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Dissolution Mysteries Solved: Interview with a Dissolution Expert, Part 2

Eleanor Lovelock, Technical Writing, Dissolution Systems

Through the previous and next few editions of Practical Solutions, we've been interviewing a true dissolution expert: Mr. Bryan Crist. Bryan is a deeply respected dissolution expert who has sat on committees for the USP and overseen some massively important changes within dissolution.



Figure 1. Seminars and learning are key

Interview, part two

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

More from Bryan

PS: To continue on from previous issues, we've been talking to you, Bryan, about best dissolution practice. What many may not realize is how instrumental you've been in the development of many of the products here at Agilent. Many of them have had your guidance, especially some of the small volume testers such as the Agilent 400-DS Apparatus 7 and novel dosage forms with microparticulates.

We're more and more not just seeing microparticles; we're moving to see nanotechnologies. This might seem like something of a sneak peek, however I'm wondering what insights you can share with some of the R&D teams for what's coming up with micro- and nanoanalysis and what's happening in this new field.

BC: Over the years, drugs have gone from oral dosages to being far more targeted. The problem with oral drugs and transdermals is that they're systemic; they're going to go in and circulate all throughout your body and may cause unwanted side effects. They move through the body in an equal concentration to render a therapeutic effect at a site.

"It's an ever-evolving thing and drug design gets more efficient and effective."

– Bryan Crist,
Dissolution Expert

USP has changed their taxonomy regarding how they look at drugs according to their route of entry. There's oral, pulmonary, inhalation, injectables or parenterals. A lot of these routes, particularly the targeted drug delivery and parenterals—for example where a drug is directly injected into a tumor—are very difficult to work

with as their concentrations are extremely low. They might be in the nanogram or picogram levels of release per day, which may go on for weeks or even months. Previous dissolution equipment was more macro-scale in comparison to what's needed today, so instead of one liter, dissolution is being performed in 900 milliliters. We're looking more at trying to dissolve drug products in five or ten milliliters in order to keep the concentration high enough where we can see it analytically.

"Automation can do a lot of things that analysts can do but it does it very precisely—the same way every time"

– Bryan Crist,
Dissolution Expert

Nanoparticles have been a very big challenge as you essentially can't filter them. Being about the size of a virus, there are sub-dialysis techniques that work very well. We had worked with developing *in-situ* fiber optic dissolution for drug products that do release from these microspheres and nanospheres. Some of these methods have proven to be very effective. It's an ever-evolving thing and drug design gets more efficient and effective. It's good for patients and it's been good to put a challenge on us to stay ahead, and I think we've done that well.

PS: Here we are, 2020, big bang, global pandemic, we can't get into labs—there's a real necessity for automation if you need to reduce the number of people standing at any one time in labs. Shift work's been brought in—batch working processes. From your experience, would you advise dissolution testing facilities now in 2021 to use automation to help them adapt their workflow and release some of these additional pressures that they're suffering?

