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Dissolution Mysteries Solved: Interview with a Dissolution Expert, Part 1

Eleanor Lovelock, Technical Writing, Dissolution Systems

Through the next few editions of Practical Solutions, we'll be interviewing a true dissolution expert: Mr. Bryan Crist. Bryan is a deeply respected expert who has sat on committees for the USP and has overseen some massively important changes within dissolution. Bryan has over 20 years of experience in dissolution, beginning in the pharmaceutical industry working directly with Abbott Laboratories, Merck Group and Bristol Myers Squibb before moving through to the development side of dissolution analytical instruments with VanKel Technology Group and Varian Inc., now a part of Agilent Technologies.



Figure 1. Dissolution testing is essential for pharmaceutical development.

A valuable source

Stephen Mayock, Director of Analytical Development and Quality Control at Collegium Pharmaceutical, Inc., says that “Bryan Crist has been a teacher, technical resource, colleague, and friend of mine since I got started in the pharmaceutical industry over 30 years ago. Bryan has always been a valuable source of information in the area of dissolution, but more importantly, he has done this not just as a professional but as someone who cares about you and your concerns.”

Improve your dissolution

We sat down with Bryan to ask him some questions about both the fundamental aspects and more complex areas of dissolution.

Practical Solutions (PS): To many people, dissolution testing is completely unknown, however, it is highly regulated in modern medicine and critical for pharmaceutical development. Why is dissolution testing so important?

Bryan Crist (BC): I think most people are familiar with just an oral drug [that will] dissolve and eventually permeate into the bloodstream to render some type of therapeutic effect. It's simple, actually: anytime you have a solid, it has to be soluble. It must be in a solution before it can permeate and then build up a concentration in the bloodstream. It's unique that the dissolution test is quite simple, except its environment is quite different from a stomach. It's more of a glass vessel and a spindle, but it has to be precise and controlled to be able to compare formulations. This is the essence of dissolution and why proper testing is so important to properly evaluate drugs.

PS: I know over the years the educational courses you've given for dissolution have taken you all over the world. You've effectively been a nonstop global traveler visiting companies and teaching all around the globe. As part of that, could you give us a little insight into your experience of global dissolution testing?

BC: Well, internationally I think things are fairly similar as far as the approach to dissolution and its importance. It really goes to the point of the pharmacopeias. There's been some effort to harmonize several of the world's pharmacopeias, primarily the European pharmacopeia, the Japanese pharmacopeia, and the US pharmacopeia. There are other major pharmacopeias, particularly China's, which has been in development (and has been for many years) and is now mature.

“...anytime you have a solid, it has to be soluble. It must be in a solution before it can permeate and then build up a concentration in the bloodstream.”

– Bryan Crist,
Dissolution Expert

[Global dissolution teaching] is not necessarily as simple as it sounds. If there are two different approaches or specifications, it's hard to meld them into one document that is consistent. For instance, the basket—a 40-mesh basket is primarily used in Europe and the Americas,

while in parts of Asia it's different, mostly because the Japanese pharmacopeia historically used a 36-mesh basket. Dimensions have been made to cover them both but it's very important in the documentation to really describe what mesh basket you're using because they provide different release rates.

Internationally I think the harmonization effort has done a lot, for not just dissolution but many other methods in testing to standardize that process so drugs can be tested similarly and transfer globally from one country to another much more easily.

PS: Your reputation has grown around the globe through your career. I know over the past 20 years, you've sat on the former USP and various Expert panels currently, Biopharmaceutics Expert Committee, AAPS In-Vitro Dissolution Committee, you're a member of the Controlled Release Society, the American Chemical Society... basically you've had a huge range of amazing influence. You've overseen some massive changes, not least in qualification, compliance, data integrity—these topics which have grown to such importance throughout the pharmaceutical world. From your background, how would you guide someone new to dissolution to make good decisions from the beginning?

