to quantitate)
- Compare to half-life via IV or PO
- Systemic levels would be evaluated for systemic effects, drug interactions or adverse events

Regulatory Expectations

IVIVC:

- Make effort for In Vitro method to reflect In Vivo rate
- Verify with animal data with deconvolution (example, pull implants or stents from animal and compare % remaining)
- Confirm with human data with deconvolution

Regulatory Expectations
For a Small Volume Dissolution Method

Method and specifications should provide:

- Characterization of release
- 80% release or asymptote
- Discrimination by process validation samples
- Consistent performance lot-to-lot
- Must show failure and ability to reject a batch

In general, methods must be:

- Relevant
- Predictable
- Specific
- Discernable

LCMS may be required

Regulatory Expectations
For Small Volume Dissolution Equipment

General preferences include an expectation to **test and show failure with conventional dissolution systems first**.

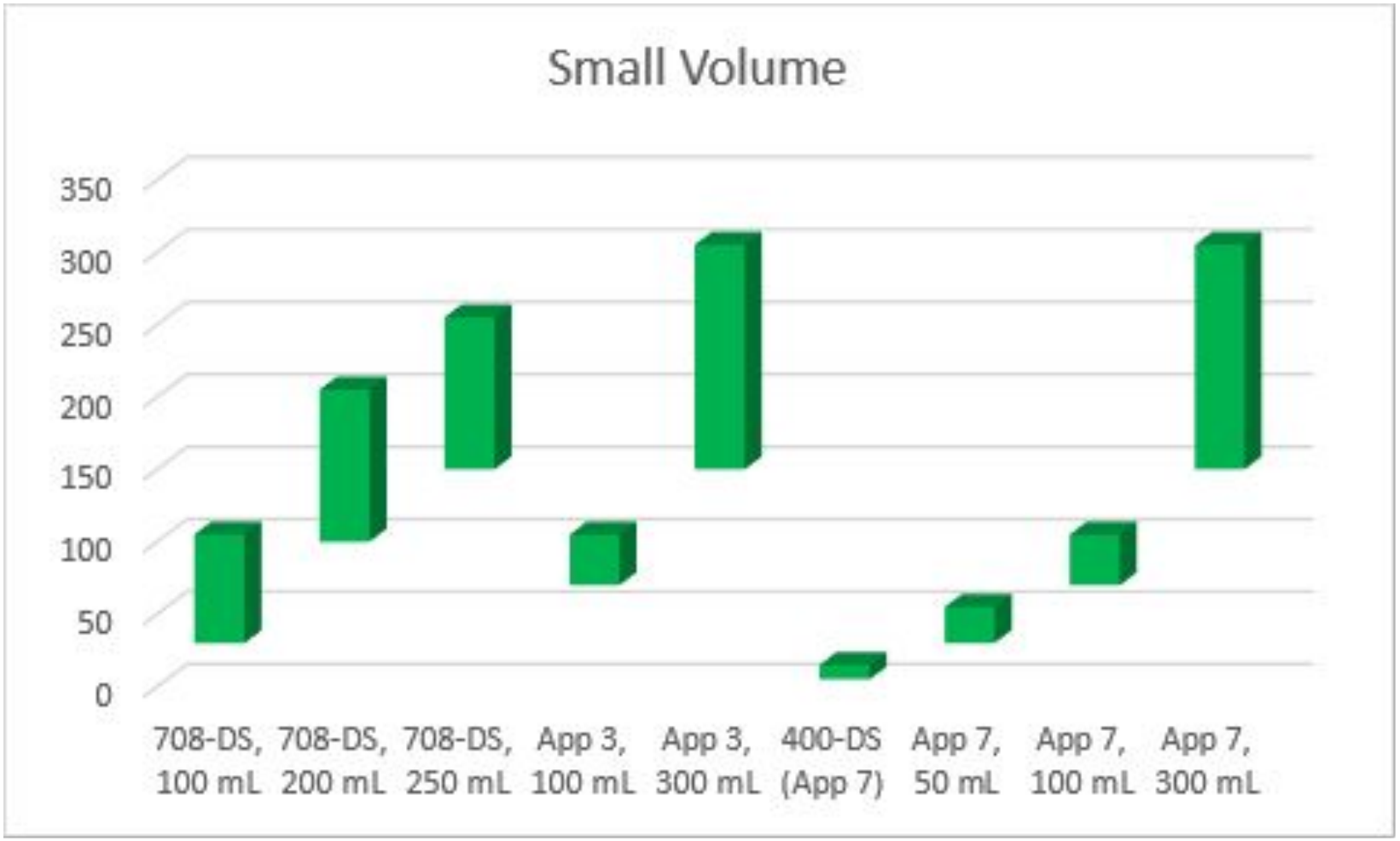
If possible, the small volume solution should be:

