Troubleshooting Differences Between Labs

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Agenda

- Dissolution Run Failure Investigation
- Differences in data between sites
- Potential causes of site to site differences
  - Preparation
  - Dissolution Unit
  - Laboratory Issues
  - Dissolution Procedure
  - Sampling
  - Analysis

Dissolution Run Investigation

Dissolution Failure Investigation

Whenever a dissolution test fails to meet specifications, an investigation should be performed to determine the cause(s) of the failure.

Failure can be due to:

- Man (analyst)
- Machine (dissolution apparatus)
- Method (SOPs)
- Materials (standards, buffers, dosage form, etc.)

Conducting an Investigation

Investigations should be performed in a sequential process to ensure all potential sources of error are investigated

•Review data as a whole

•Perform investigation in reverse chronological order

Determinant vs. Non-Determinant Errors

Determinant Errors are known and controllable

Indeterminate errors are unknown, suspected, or beyond control

Determinant errors when found will lead to a simpler investigation and require the least re-work

Indeterminate errors cannot be proven, and the burden of retesting is often higher

Investigating in Reverse

- Last thing done, first investigated
- Limits scope of investigation, if determinant error found – can stop
- Last things done can often allow salvaging of the run
- All samples/standards/etc. should be kept until results have been checked and approved or fully investigated

Investigation Track

- Calculations
- Analysis
- Sampling and Filtration
- Run Observations
- Media Prep and Sample Handling
- Pre-Run Checks
- Dissolution Unit Mechanicals
- SOP and Materials

Data Differences Between Sites

Lab to Lab Differences

Occasionally, differences occur between laboratories performing dissolution using the same methods and samples

When differences occur, investigations should be performed in order to determine the causes of the difference

