

Transferring Dissolution Methods

Session 1 – Building a Robust Dissolution Method

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Overview

- What is Robustness?
- Key Elements of Dissolution
- Media Selection
- Agitation Speed/Type
- Sampling
- Filtration
- Cleaning and Carryover
- SOP Wording



Dissolution Method Goals

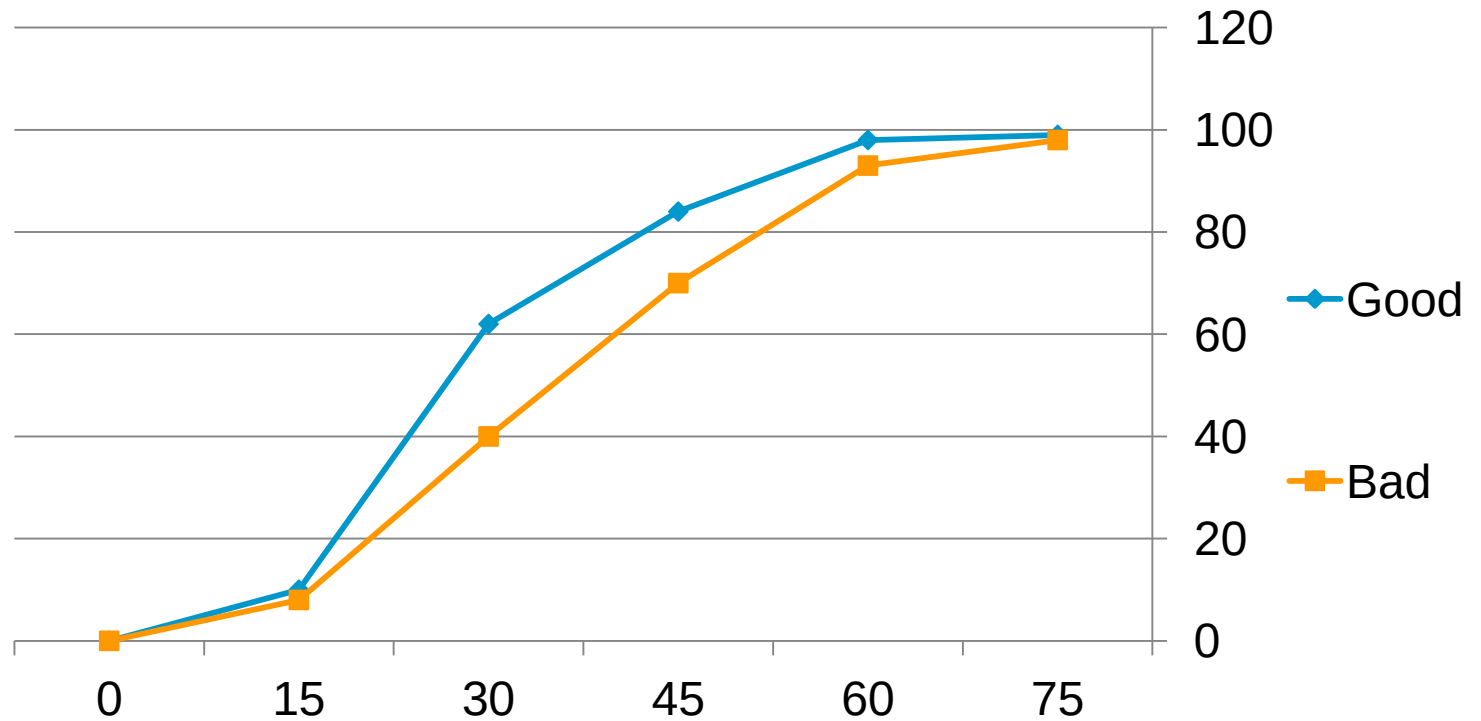
A successful dissolution method will be:

- Discriminatory
- Robust
- Correlated to In Vivo
- Transferrable
- Controlled Variability



Discrimination

Discrimination in Dissolution simply means being able to tell the difference between good and bad formulations



Robustness

While discrimination is important, your method should not be so sensitive that minor differences in the test lead to different results