- Compendial USP Apparatus in <711>, <724>, etc.
- If Apparatus is not compendial, modifications should be commercially available
  - Small Volume Conversion Kits for App 1, 2, 3, and 7

250 mL Vessel kit (CP)

Options for Small Volume Dissolution

Small Volume Options



USP Apparatus 1 and 2

USP <711> Apparatus 1 & 2

- 1000 mL Vessel
- Typical 900 mL vessel volume
- Operational minimum – 500 mL vessel volume
- Tablets, capsules, suspensions, suppositories, chewables
- Transdermals (USP Apparatus 5 & 6)
- Water Bath Systems can often utilize smaller vessels

Modifications to USP Apparatus 1 and 2

Small Volume Options for USP Apparatus 1 and 2

- 100, 200, and 250mL CP vessels available
- Can be used with mini-paddles, mini-baskets, or USP baskets
- Operational minimum is about 40mL in 100mL vessels
- Samples can be taken manually or with automated systems
- Can quickly convert back to 1-L

Enhancer Cell

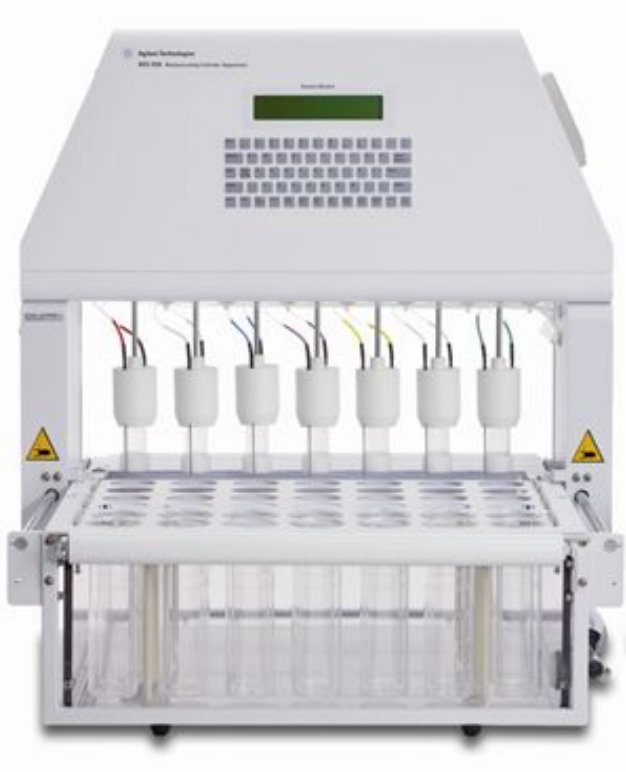
- Used for semisolids
- Typically operated in small volume vessels (w/ flat bottom)
- Agitated w/ mini-paddle

Qualification of Small Volume Apparatus 1 and 2

- Qualify system as a standard 1-L system to verify overall alignment and function
- Replace 1-L components with small volume accessories
- Verify modified setup
  - Set height with appropriate tool
  - Check centering of shaft at top of vessel
  - Check vessel and shaft verticality, if possible

Smaller size means some measurements will not be practical or possible.