First need to eliminate possibility of single run/unit/user issue

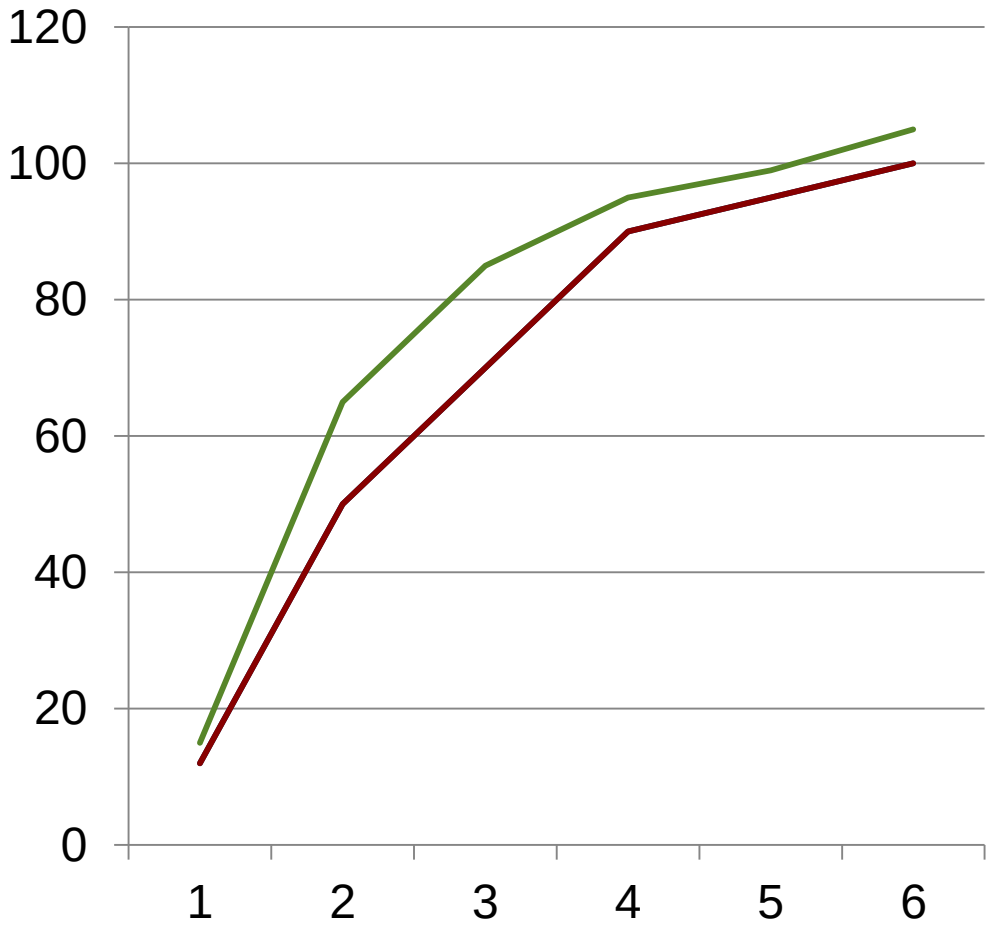
Overall Trend of Data

The Difference itself can help narrow the focus of the investigation:

- Data trending low
- Data trending higher
- High RSD or outliers

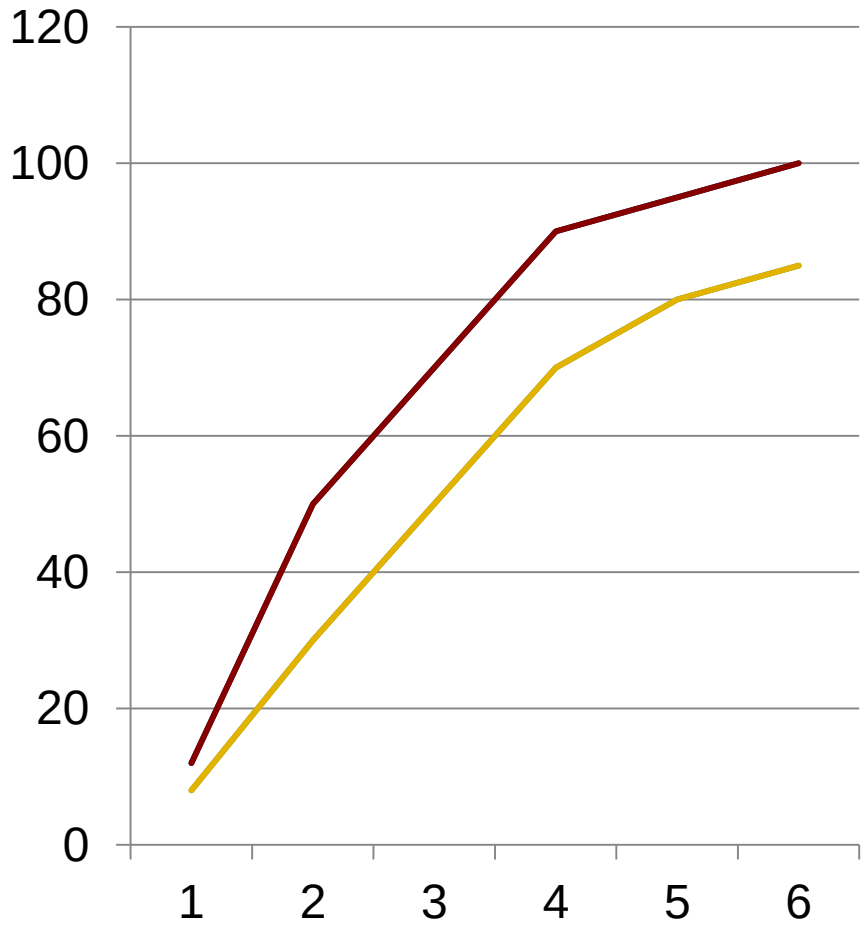
Data trending high

- Vibration (paddles)
- Deaeration Method
- Media prep
- Sampling Technique
- Filtration
- Cross-Contamination
- Vessel type
- Evaporative loss