- Analyst to analyst
- Lab to lab
- Vendor differences
- Overly sensitive method parameters



Find a Balance

Blender



Stagnant Water



Key Elements of Dissolution

Dissolution is made up of 3 components:

- Inert vessel
- Rotating Shaft
- Dissolution Media

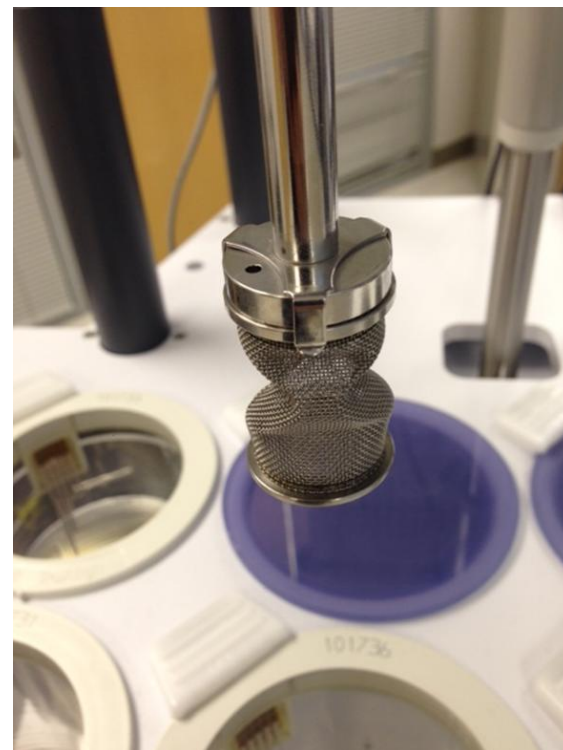
Proper Alignment is key to ensuring consistency



Key Elements of Dissolution

Dissolution Systems used for method development and testing must be:

- Qualified by PVT or MQ
- Not have significant vibration
- Components should be in proper condition

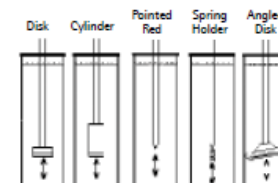
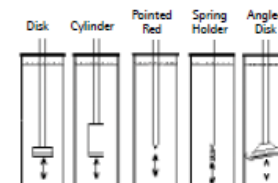
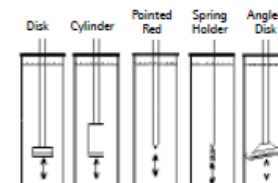
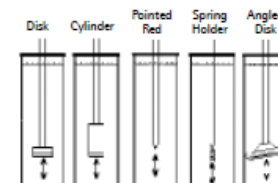
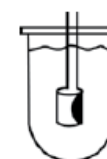
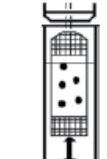
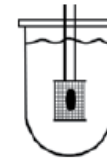


Dissolution Tester Choice

Paddles and Baskets tend to be the choice for most solid oral dosage forms.

If pH changes, greater/smaller volumes, or different agitation is needed then Apparatus 3 and 4 are often considered after exhausting Paddle and Basket testing