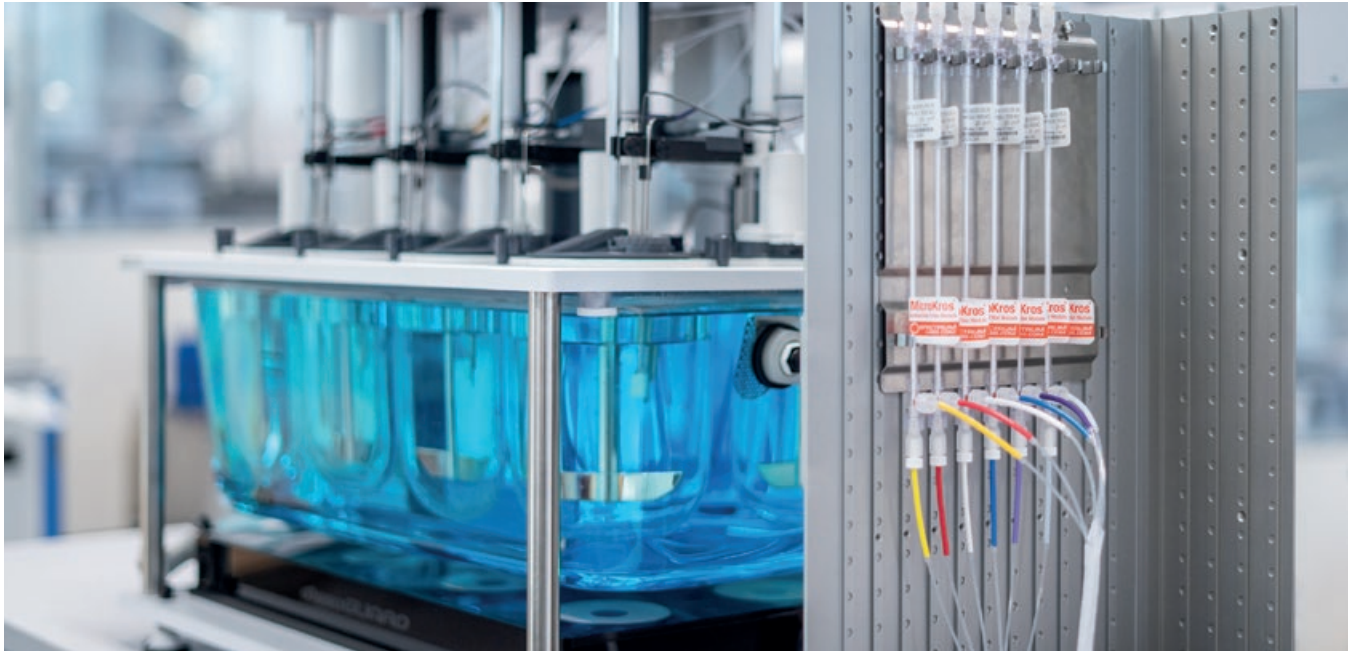


Figure 2. Nanoparticle dissolution

BC: That’s usually the first thing we think of when we have more workers coming in and they say ‘no more extra people’ especially during a product launch. The first thing people usually think about is automation. In fact, one of my good colleagues over the years put it that you’re actually buying time. That’s really a key component of your question because we do create automated approaches that can allow the analysts more time to do other things, for example develop more methods, refine methods, validate them. This ensures that these methods are analytically sound and accurate and precise.

There’s a lot of little intricate things that come with automation. We are always seeking a very efficient process with workflows, and semi-automation to total automation can handle that. Automation can do a lot of things that analysts can do but it does it very precisely—the same way every time. Timings are not missed because of human error: there are no phone calls or interruptions or losing count or losing the order of the vials that we’re processing. Automation is really quite an advantage in those areas.

Finally the last is documentation. Recording the times that these things are done is important, because these are some of the bigger violations that happen in audits, the timing is not properly recorded or the testing is not done within certain windows and automation gives us a way to accomplish that and also to show the audit trail is documented.

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 final installment of our three-part interview with Bryan.

Flexibility with Your Needs for Small Volume Dissolution

Karen Krauel-Göllner, Product Manager Dissolution Systems

Dissolution testing is typically performed with standard Agilent USP Apparatus 1 (Rotating Basket) and Agilent USP Apparatus 2 (Rotating Paddles) with a media volume of 500 to 900 mL. There is, however, a growing requirement for deviation from these parameters to properly test new dosage forms. Due to release characteristics, media volume may need to vary to achieve the necessary concentration level in the vessel.



Figure 3. Agilent 708-DS conversion kit (p/n 12-6368), 200 mL vessel

Dissolution portfolio for small volume

Thankfully, the Agilent Dissolution portfolio offers various solutions for your small volume dissolution needs. These range from conversion kits for your standard dissolution apparatus to dedicated equipment designed for testing in as little as 3 mL of media volume.

The Agilent 708-DS Dissolution Apparatus makes adaptation to a smaller volume simple. A conversion kit for each vessel location includes an adapter ring and evaporation cover. If the system is automated, the manifold is easily adjusted to accommodate the smaller vessel size. TruAlign vessels (100, 200 or 250 mL) and mini-basket or paddle shafts complete the conversion. The 100 mL vessel allows for dissolution in as little as 50 mL.

This is also possible in the Agilent BioDis Apparatus 3 and Agilent Reciprocating Holder Apparatus 7 models. These units provide a simple mechanism to move the dosage form to fresh or alternate concentrations of media when necessary. Vessels come in sizes from 50 mL up to 1 L. The release rate is cumulative based on the number of rows necessary for the method. For some applications, particularly combination products or medical devices, an even smaller volume is required. If a compendial dissolution apparatus for small volume dissolution is required for a method, then the Agilent 400-DS Apparatus 7 should be considered.