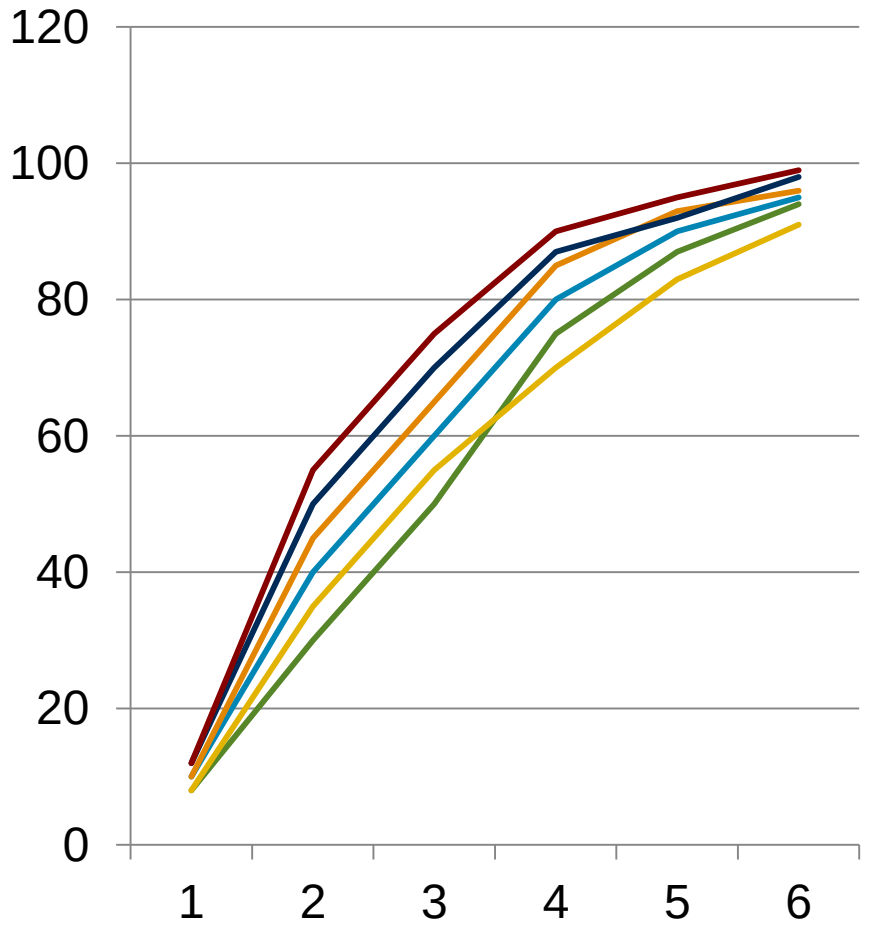
Data Trending Low

- Vibration (baskets)
- Media Prep
- Sampling Technique
- Filtration
- Vessel Type
- Cross-linking (capsule shells)
- Standard purity/moisture?