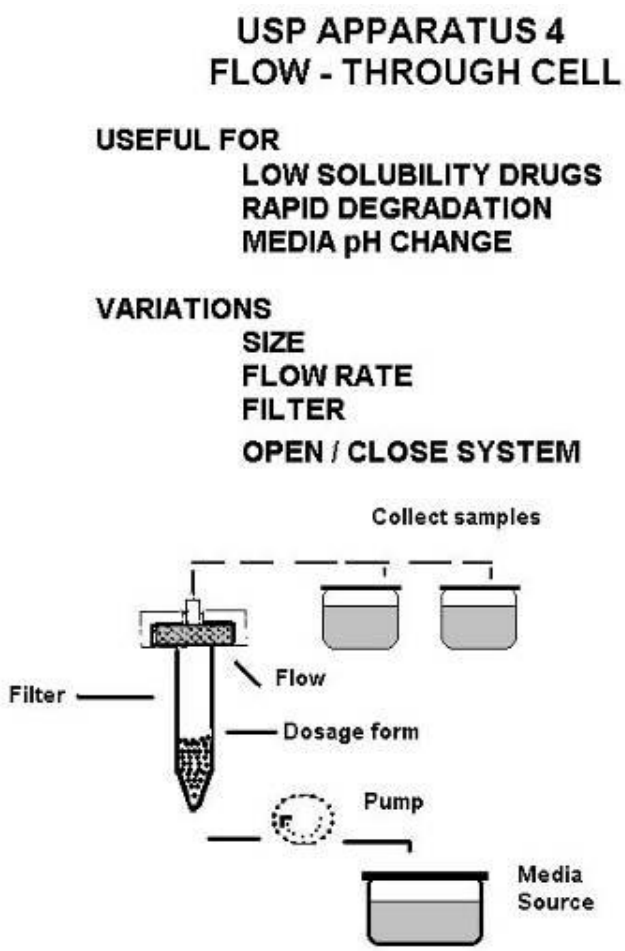
USP Apparatus 3
Reciprocating Cylinder



USP <711> Apparatus 3:

- 300 mL Vessel
- Normally 200 mL to 275 mL vessel volume
- Operational minimum – 150 mL vessel volume (sampling limited)
- 100mL vessel also available
- Extended-release tablets, capsules, beads
- Simple Qualification Approach

USP Apparatus 4



USP <711> Apparatus 4

- Initially designed for poorly soluble extended-release compounds
- Typical flow rates from 4 mL per minute up to 16 mL per minute
- A Closed system with a small media reservoir could reduce volume to 30 mL
- Extended-release tablets, beads, suppositories and implants

USP Apparatus 7
Reciprocating Holder

USP <724> Apparatus 7

- Typical volume is 40 – 50 mL
- Operational minimum around 25 mL
- Modifications have been made to accommodate 300 mL vessels
- Extended-release tablets, capsules, beads, implants, transdermals, osmotic pumps, and other novel dosage forms
- 400-DS Small-Volume Apparatus 7 has 5 and 10mL vessels, operational minimum as low as 3mL

Rotating Bottle

- Developed in 1958
- Vessel volumes 500, 250, 100, 50, 15, 4 mL
- No evaporative loss
- Long term extended-release testing
- Tablets, Capsules, Suspensions, Implants
- Downside – cannot be automated for sampling

Sampling Considerations and Options

Since sample volume is limited, automation can be helpful:

- Semi-automated systems:
  - Low sampling volumes
  - Media replacement
- Online UV-Dissolution with flow cells
- Online UV-Dissolution with fiber optics

Semi-automated Systems
Sample Collection and Filtration

- Decrease Sample Volume
  - Sample Volume as low as 0.25 mL
  - Be mindful of waste volumes
  - Prime and purge often returned to vessel (closed loop)
- Enable Media Replacement Option
  - Can replace aliquot of volume removed
  - Maintain sink condition and initial media volume
  - Generally recommended when volume loss is 10% or more

Compatible with most dissolution apparatuses and small-volume modifications.