For Transdermals Apparatus 5-7 are the primary choices

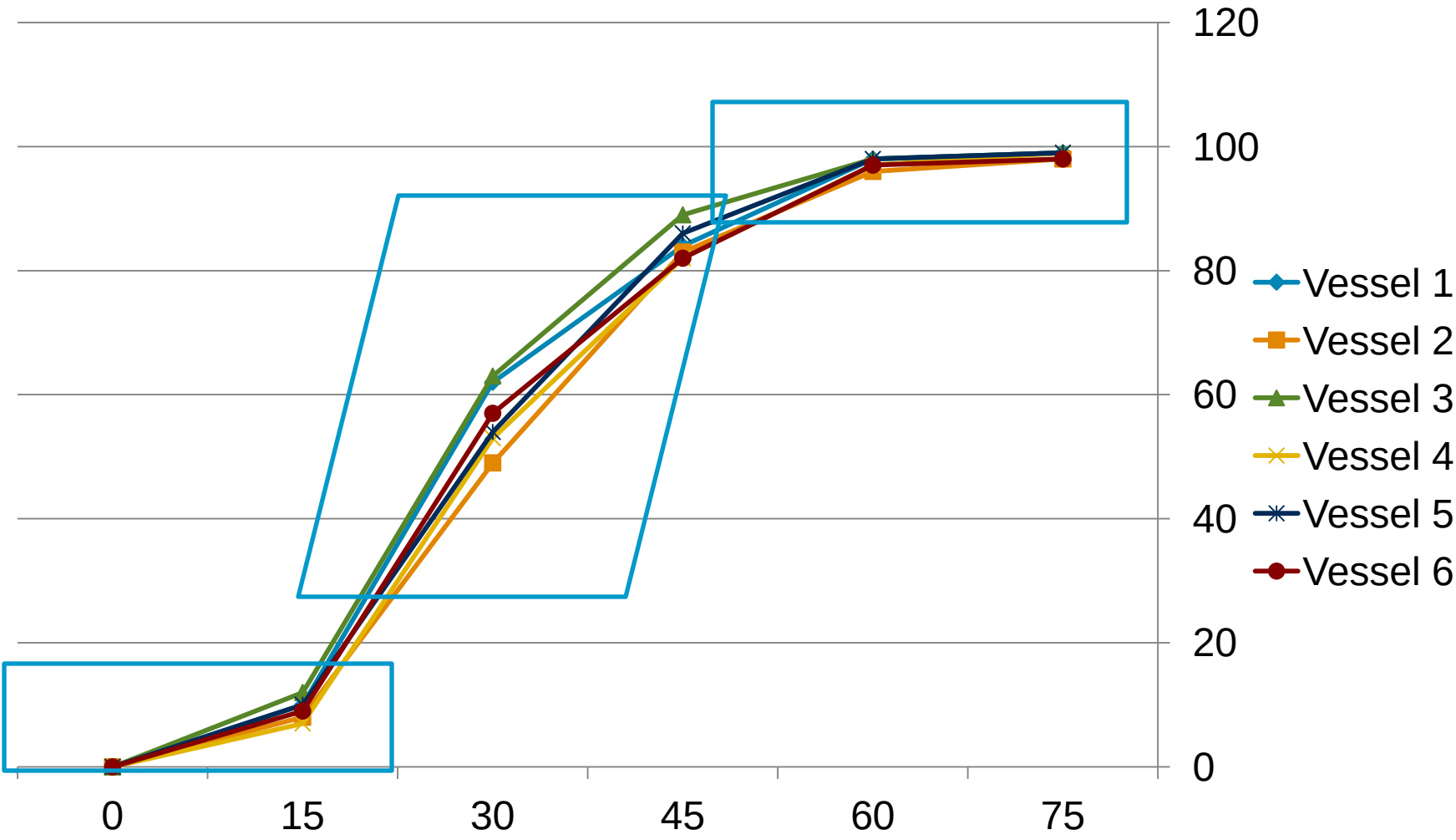


What does a proper method exhibit?

- Low variability (<20% at initial timepoint, <10% at later points)
- Proper understanding of dissolution release
- Discrimination between batches
- Reproducible results



Dissolution Data



1st runs for Apparatus 1/2

For most products, try paddles first

- 50, 75, 100 RPM
- 2-3 media from solubility studies, surfactant if needed
- Deaeration is important
- Evaluate for potential issues
 - Floating, dancing, spinning, etc. dosage forms
 - Coning Issues
 - High variability
 - Release too high/too low



Acceptable Method Requirements

- Low – Moderate Variability
- Complete Release (85%+ or Asymptote)
- Characterizing timepoints below 85%
- Challenged with other formulations
- Evaluated to ensure they are rugged and reproducible enough for repeated testing by multiple people/units