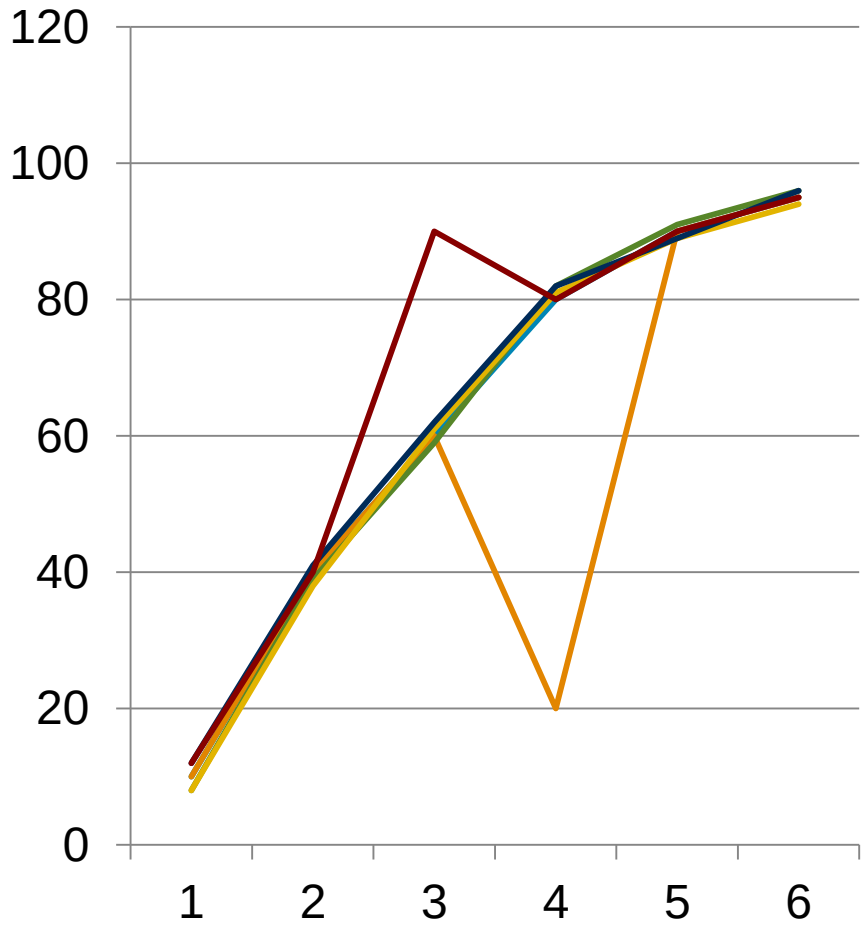
High % CV or Outliers

- Poor techniques
  - Sampling/filtering
  - Pouring
  - Media Prep
- Vibration (may trend)
- System Misalignment (may trend)
- Poor quality vessels/baskets/paddles
- Issues w/ formulation



Data that doesn’t make sense

- Filtration Issues
- Bad Sample Readings
- Air bubbles (prime/purge low)
- Contamination



Areas to Investigate:

Man:

- Sampling/Filtration Technique
- Media Prep/Degassing/Pouring

Method:

- Special Techniques
- Filtration definition
- Media Definition
- Autosampling

Machine:

- Vibration
- Alignment
- Vessels

Materials:

- Buffers/Surfactants
- API (purity/moisture/etc.)

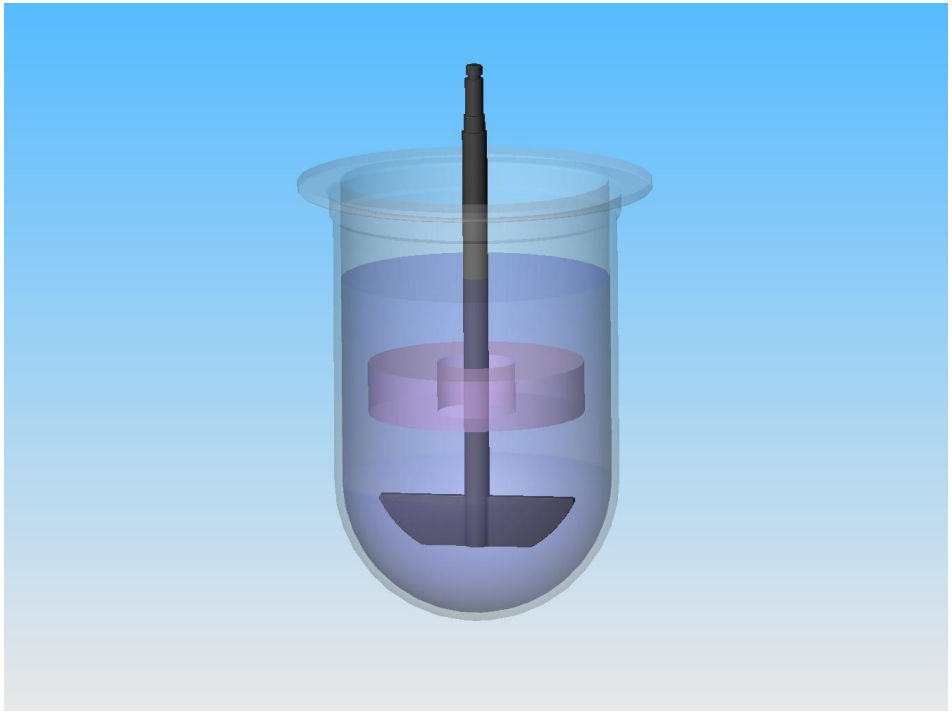
Sampling and Filtration

Sampling and Filtration

Sampling and Filtration are one of the most common causes of dissolution failures:

- USP Position
- USP Timing
- Filtration

USP Sampling Area



Sampling takes practice and attention!

