Transferring Dissolution Methods
Session 1 – Building a Robust Dissolution Method

Ken Boda
Applications Engineer
Agilent Technologies
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 with 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*

*when validated against USP method

Unacceptable Methods
• Nitrogen Sparging
• Sonication
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 Sinker is necessary if 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.
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 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.
How To Sample Properly

Filtration Must Occur at USP Location and at Appropriate Time

• +/- 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 can eliminate many of the variables with manual sampling:

- Time
- Location
- Pull force

Method must always be validated as 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.

<table>
<thead>
<tr>
<th>Aliquot</th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; mL</td>
<td>94%</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; mL</td>
<td>96%</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; mL</td>
<td>98%</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; mL</td>
<td>99%</td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt; mL</td>
<td>99%</td>
</tr>
</tbody>
</table>
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
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/
Feel free to contact me

Ken Boda

Ken.boda@agilent.com

http://www.linkedin.com/in/kenboda

919-677-6797