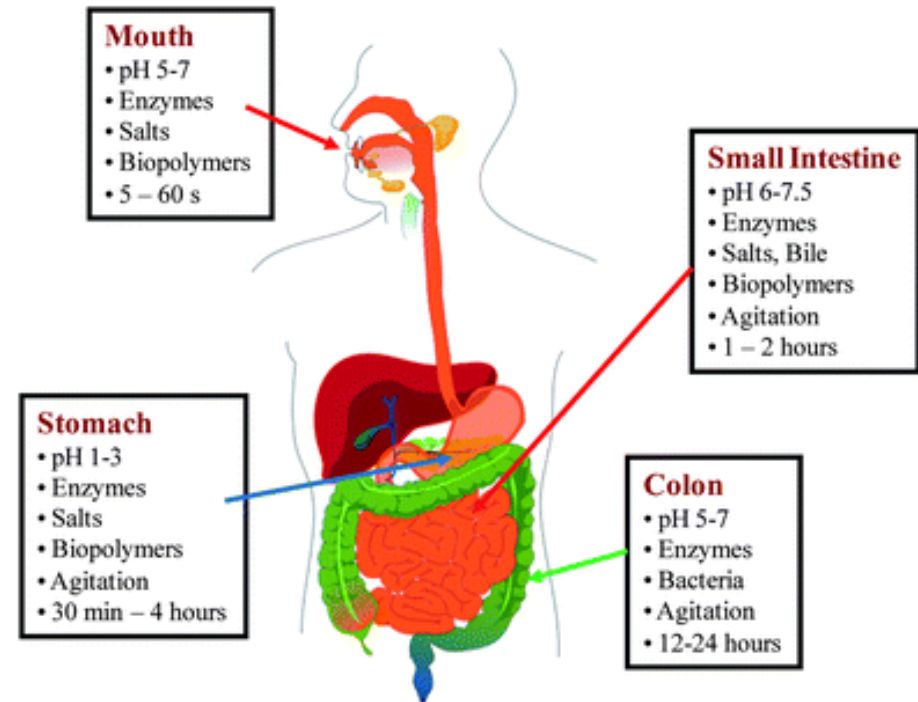
Areas with most robustness issues

- Developing method on unfit system
- Not meeting sink conditions
- Degassing needs not defined
- Sampling Issues
- Filter selection/use
- Cleaning/carryover
- SOP writing unclear



The Ideal Dissolution Media

- Meets sink conditions
- Simple preparation
- Drug is Stable in media 24 hrs+
- Uses as little extras as possible
 - Surfactants
 - Alcohol
- Biologically relevant for site of dissolution in vivo
 - IR typically in acid
 - DR typically in acid, then neutral
 - MR typically in neutral solution



Determination of Solubility

For proper dissolution, you first need media which is capable of dissolving 3x your API

This is referred to as sink condition



Sink Condition

Having sink conditions met means that the amount of drug dissolved already in the media should not impact the dissolution rate as the run progresses.

If sink is not met, the rate will artificially slow as the API nears saturation

- Overly discriminatory
- Not reflective of in vivo environment



Media Selection

- Solubility screen in multiple media should be done to determine optimal solubility
 - pH 1.1
 - pH 2-3
 - pH 4-5
 - pH 6.8
 - pH 7.5
- If needed, use as little surfactant as necessary
- Evaluate multiple surfactants (pay attention to grades and vendors)

Rules of Thumb for Media Limits

- Surfactants below 1% tend to be accepted w/ appropriate checks that lower limits aren't acceptable
- >1% require greater scrutiny, other surfactants usually
- >1.5% tends to be very difficult to handle with automation
- Alcohol is generally a last resort – unless doing a dose dumping study specifically
- Stay within pH 1.1 – pH 7.5 if at all possible



Media Cautions

- Be careful with water
 - No buffering capacity
 - Quality can differ b/w sites
 - Quality can differ b/w DI systems, filters, etc.
- Check pH before and after run to ensure buffering capacity is acceptable
- Beware of methods needing tight pH limits
- Do not use SLS with Potassium Phosphate Buffers – Sodium Phosphate only

Degassing

Media should be degassed per USP unless another approach is validated

- Heat to 41-45 C
- Vacuum degas through 0.45um filter
- Hold under vacuum 5 minutes after media has passed through



Common Degassing Methods

Acceptable Methods

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

Unacceptable Methods

- Nitrogen Sparging
- Sonication

*when validated against USP method



Agitation Rate

- Should be sufficient to allow for media to interact with dosage form
- Too much agitation can result in non-discriminatory profiles
- Baskets – 50-100 RPM
- Paddles – 25-100 RPM



Apparatus 1 and 2

For solid oral dosage forms, dissolution method development should begin with Apparatus 1 and 2

- Well understood
- Flexible for a variety of methods
- Easily Transferrable



Sinkers

Dosage forms should not float or move during the dissolution as this will greatly increase variability.