All samples must be withdrawn:

- ½ way between top of paddle/basket and media
- No closer than 1cm from vessel wall
- Recommend not sampling within 1cm of spindle

Imagine A Donut

Sample Timing

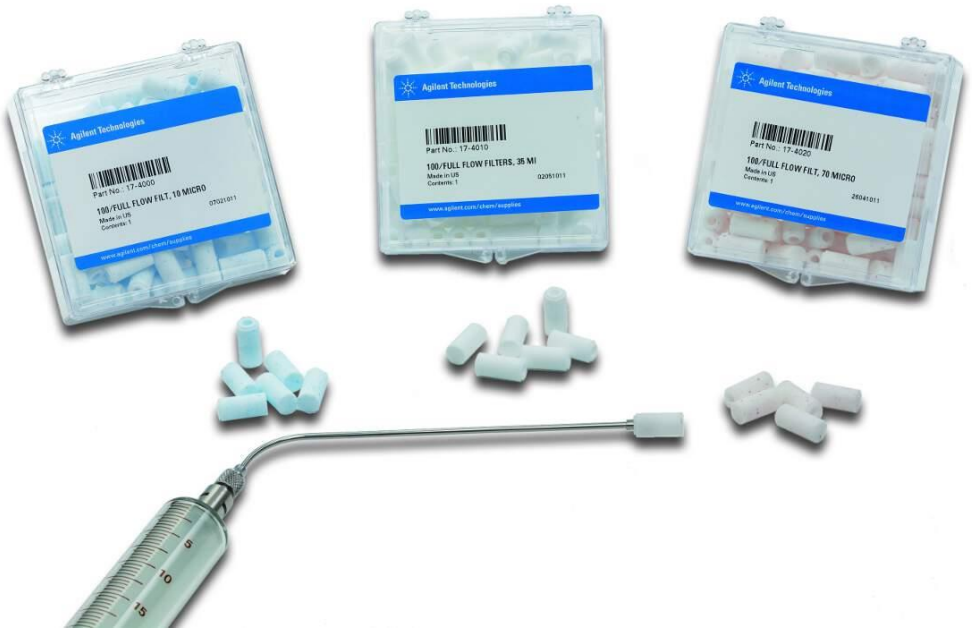
•Must sample (and filter) within 2% of the timepoint or 15 minutes, whichever is less

•Paddles/baskets must still be stirring while sampling

Filtration

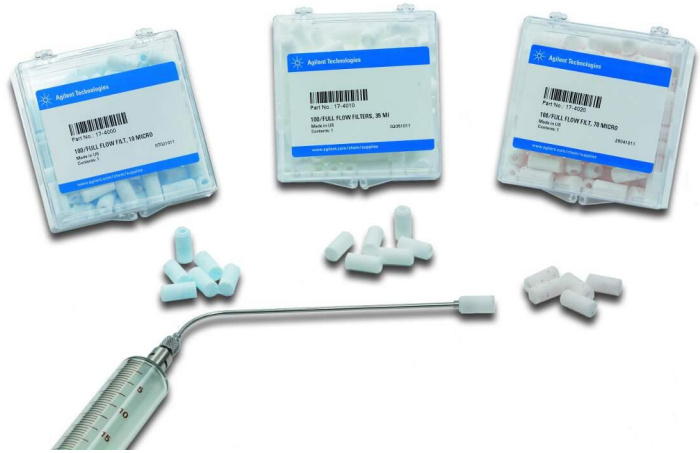
When was the sample filtered?

- At time of sampling?
- Immediately after sampling?
- After time point collected?