Online UV-Dissolution (with Flow Cells)

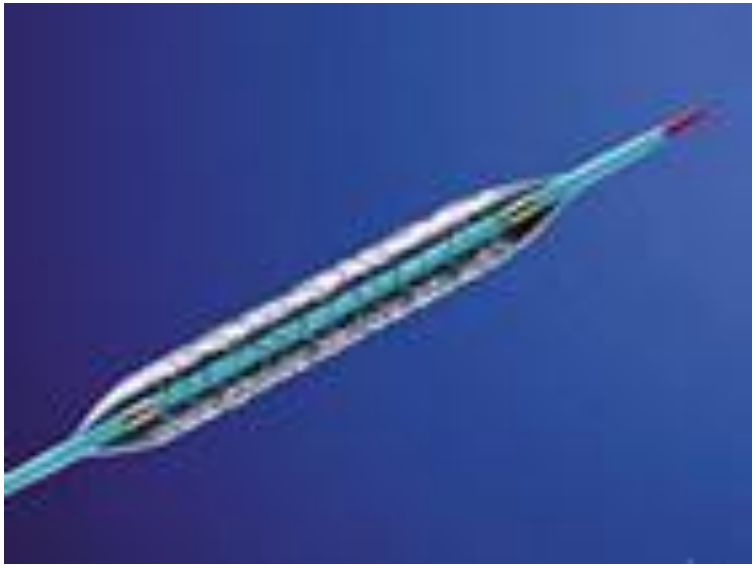
- Volume only temporarily removed from vessel (typically ~5 mL)
- Time points essentially unlimited
- Compatible with USP Apparatus 1 and 2 with small-volume vessels
- Only works with UV-vis analysis

Online UV-Dissolution (with Fiber Optics)

- No volume removed from vessel
- Useful for rapid time points
- Analysis limited to UV-vis
  - Some sample and/or media restrictions

Modification of USP Apparatus 7 for Drug Eluting Stents

Case Study: Drug-Eluting Stents
Early Development



Physicians and companies began testing a variety of drugs that were known to interrupt the biological processes that caused restenosis.

Stents were coated with these drugs, sometimes embedded in a thin polymer for time-release, and clinical trials were begun.

Case Study: Drug-Eluting Stents
Instrument Evolution

Initially, most drug eluting stent manufacturers utilized a rocking “incubator,” shaker tables or USP Apparatus 4 or 7 as their instruments of choice.

Modifications to App 7 allowed smaller volumes and automated sampling.

Custom holders have been designed for various stents and other medical devices.

Case Study: Drug-Eluting Stents
FDA Concerns

Challenges with Drug-Eluting Stent Methods:

- 10%-20% of drug in vitro
- Sensitivity, poor LOQ
- Non-physiological media able to reject lots?
- Aggressive handling/battering of stents
- SUPAC-MR
- Variability of data (bad manufacturing or bad method?)
- Cost (up to $3,500 each)
- Validation of methods
- Specification setting

Case Study: Drug-Eluting Stents

Challenges with Traditional Apparatus 7

- Instrument was not originally designed for extremely low volumes.
- Evaporation control was difficult due to reciprocating rod (which held the dosage form/device). Many methods allowed for media addition (“top up”) prior to analysis.
- Initial design was difficult to automate as the smaller volume tubes had smaller diameter openings; as a result, clearance was tight for sample and return lines.
- The requirement for testing 12 stents at a time lead to the development of a 12-position fraction collector.