A Sinkers is necessary is floating or moving is seen

Sinkers should be chosen based on:

- Media access
- Weight
- Reproducibility
- Hydrodynamic Impact



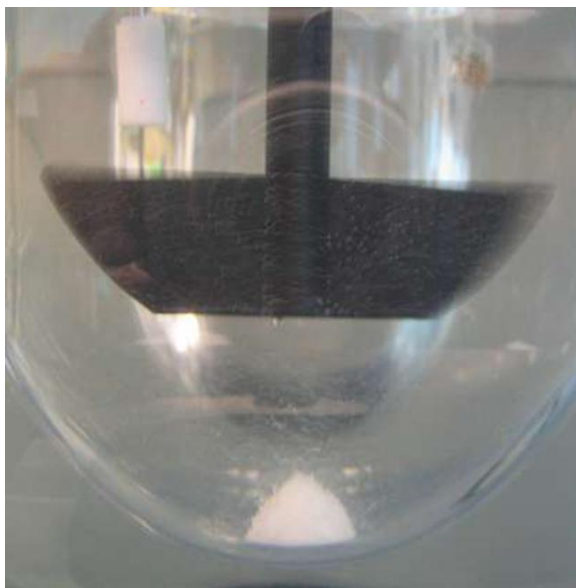
Coning

Coning is a normal and expected occurrence for disintegrating dosage forms

Coning may still be present if drug is fully dissolved

Cone should be moving somewhat

If Severe, Peak Vessel or Apparatus 3 can be used with justification



Coning Problem



Apparatus 3 – Bio-Dis

- 300mL standard volume
- Able to expose each dosage form to 6 media changes
- Programmable dip speed in each row
- Allows to more closely mimic in vivo conditions
- 10 cm stroke distance



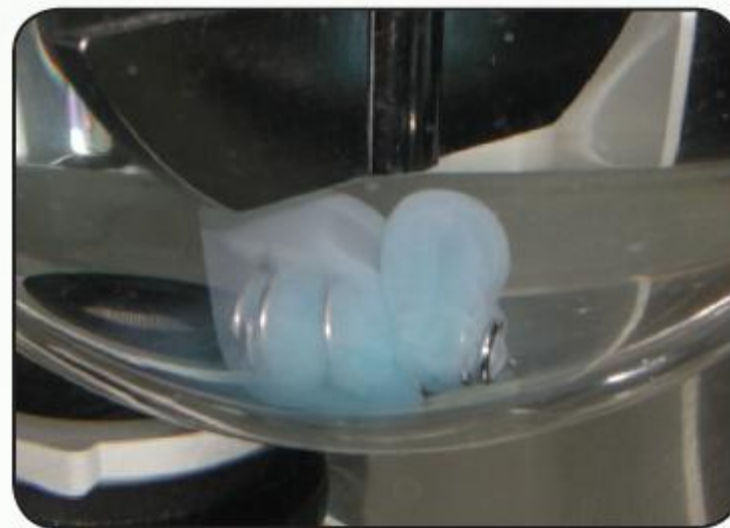
Cross-linking and Capsule Shell

Cross-linking of capsule shells can result in hardened and chemically resistant shells.

