

Volume 19, Issue 3

Page 1

Are You a Member of the
Dissolution Community?

Page 2

Broaden Your Dissolution
Horizon

Page 4

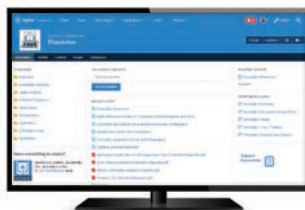
Dissolution Filtration Do's
and Don'ts

Page 7

Questions You Asked

Are You a Member of the Dissolution Community?

Allan Little, Director of Marketing, Dissolution



Agilent is committed to providing you with all the information you need to use and maintain our equipment. To that end, we've created an Agilent Dissolution Community accessible from www.agilent.com.

The recently launched Dissolution Community gives you access to Agilent application and technical support. You can search for product information, review frequently asked questions, or post a question yourself.

To join, visit www.agilent.com today and click **RESOURCES > Agilent Community > Dissolution** to access the Dissolution Community.

From there you can join the Agilent Community and solicit help on not only dissolution, but many other product areas as well.

The Agilent Community is dedicated to owners of Agilent instrumentation and software. To post a question (or search the archive) of the dissolution community at large, visit the Dissolution Discussion Group at www.dissolution.com.

Broaden Your Dissolution Horizon

Karen Krauel-Göllner, Product Manager, Dissolution

Bryan Crist, Scientific Affairs Manager, Dissolution

Are you new to dissolution? Or could you do with a refresher on the latest regulatory developments?

The Agilent dissolution team offers a unique series of seminars tailored to your needs. We provide the latest in theory, techniques, and hands-on training for those involved with dissolution testing.

Our instructors include Agilent employees with close links to industry, as well as prominent scientists from academia and the dissolution industry.

The courses are not disguised sales presentations. All course materials are vendor-neutral and designed to provide a solid base of knowledge. Also, course materials are relevant to a GMP environment. Our chemists understand the latest regulations and what it takes to comply.

These courses are offered at various locations around the world and can also be scheduled at your facility.

For more information on dates or to request a seminar, please contact the Dissolution Hotline:

Dissolution.hotline@agilent.com



Topics include:**General**

Fundamentals of Dissolution (4 hrs)

Dissolution Aberrant Data Investigation (60 min)*

Overview of In Vitro Dissolution (20 min)

The Dissolution Procedure (60 min)*

The Benefits of Dissolution Automation in Your Laboratory (45 min)

Trends in Small Volume Dissolution Testing (60 min)

Agilent Dissolution Product Portfolio 2018 (20 min)

Applications of USP Apparatus 3: Reciprocating Cylinder (25 min)

Concepts of Qualifying Non-Compendial Apparatus (40 min)

Dissolution SOPs: Do What You Say and Say What You Do (45 min)

Breaking Bad... Dissolution Habits (60 min)*

Dissolution and the Analytical Method Transfer (45 min)

USP Apparatus 7: Reciprocating Holder Apparatus (20 min)

Compendial

USP <1058> Analytical Instrument Qualification (Revision) and Its Impact on Dissolution Apparatus Qualification (30 min)

USP <1724> Semisolid Drug Products Performance Tests (25 min)

USP <1092> The Dissolution Procedure: Development and Validation (25 min)

USP <1087> Apparent Intrinsic Dissolution (20 min)

USP <1711> Dissolution Procedures for Oral Solid Dosage Forms (30 min)

USP <1236> Solubility Measurements (15 min)

USP <711> Dissolution and <1094> Capsules: Dissolution Testing, Crosslinking, and Related Quality Attributes (25 min)

USP <724> Drug Release Testing and Analysis of Transdermal Systems (30 mins)

Regulatory

FDA Guidance: Dissolution Testing and Acceptance Criteria for IR Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances (20 min)

FDA Guidance: Dissolution Testing of Chewable Tablets (25 min)

PIC-S Pharmaceutical Inspection Cooperation Scheme (15 min)

Enhanced Mechanical Qualification of the Dissolution Apparatus (60 min)

** Select no more than one since these three topics are variations of each other*

Dissolution Filtration Do's and Don'ts

Bryan Crist, Scientific Affairs Manager, Dissolution

In the dissolution test, the filter has two primary requirements:

1. It must stop the dissolution process.
2. It must clarify the sample for analytical measurement.

Many filter types and pore sizes are available that should cover these two requirements adequately. Filters used in the typical dissolution test range from 0.45 μm up to 70 μm .



In this article, we will suggest considerations for the proper use of filters to ensure that they provide the best performance. The examples provided are commonly used for manual filtration of dissolution samples. The same considerations should be applied to filters used with automated equipment. However, automation may also present additional challenges to filters. This is due to the higher volumes that may be passed through a filter because of the length of sample lines and multiple timepoint use. If the sample is difficult to filter, multiple filters may be required to handle large amounts of suspended materials, which may block the primary filter flowability.