Case Study:
Drug-Eluting Cardiac Leads
Medtronic

Small-Volume USP Apparatus 7

400-DS: Key Features and Benefits

- **Small volumes:** 5 mL or 10 mL dissolution cells can use from 3 mL to 12 mL media for testing
- **Bathless:** heater jackets provide stable temperature control for extended run times
- **Automated media replacement:** Integrated fluidics module provides total media replacement with up to four different types of media
- **Negligible evaporation:** <0.2% volume per 24 hrs. ensures reliable results even for long test runs

- **Smaller size:** Occupies about 35% less space on a lab bench compared to traditional Apparatus 7

Small-Volume USP Apparatus 7

400-DS: Key Features and Benefits

- **Integrated autosampler:** samples 1 mL – 4 mL from dissolution cells into sealed vials for analyses
- **Automation of convenience and throughput:** One instrument can run 13 test samples (two sets of six, plus a standard or control) and 400-DS software running on a single PC can control up to four instruments (up to 52 test samples)
- **Regulatory Compliance:** the 400-DS is a compendial USP Apparatus 7 device and the software is compliant with 21 CFR Part 11 guidelines for electronic records

Case Study: Drug-Eluting Cardiac Leads
Medtronic

Method for the elution analysis of dexamethasone acetate from silicone matrix for drug-eluting cardiac leads.

- Dosage < 1 mg
- Designed to deliver drug over a significant period of time (i.e., months)
- Investigated usage of USP Apparatus 2 with mini-paddles, vessels, and low-loss evaporation covers
  - Variability due to uncontrolled evaporation over multi-day analysis.
  - Low sensitivity since media volume at 50 mL minimum
- Chose modified USP Apparatus 7
  - Little-to-no evaporation
  - Reduced vessel volume (10 mL)
  - Fully automated (fill, media changes, sampling) reduces sampling error and is more analyst friendly (e.g., no need for analyst to come in at 2:00 am to pull a sample)

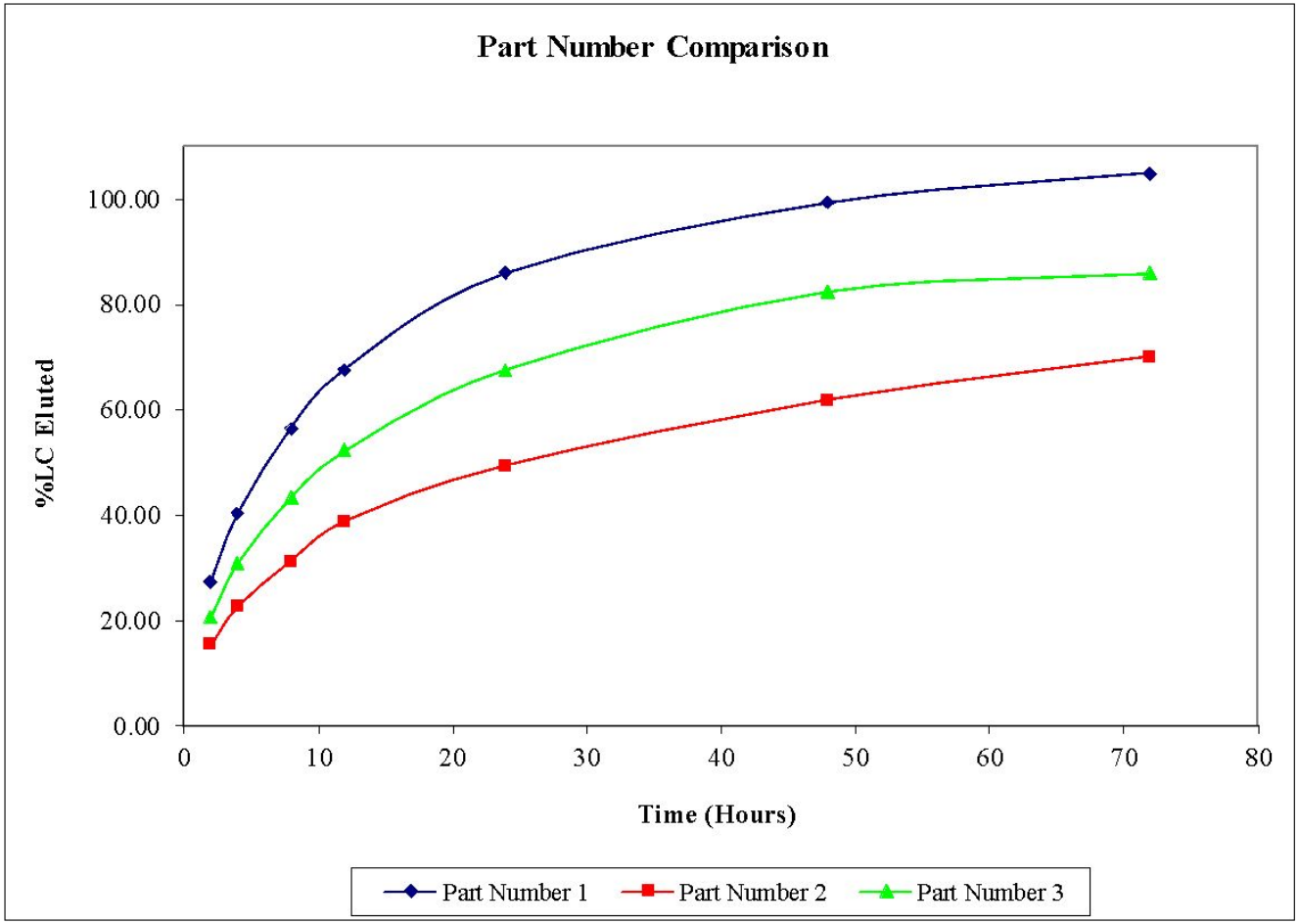
Case Study: Drug-Eluting Cardiac Leads
Medtronic