- Delay opening
- Trap Drug Product
- Pellicle Formation

If Cross-Linking is seen, testing with pepsin or pancreatin should be performed

Opening time important regardless of cross-linking in MD



Pellicle Formation Problem



How To Sample Properly

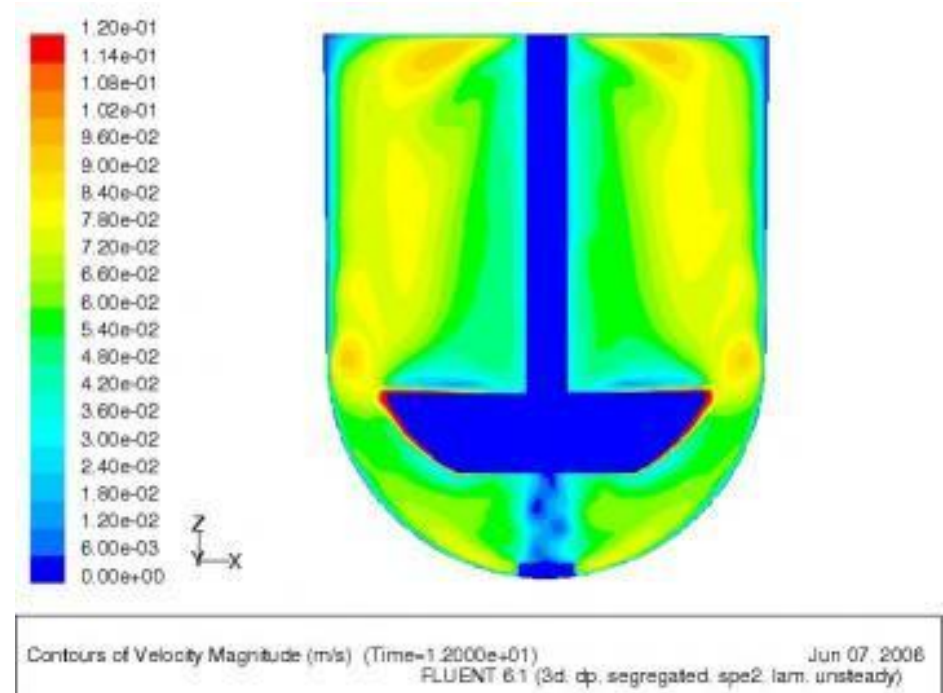
Filtration Must Occur at USP Location and at Appropriate Time

- $\pm 2\%$ from timepoint or 15 minutes (whichever less)
- Halfway between top of paddle or basket and media
- No closer than 1cm to vessel wall
- Recommend not sampling close to shaft due to poor hydrodynamics