Use the proper filter

Do use the exact filter specified in the dissolution method. Otherwise, ensure that the filter you are using has been properly validated in terms of stopping undissolved particles from passing through and that it does not unduly bind the active drug substance. For assistance with the validation of filters, please refer to the Agilent publication "Dissolution Filtration: Requirements, Validation and Troubleshooting" www.agilent.com/lifesciences/filter_validation. Because there are so many filters available from a variety of manufacturers, we may often see the term "or equivalent" to describe that an alternative to a specific filter and manufacturer mentioned in the method may be used. As a caution, before the terms "or equivalent" may be used in any method, the validation should have demonstrated equivalence under similar conditions with each of the filters to ensure that they are truly equivalent. The original validation should list the filters that were tested and found to be identical in performance to the filter listed.

Don't use filters that have not been properly validated or listed as equivalent filters. Unvalidated filters may let undissolved particles through if the porosity is too large or may bind the drug substance.

Filter conditioning

Do ensure that the proper volume of sample is flushed through the filter to avoid binding the drug substance when collecting the filtrate. The volume required to flush through a filter must be contained in the dissolution method, and this volume should have been validated on the lowest concentration, which is usually the first timepoint. In other words, when a filter is validated profiling the release rate of a formulation, the concentration of the timepoint should be used to determine the volume that should be flushed through a filter prior to collection for analysis.

Don't skip this conditioning process for filtration. Remember that membrane filters sometimes exhibit more binding characteristics than cannula tip filters. If the filter is used for subsequent sampling points within the run.

Direction

Do pay attention to the direction that the sample will flow through the filter. Most filters are uni-directional. That means the flow through the filter should occur in a single direction, which is usually pushed from the luer-lock side that is commonly attached to a syringe or pumping source. These filters have a support that keeps the filter from rupturing when pressure builds during the filtration process. If an opposite direction is desired or if flow is intended to move through a filter in both directions, bi-directional filters are available and should be used.

Don't use a filter in the wrong direction, for instance by pulling through the filter when connected to a syringe. This could rupture the membrane and allow undissolved drug and excipients to pass into the sample for analysis.

Back pressure

Do expect some back pressure when using membrane filters. Due to excipients and drug load, some samples may be quite difficult to push through an 0.45 µm filter. If sampling for UV, then cannula tip filters may be preferable if they stop the dissolution process. Due to hydrophobicity of some membrane filters, alternative filters may be better suited for filtering aqueous samples. Membrane compatibility charts from most filter manufacturers may be especially useful in membrane selection for dissolution samples.

Don't use glass syringes for samples that build significant back pressure. For automated sampling systems that are dealing with difficult samples, it is important to remember: if you have difficulty manually pushing 10 mL of sample through a syringe filter, then automated sampling systems will not perform any better than the strength of human hands.

The 2% rule

Do filter the sample immediately when withdrawing from the vessel because the USP requires that samples be taken within $\pm 2\%$ of the time they are dropped, and we do not have a dissolution sample until it is filtered because the filter stops the dissolution process. When introducing dosage forms to dissolution media, allow sufficient time to acquire and filter the samples at each timepoint.

Don't pull all six samples then begin pushing through filters afterward, as this may easily exceed the time required for "obtaining" samples. Remember that the dissolution process continues until filtration is performed. Paper or drip filters are not suitable for clarification because the sample is still in contact with undissolved particles for an excessive time.

These suggestions are provided to ensure the proper use of filters for dissolution samples. Due to its simplicity, the filter may easily be overlooked in troubleshooting issues that may occur during a dissolution test where, in fact, the use of the filter *may be the cause* of problems in dissolution testing. Our procedures state the filter to be used, but our training should center around the proper use of filters to stop the dissolution process and clarify it for analytical measurement. In closing, it is vitally important that filters are used as intended to protect the integrity of the sample concentration.





Questions You Asked

- Q.** We are developing dissolution method for an oral suspension and when we introduce the sample with a syringe into non-rotating medium it pools in the bottom of the vessel and the results are out-of-specification (OOS). What can we do?
- A.** USP <711> requires that we drop dosage forms into non-rotating media. However, since this appears to be a dissolution anomaly in which the product is pooling, which would not happen in vivo, you should be able to justify introducing the sample into media while stirring. Viscous suspensions often encounter this problem, especially when the media speed is low; 25 – 50 RPM, and it may be warranted to introduce it into moving media which in this case would be more biorelevant than allowing it to remain trapped in the lower portion of the vessel. In justifying, you should document the OOS at the lower speed as a reason to justify introducing the sample into rotating media. While increasing the speed may seem like a solution, this may greatly reduce the discriminatory power of the test for the suspension and for this reason, introducing into moving media may be preferred.

Learn more:

www.agilent.com/lifesciences/dissolution

Agilent Community:

<https://community.agilent.com/>

Register to receive the eNewsletter quarterly by email:

<https://www.agilent.com/en/promotions/practical-solutions>

Buy online:

www.agilent.com/chem/store

Contact Agilent's dissolution chemists:

dissolution.hotline@agilent.com

U.S. and Canada

1-800-227-9770

agilent_inquiries@agilent.com

Europe

info_agilent@agilent.com

India

india-lsca_marketing@agilent.com

Asia Pacific

inquiry_lsca@agilent.com

This information is subject to change without notice.

© Agilent Technologies, Inc. 2019
Published in the USA, June 25, 2019
5994-0988EN