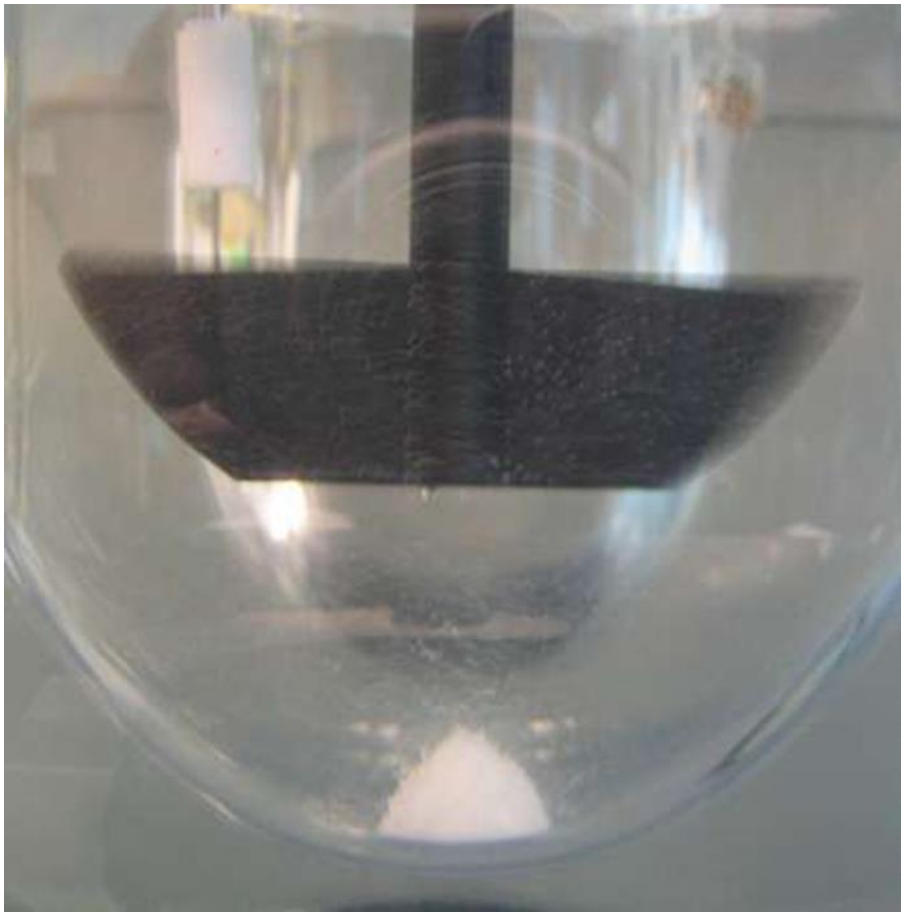
Is the filter actually validated?

- Is the filter the EXACT one used at the initial lab?
- Unvalidated filters are one of the largest causes of differences
- If not, has the filter been validated to be equivalent:
  - Efficiency
  - Adsorption
  - Leachability



Vibration

Vibration



- Tends to lead to higher, and more variable results
- Increases agitation energy, and accelerates dissolution
- In baskets, vibration can lower results by sieving material out of basket to bottom of vessel where it is relatively unstirred

Sources of Vibration

- Worn parts or bearings
- Heater circulators or pumps
- Fume hoods
- Vacuum pumps
- Construction
- Shakers
- Centrifuges
- Sonicators

Remedying High Vibration

- Identify source of vibration
  - Turn on/off various components
  - Feel or monitor with sensor
  - Listen for vibration
- Remove/Repair vibrating systems
  - PM/Repair disso equipment
  - Remove non-disso equipment if possible
- Evaluate lab-wide vibration
- Ensure waterbaths full, etc.
- Vibration dampening pads

Media Preparation

Degassing

Dissolved gasses can have a variety of impacts to the dissolution test:

- Alter hydrodynamics
- Cause Agglomeration
- Cause spinning and other motion
- Alter pH
- Clog screens

Degassing should be USP procedure unless otherwise validated

Common Degassing Methods

Acceptable Methods

- USP Vacuum Filtration Method (default unless another approach is validated)
- Helium Sparging*
- Automated Degassing*
- Superheating*
- Not Degassing At All*

*when validated against USP method

Unacceptable Methods

- Nitrogen Sparging
- Sonication

Other Media Concerns

Media may vary between sites for a number of reasons:

- Lot/Vendor of Surfactant
- Water quality differences
- Lot/Vendor of Buffer
- Age of chemicals
- pH meter not calibrated

Standards and Samples

Standard Preparation

- Ensure same API being used for standard prep
- Are moisture and purity are accounted for?
- Factors need to be applied?
- Is standard stability being maintained?
  - Amber glassware
  - 4C conditions

Storage

- Were samples within expiration period?
- Covered?
- Stored Properly?
- Labeled?