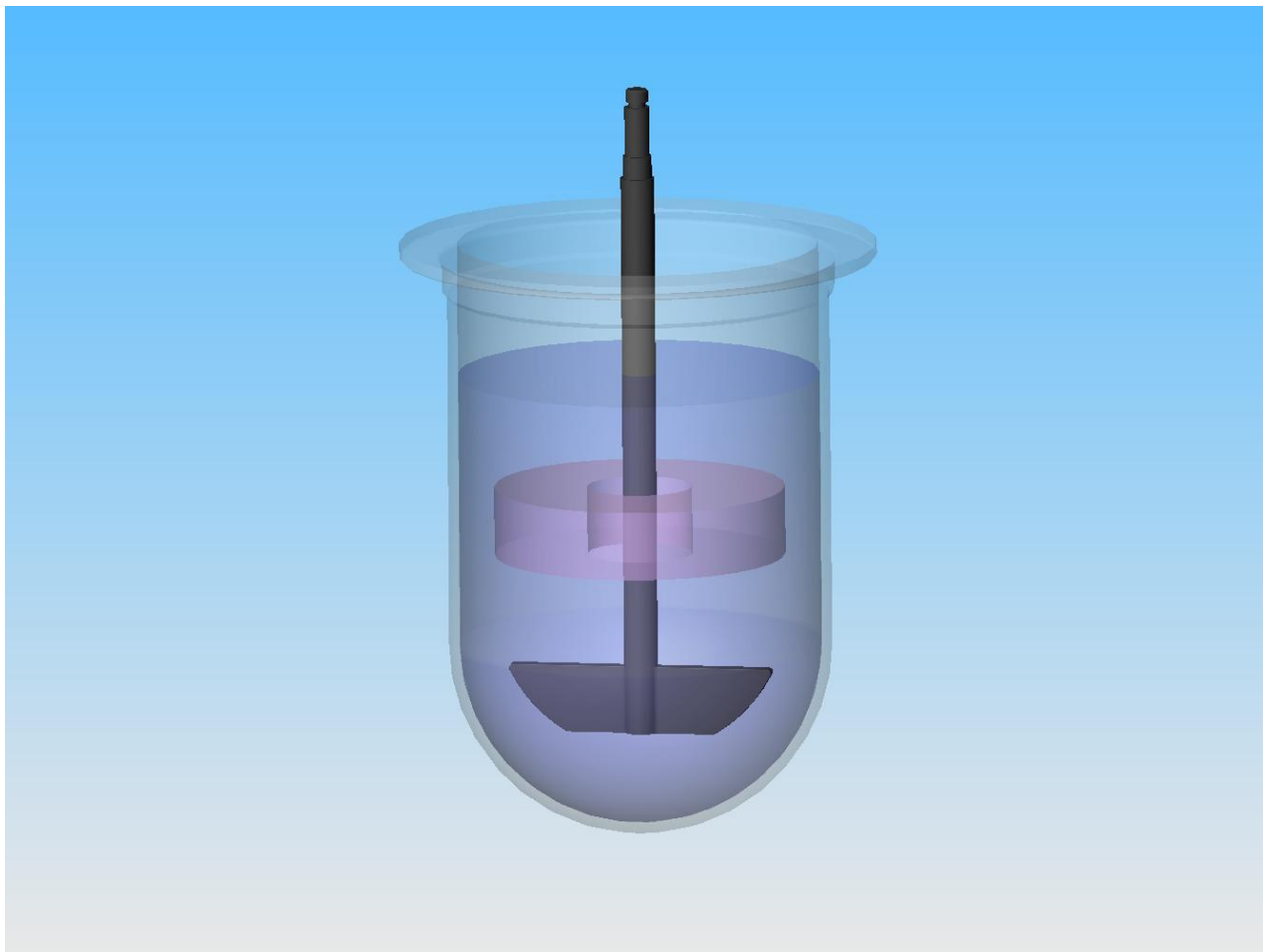


Why is the Sampling Location So Important?

You need to sample in an area of reproducible hydrodynamics and a representative concentration



The Sampling Donut



Automated sampling

Automated sampling can eliminate many of the variables w/ manual sampling:

- Time
- Location
- Pull force

Method must always be validated a manual method, and automation shown to be equivalent



Filter Selection

Filtration stops the dissolution process.
Filtration must:

- Occur during or as soon after sampling as possible
- Use a validated filter(s)



Centrifugation is **not** a replacement for filtration



How Do I Validate A Filter?

3 Factors Should Be Tested:

- Efficiency – does it remove undissolved drug?
- Leachability – does it leach a coeluting peak?
- Adsorbance – does the filter hold drug?



Validating a Filter

Efficiency:

Take 3 samples with filter

Sample 1 – scan immediately

Sample 2 – sonicate 5 minutes and read

Sample 3 – sonicate 10 minutes and read

If <1% increase, filter is acceptable

Leachability:

Take filtered sample of blank media

If there is a peak >1% of standard response then a different filter is needed or a pre-rinse



Validating a Filter

Adsorbance

Filter standard in small aliquots, 1mL at a time and analyze individually. When you reach 99% recovery, filter has been properly filtered.

Method will need to define amount to waste

Aliquot	% Recovery
1 st mL	94%
2 nd mL	96%
3 rd mL	98%
4 th mL	99%
5 th mL	99%



Cleaning

Cleaning is often not validated to ensure that it is effective in:

- Removing drug from dissolution unit from previous run
- Removing residues from surfaces and sampling paths
- Preventing corrosion



Cleaning The Apparatus

- Clean as soon as possible after run
- Soap and Water usually effective
- Raise head and clean spindles
- Remove vessels, back first
- No abrasives!
- Handle baskets with care (sonicating in alcohol preferred)
- Replace components to bath or proper storage containers



Autosamplers/Carryover

Carryover and proper cleaning should be validated if using autosamplers:

- Multiple clean cycles may be needed
- Hot Water and Alcohol work well for many samples
- Difficult samples may require cleaning w/ each timepoint
- Carryover should be checked by sampling disso media post cleaning and verifying <1% carryover vs. standard