Method for the elution analysis of dexamethasone acetate from silicone matrix for drug eluting cardiac leads.

- Media is a surfactant system containing a strong non-polar solvent to accelerate elution time
- Developed to be discriminating between dosage size and dose shape
  - Several different sample configurations of the same drug/silicone mix

Case Study: Drug-Eluting Cardiac Leads
Medtronic

Elution Results - Part Number Comparison



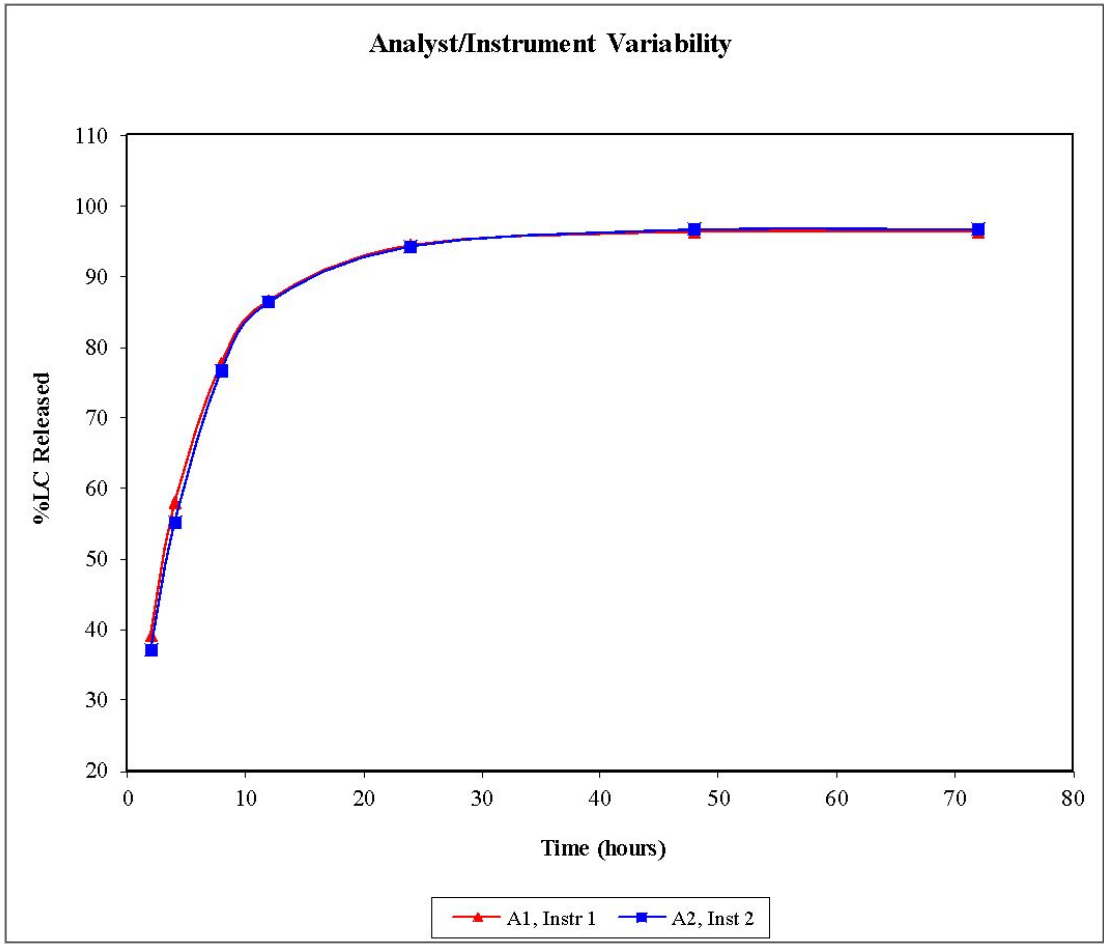
Case Study: Drug-Eluting Cardiac Leads
Medtronic