It is a modified Agilent USP Apparatus 7 (Reciprocating Disk) and was designed to provide an integrated system that can perform dissolution in as little as 3 mL of dissolution media. The system comes with a built in autosampler, has tightly controlled temperature monitoring, excellent evaporation control and gives you the freedom to choose from various sample holders. Topical formulations—such as gels, creams and ointments—can also utilize smaller volumes for evaluation. The 708-DS easily accommodates a 200 mL flat-bottomed vessel and the Agilent Enhancer (Immersion) Cell for this type of testing.



Figure 4. Agilent Reciprocating Holder Apparatus 7, 50 mL, shown in 6 x 7 automated configuration

To summarize the capacity of Agilent dissolution products:

Model	USP Apparatus	Vessel Volume (mL)
708-DS	1, 2, 5, 6	100, 200, 250 (cp), 1000, 2000
Recip. Cylinder (BIO-DIS)	3	100, 300, 1000 (per row)
Reciprocating Holder	7	50, 100, 300 (per row)
400-DS	7	5, 10 (up to 36 media changes)



Watch a video

on small volume accessories



[agilent.com/chem/708-conversion](https://www.agilent.com/chem/708-conversion)

Contact us

Contact your local Agilent representative or contact us directly through the dissolution hotline (dissolution.hotline@agilent.com) for further assistance.

Molecular Spectroscopy Site Combines with Dissolution

Keegan McHose, Sales Development Manager - EMEAi, PLMX

Dissolution is an important part of a pharmaceutical development process—however, it is not the only part. With that in mind, Agilent has developed the ‘Molecular Spectroscopy for your Pharma/Biopharma Labs’ webpages.



Figure 5. Vaya Raman technology

The cGMP lifecycle can be confusing, so to make things clearer Agilent has designed the Molecular Spectroscopy in Pharma/Biopharma website. These pages were designed to be a living document, accessible by our customer base to learn, explore and dive into new areas to drive continuous improvement in the regulated markets we serve. This includes all the way from raw material identification to finished product release and cleaning verification, through all stages of the drug development cycle from R&D to full-scale commercial manufacturing.

As a living document, we hope to provide timely updates for you to recognize that we as an organization are more than just an instrument provider, we are also a resource into the best practices of the industry. Use it, share it, but most of all let us help you reduce waste, break through roadblocks and transform your business.

Looking for more info?

Visit the Molecular Spectroscopy for Biopharma page here: gateway.on24.com/wcc/eh/2610203/category/42437

Questions You Asked

Large scale capsule sinker concerns

Q I need to perform dissolution on a large capsule that will not fit into the Agilent USP Alternative Sinker shown in the USP <711> Dissolution chapter which I believe is the sinker harmonized from the Japanese Pharmacopeia.

The capsule dimensions are 27 mm closed length x 12 mm diameter so, what can I use?

A The capsule you mentioned is extremely large. One of the largest commercially available capsules for human use is the #000 size capsule which is 26.1 mm closed length and 9.9 mm in diameter. The capsule you mentioned (27 x 12 mm) and the 000 capsule will not fit properly within USP <711> Alternative Sinker.

Due to the size of the capsule, I suggest that you use the USP recommendation: "A small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float." To make your sinker, I suggest making it with stainless steel which is available for this specific purpose:

Capsule weight wire, 316 stainless steel, 0.032 in. dia., 50 ft. (Agilent p/n 12-3000). I would simply find a metal rod, wooden dowel or a set of cork bores of 12 mm diameter to wind the wire around several times to form a sinker which should hold this extra-large capsule.

A full description of how to make dissolution sinkers are described in USP chapter <1092> The Dissolution Procedure; Development and Validation. The chapter describes construction of smaller capsule sizes #0 through #4 by wrapping stainless

steel wire around various cork bores with similar diameters to the capsule, but the same process could be used to create larger sinkers made with larger cork bores similar to your size of capsule. The cork bores are a set of tools used to cut various size holes in stoppers and corks used in the laboratory equipment. They are commonly available worldwide from laboratory equipment suppliers.



Figure 6. Capsule weight wire

Got a question of your own?

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

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