“Most pharmaceutical companies [...] really drive home the importance of good manufacturing practices”

– Bryan Crist,
Dissolution Expert

BC: I think when most pharmaceutical companies bring new people aboard, they really drive home the importance of good manufacturing practices. The US FDA has its Code of Federal Regulations (CFR), which it enforces to ensure they're followed. Many countries have the same type of principles, also known as GMP—good manufacturing practices. Chemists are trained to follow these. GMP is really a whole organization of systems in place to make sure that testing is done correctly: that methods are followed, that they're scientifically accurate, that they've been validated, that instruments that are used have been qualified.

I think a big part of my career has been enforcing the use of well-structured GMP to be able to guide people and their decision making.



Figure 2. Basket dimensions have been a key aspect of international harmonization.

Some companies have a pretty elaborate bootcamp where employees are trained well in the handling of products, in how to measure things, in how to use analytical instrumentation and, very importantly, how to document. This GMP umbrella is what I spent much time in the past developing seminars and courses about. It helped people assimilate to the pharmaceutical world. It has been quite an honor to be on some of the committees I've been on with USP and other international agencies and pharmacopeias.

Questions and answers have been adjusted for clarity.



Bryan Crist
Dissolution Expert

Bryan is internationally recognized as an expert in the field of dissolution with more than 35 years of pharmaceutical testing experience.

Look out for our next Practical Solutions newsletter for the next two further installments of our three-part interview with Bryan.

Dissolution Product Support, Education and Resources: We've Got You Covered

Dan Spisak, Product Manager, Dissolution Systems

No matter your question, we can help

- Do your laboratory personnel lack experience or training?
- Does your Agilent 708-DS Dissolution Apparatus have the latest firmware?
- How does the USP recommend testing semisolids?
- What is the impact of moving to Mechanical Qualification for your Dissolution Apparatus?

Find the answer to questions like these by taking advantage of the various resources provided by the Agilent dissolution team. The following list will help guide you to the proper source of information to keep your lab updated and running smoothly. Connect with our team of experts to make sure you are able to take advantage of all the benefits of partnering with Agilent for your dissolution needs.

Agilent Dissolution Resources

Connect with an expert for all your dissolution needs



Education

From fundamentals to expert-level, there's always something new to learn.

Dissolution 1-on-1

Access this free, self-paced, online course to learn dissolution fundamentals, technique, regulations, and more.

www.coacssoftware.com/Dissolution2

Dissolution webinars

Browse a vast repository of recordings with topics ranging from qualification practice to method development to updated regulatory guidance.

www.agilent.com/chem/dissolution-webinars

Labcast OnDemand

Want a live product demo? Do you need product support? Contact us at the Dissolution Hotline to request a virtual session with our team.

dissolution.hotline@agilent.com



Product info

Looking for brochures, manuals, product updates or application-based information?

Dissolution product information

For the latest product information, including brochures, videos, specifications and more, visit our website.

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Accessories in the online store

The easiest way to order replacement dissolution accessories or consumables and keep your lab stocked with the necessary supplies.

www.chem.agilent.com/store

Dissolution sourcebook

The complete PDF and virtual catalog of all Agilent dissolution products and accessories. **Download it today.**

www.agilent.com/chem/dissolution-source-book



Failing results?

Are you having problems developing methods or finding the source of dissolution testing errors?

Dissolution discussion group (DDG)

Dissolution Discussion Group provides a free forum for international discussion for dissolution users. Recorded sessions are also available. **Registration recommended!**

www.dissolution.com

Agilent dissolution hotline

Contact us with any questions related to product, industry, or application-based information.

dissolution.hotline@agilent.com

Agilent community

Agilent Community is the best place to locate information and find trusted answers about dissolution products, best practices, and applications.

www.agilent.com/chem/dissolution-community

Dissolution Product Updates: New Software Release

Dan Spisak, Product Manager, Dissolution Systems

Version 1.7 of the Agilent Dissolution Workstation (DWS) is now available. This update replaces version A.01.05. A series of improvements is contained in this release, including:

- Implementation of the new Agilent NanoDis System for automated nanoparticle dissolution testing (visit www.agilent.com/chem/nanodis for complete details)
- Enhanced e-signature capabilities with five customizable levels of test report review
- Validated for use with updated Microsoft SQL Server (version 2019)

An update to the Agilent Cary WinUV Dissolution Software that supports Agilent Online UV-Vis Dissolution Systems has been released.