Analyst-to-Analyst, Instrument-to-Instrument

- To assess the variability of the method, two separate analyst ran the method on separate days and instruments.

Case Study: Drug-Eluting Cardiac Leads
Medtronic

Analyst-to-Analyst, Instrument-to-Instrument Results:



Small-Volume USP Apparatus 7

400-DS: Applications

- Drug Coated Stents
- Contact lenses
- Pacemaker leads
- Catheters
- Transdermals
- Extractables/Leachables
- Other Medical Devices
- Novel Dosage Forms
- Micronized powders

Small-Volume USP Apparatus 7

400-DS: Improvements and Advantages

The 400-DS successfully addresses the many challenges associated with the testing of combination products:

- Small volume
- Low evaporative loss
- Use of organic solvent media
- Automated sampling and media replacement
- Bathless
- Regulatory compliance
- Small footprint

Small-Volume Dissolution

Summary

Small-volume dissolution apparatus should not contribute to or produce unreliable data that was characteristic of early dissolution apparatus.

The two essential components of the dissolution assay must be properly evaluated and validated separately.

Small-Volume Dissolution

Summary

The greatest value in developing and validating small-volume dissolution methods and apparatus is not in the fulfillment of regulatory requirements, but in providing accurate, reliable data for decision making during drug development stages and assurance of quality when the product reaches full scale production.

Small-Volume Dissolution
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Small-Volume Dissolution
Questions / Contacts

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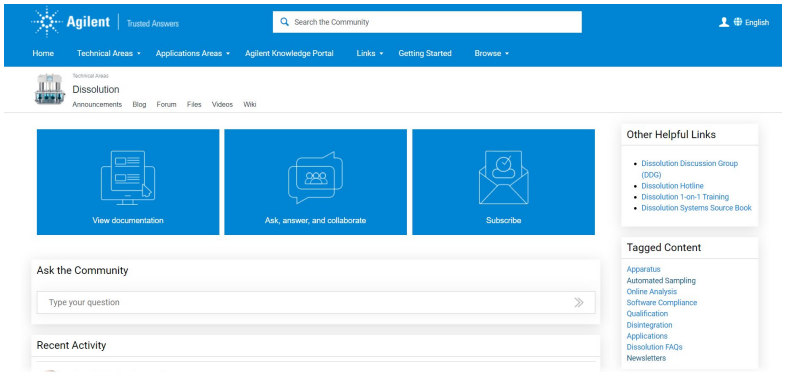

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