System Differences

Dissolution Vessels

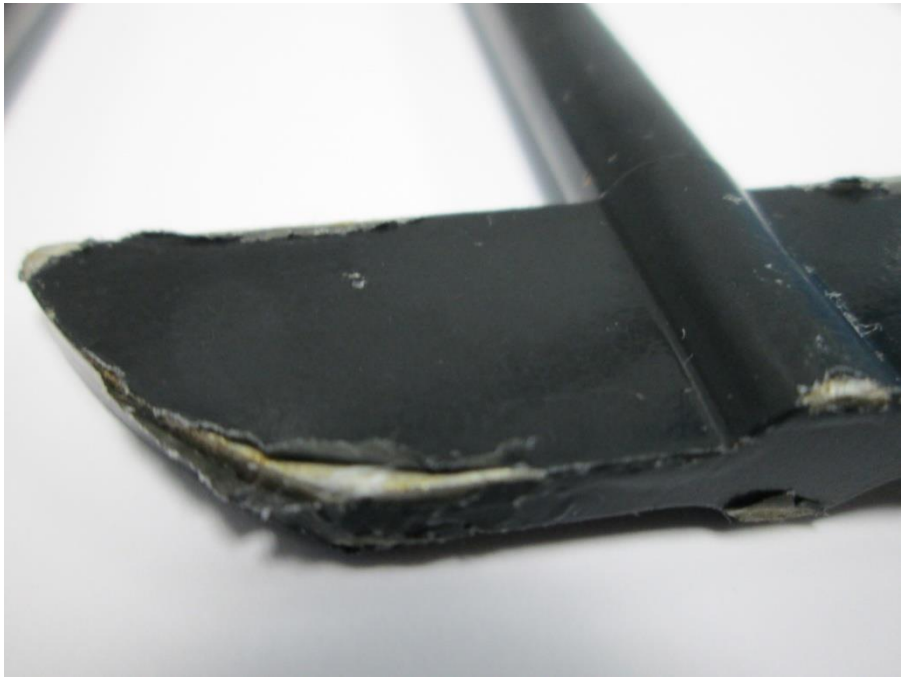
1L Dissolution vessels are defined in USP as 160 – 210mm height and 98-106mm diameter, and is cylindrical with a hemispheric bottom

- Hand blown
- Vessel manufacture is key
- Proper attachment device
- Condition and Cleanliness

Dissolution Vendor Differences

- USP Range for vessels is very wide
- Vessel Quality is key to low %RSD
- Differences in vessel dimension “target” within USP range does differ – and has occasionally led to different results
  - 1 vendor known w/ vessels on short + wide end of range
  - 1 vendor known w/ vessels on tall + narrow end of range

Teflon Paddles – Good, Okay, and Terrible



Baskets – From New to Dead

Evaporative Loss

Evaporation can skew results high if not properly controlled

- Older covers may have 5-10% evaporation over 24 hrs
- Low-loss covers have <1%
- Evaporation can be worse if air drafts/vents/etc. near unit

Other considerations

- Automated vs. Manual sampling?
- Sampling Location? USP Zone?
- Pre-stir being done for equilibration?
- Same sinkers utilized?

Cleaning and Carryover

Dissolution Cleaning

Cleaning of the dissolution unit for a method should be validated

Unclean systems can:

- Cross-contaminate runs
- Make surfaces non-inert
- Alter mixing

Cleaning solutions

Cleaning can usually be achieved with:

- DI Water – good for salts and surfactants
- Soapy Water, non-abrasive surface
- Methanol or Ethanol – sticky excipient residues
- Nitric acid – if severe deglazing of vessel needed