Version 5.2.2 now accommodates:

- Support of methods utilizing Agilent USP Apparatus 5 (Paddle Over Disk) and Agilent USP Apparatus 6 (Rotating Cylinder) for transdermal patch testing.
- Enhanced data processing functionality to execute methods with an increased number of time points.
- Compatibility with current version (5.1.3) of the Agilent Spectroscopy Configuration Manager Software and Agilent Spectroscopy Database Administrator Software to facilitate 21 CFR Part 11 compliance.

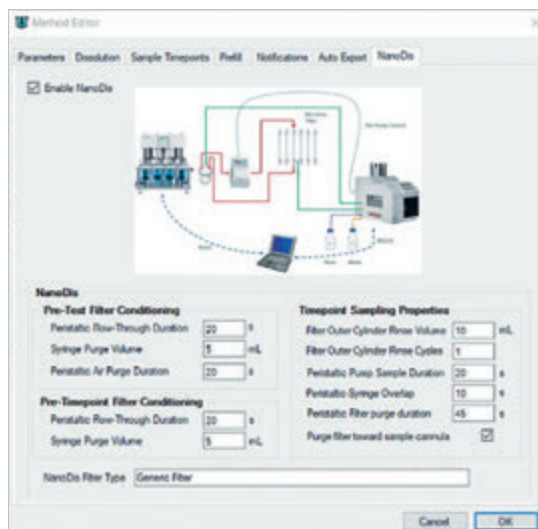


Figure 3. The Agilent Dissolution Workstation Software (DWS) helps make your workflow compliant.

Learn more

Existing users should contact their Agilent representative for upgrade details of current systems. For more details about the Multicell or Fiber Optic Online UV-Dissolution systems, please visit:

www.agilent.com/chem/online-uv-dissolution

Questions You Asked

Variability of results when troubleshooting an online UV dissolution system

Q We have an out-of-tolerance (OOT) warning for a product with two active substances. The results are within limits, but out of trend with respect to the previous test point, and the variability between time points is also higher than expected. Testing was performed originally on two separate online UV systems with 1 mm flow cells and the original results were not out of trend, but we had more concern about excessive variability.

Another investigation had been conducted earlier for the same drug product due to high values in results and the root cause was attributed to equipment. We feel that the issue may be due to turbulence issues in the individual test solution cuvettes because readings are taken immediately (as stated in our procedure). Is it possible that turbulence could be an issue for a product that has historically been quite sensitive?

A When a product contains two active drugs and both have variable results, it could be viewed as related to the product issue, an equipment issue or a procedural one. From the description, it appears to be a procedural or method problem due to the excess of movement of aqueous sample within the cuvette as mentioned. Observing that a 1 mm flow cell was required for this test, it could be part of the problem with variability.

When fluids move through a flow cell, the turbulence causes refractive issues within the cuvette which can scatter light with high variability. This phenomenon is commonly referred to as Brownian motion and it has a dramatic effect on accurately measuring UV absorbance of components within a moving fluid. Due to this, the fluid motion must stop for a few seconds prior to taking absorbance readings. Software with Online UV-Dissolution automated systems should allow you to enter a “dwell time” so once a cuvette is filled, it sits idle for several seconds without movement before the reading is taken. It sounds to me that this may potentially be a problem since the method appears relatively straightforward.

The only other recommendation that comes to mind is a potential degassing issue. 1 mm cuvettes are notorious for air bubbles forming inside the flow cell, and without proper and efficient degassing, bubbles will form which unfortunately causes similar variability, which cannot be readily seen during the analytical portion of the test.

Got a question of your own?

Submit it to our dissolution hotline at dissolution.hotline@agilent.com for an answer.

Learn more:

www.agilent.com/chem/dissolution

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<https://community.agilent.com>

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