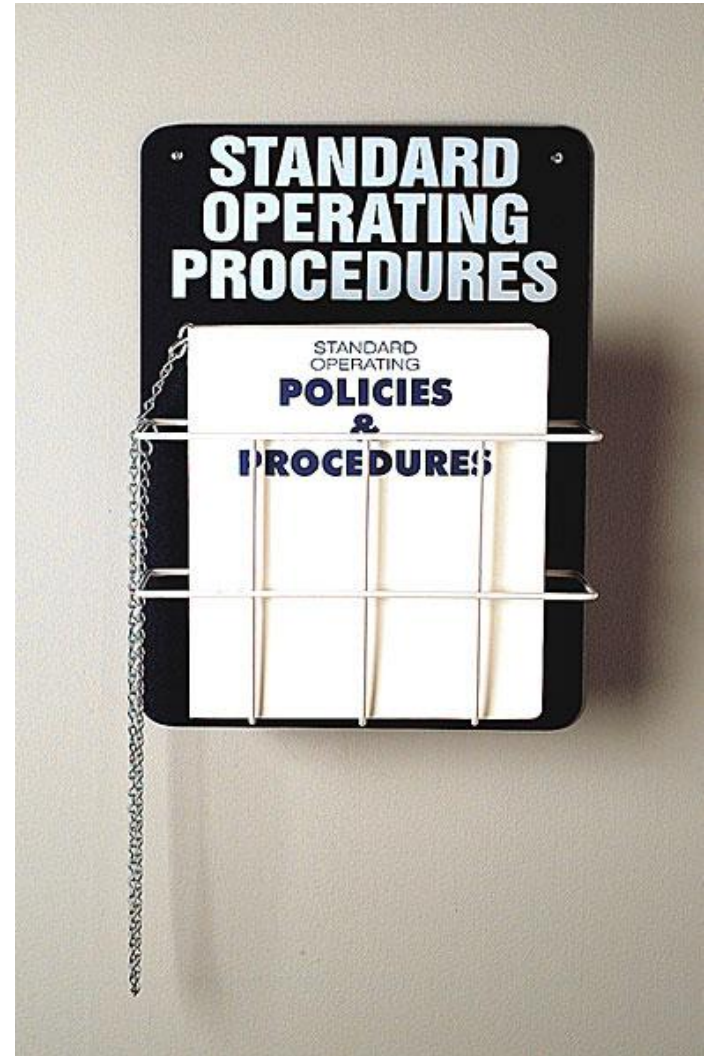


SOPs

A properly written SOP along with training is critical to ensure dissolution method is properly performed

Define:

- Dissolution conditions
- Filters used
- Media prep + degassing
- Sinkers
- Special concerns



“Or Equivalent”

The use of the term “or equivalent” is often used to widen the SOP for future changes

Can be problematic as items thought to be equivalent, may not be equivalent:

- Filters
- HPLC Columns
- Reagents used in Media Preparation
- Product contact equipment



SOPs

- Recommend replacing “or equivalent” with “or another validated...”
- Have SOP reviewed by someone else to ensure variables have been captured – similar to intermediate precision
- Once SOP is signed, train employees on use



Method Development Resources

- USP <1092>
- FDA Dissolution Method Database (<http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>)
- Dissolution Discussion Group (www.dissolution.com)
- Dissolution Technologies (www.dissolutiontech.com)
- LinkedIn “Dissolution” and “Dissolution Challenge” groups

Dissolution Exchange

<http://dissolution.chem.agilent.com/>

New Dissolution Focuses website which is a one-stop location for information



- Online course on dissolution fundamentals
- FAQs
- Dissolution Hotline
- Dissolution Discussion Group
- Previously recorded webinars on various topics including MQ
- Upcoming Talks

Upcoming Calendar

March 6th – Session 2 – Validating Dissolution Methods

April 3rd – Transferring Dissolution Methods

May 1st – Troubleshooting Differences Between Labs

Register at: <http://dissolution.chem.agilent.com/>

Dissolution Method Development Webinars at:

<http://www.dissolution.com/>



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