Formulation Issues

Cross-linking

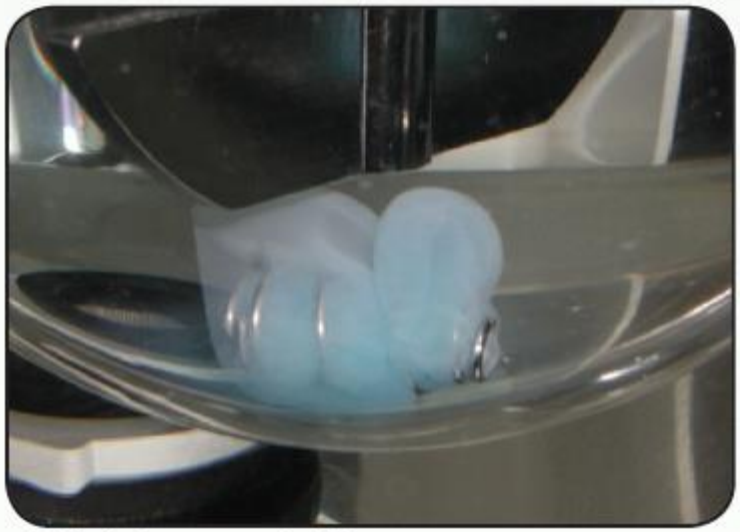
Cross-linking of capsule shells can result in hardened and chemically resistant shells. Very common to see in stability testing.

•Delay opening

•Trap Drug Product

•Pellicle Formation

If Cross-Linking is seen, testing with the appropriate enzyme should be performed



Pellicle Formation Problem

Enzyme use

- Pepsin – Used in acidic media, pH 1-2.5
- Pancreatin – Used in buffered solutions, typically pH 6+
- Bromelain and Papain – To be used in mid-pH range, more information to come in USP <711>
- Pre-soaking may be used, preferrably with agitation, in certain situations (surfactant use)

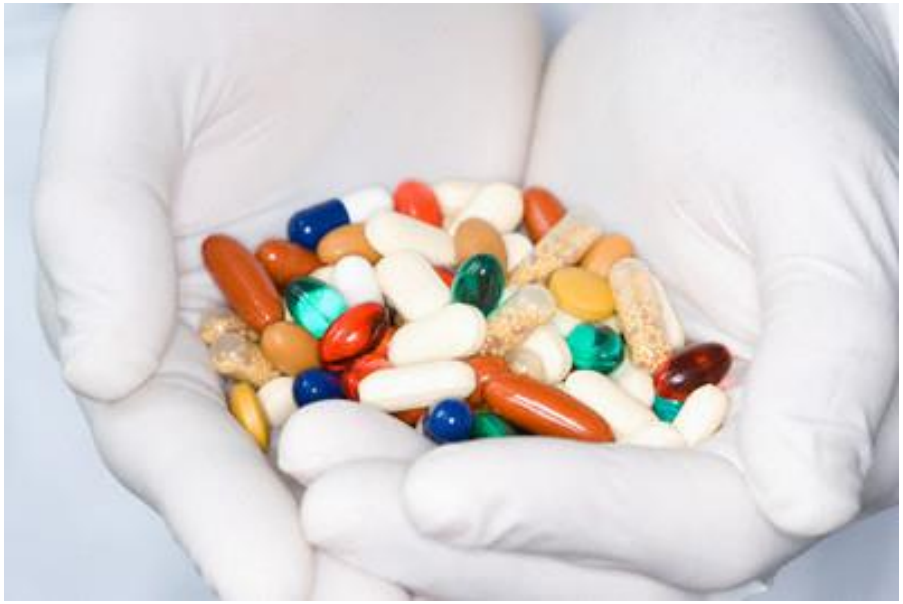
Formulation storage/transport

Formulations should be relatively robust and not impacted by the environment, but changes have been seen:

- Sub-zero temperatures in transit
- Being left in very hot warehouses, etc.
- Friability issues due to handling/packaging
- Exposure to humidity

Sample Handling

- When exposed to air?
- Weighed?
- Inspected?
- Where placed?
- How handled?
  - Bare hands
  - Gloves
  - Tweezers



Summary

Pinpointing the causes of differences can be difficult at times, make sure that all aspects of the units, analysts, method transfer, and the materials used are reviewed.

Observations of the dissolution behavior are often key in determining the source of the bias.

Upcoming Seminars In Process

What topics would you like to see discussed?

Questions?

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Dissolution Discussion Group

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