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Introducing NanoDis: Your Automated Solution for Nanoparticle Dissolution Testing

Dan Spisak, Product Manager, Dissolution Systems

Is your laboratory developing nanoparticle-based formulations? Are you struggling with achieving consistent, reliable dissolution results? Would you like to automate this process in a cGMP compliant manner?

If you've answered yes to any of these questions, Agilent now has a solution for you. Using instrumentation and software that meets current regulatory requirements, we've developed the system you need for dissolution results that will help you optimize the right formulation and ensure repeatability in a QC environment.



New Agilent NanoDis System

Why “Nano?”

The industry trend toward smaller micro- or nano-based formulations is still in its infancy. Projections from various sources estimate growth of over 20%^{1,2} in this area during the coming years. This is due to the advantages that nano-based formulations have compared to traditional drug delivery, such as³:

- Enhanced drug-release mechanisms
- Delivery to targeted therapeutic sites
- Optimization of drug concentration (at therapeutic site)
- Decreased side effects (to nontherapeutic site)

The demand and subsequent increase in R&D spending continues to drive development of pharmaceutical nanotechnology. As benefits including less active drug and increased patient compliance continue to materialize, the future looks bright in this area.

A “small” problem... the dissolution test

Dissolution laboratories continue to explore ways to achieve the desired results when performing dissolution tests of nanoparticle-based formulations. As a required QC test and critical step to help determine the best formulation for expected in-vivo performance, the proper system to evaluate these results can make or break a drug-development cycle.

The separation of nanoparticles from the dissolution media prior to quantification of dissolved drug has proven to be quite challenging. Traditionally, the sample removed from the vessel at the required times is filtered prior to analysis—conventional filters, however, are inadequate when dealing with particles on the nano-scale. Other separation methods, such as centrifugation or dialysis membranes, also have limitations that prevent the consistent, repeatable results that you need to make an informed pass/fail decision about a particular formulation or manufacturing process.

Ideally, laboratories in both an R&D and QC environment should have a way to achieve a dissolution profile that determines a successful drug formulation or batch in an automated fashion—a system capable of adequately and repeatably separating the nanoparticles from the dissolved drug prior to sample analysis.

The Agilent NanoDis System

Using the well-established semi-automated dissolution system from Agilent at its core, the NanoDis System combines hardware and software specifically designed for nanoparticle dissolution. This leverages the consistent, repeatable design of traditional dissolution testing with a touch of customization for these specific formulations.

The combination of a proven, existing solution and a few critical accessories creates this innovative system that allows you to automate your dissolution test for nanoparticle formulations and achieve consistent results. The secret lies in the software, which allows the user to customize—and optimize—key parameters of the dissolution method specific to the formulation being evaluated. This means that as the formulation or product changes, you can adjust the method(s) accordingly.

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Agilent NanoDis System

Agilent 708-DS Dissolution Apparatus

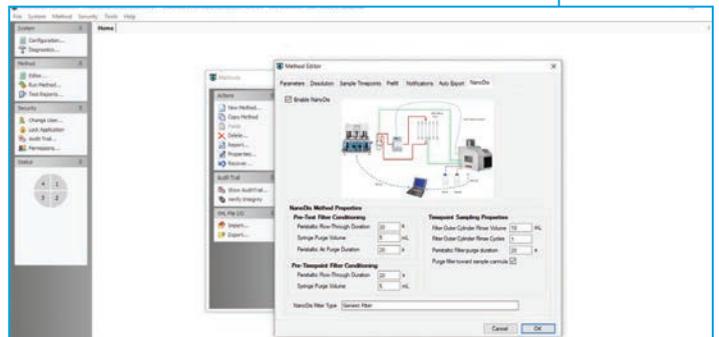
Includes standard apparatus for USP 1, 2, 5, and 6 with volume flexibility

Peristaltic pump

An 8-channel peristaltic pump moves sample from the vessel to the hollow fiber filter

850-DS Dissolution Sampling Station

The autosampler collects filtrate from the hollow fiber filter for analysis



Hollow fiber filter holder

Adjust to accommodate hollow fibers of various lengths

Agilent Dissolution Workstation Software

Controls system, optimizes test parameters, and ensures compliance by electronically documenting all activities

Learn how to automate your dissolution testing for nanoparticle formulations—and achieve consistent results. Contact your Agilent representative or visit [explore.agilent.com/nanodis](https://www.agilent.com/nanodis)

Measuring Drug Release from Orally Inhaled Products with the Enhancer Cell

Bryan Crist, Scientific Affairs Manager, Dissolution System

This is a review of a publication entitled: Dissolution of Fine Particle Fraction from a Truncated Anderson Cascade Impactor with an Enhancer Cell.¹ The work was conducted by GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore.

Dissolution apparatus, methodology, and techniques for most drug products designed for various routes of administration are well described in the harmonized Pharmacopeias as well as guidance from the U.S. Food and Drug Administration. Yet, for inhaled solids there appears to be a lack of universally acceptable dissolution methodology for determining the drug release from orally inhaled products (OIP).

Inhalation presents benefits for targeted drug delivery to treat various pulmonary diseases. Even though absorption of most bronchodilators is not limited by dissolution, absorption of inhaled corticosteroids is largely dependent on dissolution due to poor solubility.² Additionally, inhaled antibiotics are required at high concentrations in the lungs and are dependent on dissolution of the active ingredient. In general, proposals have been made to extend the oral BCS system to inhaled products—iBCS (inhalation BCS).³

Limitations exist with traditional dissolution apparatus for testing OIP and powders in general; USP 1 may utilize special fine-mesh baskets that may additionally utilize a sachet containing the powder to keep fine particles

from escaping or a powder may be added directly to USP 2. However, powders do not disperse well due to the surface tension of the media. Micronized actives are more difficult to disperse and tend to stick to surfaces of the dissolution apparatus.

To obtain a proper sample for a biorelevant dissolution test, you should evaluate the particle fractions that will reach the site of absorption, not the entire formulation. In this study, a modified Anderson cascade impactor (ACI) collected fine particle fractions that would be equivalent to those fractions eventually deposited deep in the lungs, which is only a portion of the emitted dose. Most dissolution studies to date have been conducted on un-fractionated powders.

In this study, the collection of fine particle fractions (FPF) utilized a special PTFE funnel over the final small collection plate contained in the truncated ACI.



Agilent Enhancer Cell

After determining the FPF for the drugs under study, various stages were removed to truncate the ACI, creating a simplified and robust means of collecting only the fine particles on the final small collection plate (sCP). The sCP was coated with a film of silicon oil to retain the particles. Next, a portion of adhesive tape equivalent in size to the 4.0 cm² enhancer cell was used to recover the dose deposited on the sCP and mounted in the enhancer cell facing upward.

The Agilent Enhancer Cell is a drug diffusion device developed for evaluating the release rate of active drug substance from semisolids. It is described in USP <1724> Semisolid Drug Products - Performance Tests as the Immersion Cell Model A. The membranes containing the FPF are placed in the enhancer cell to provide a fixed exposed surface area for dissolution to occur.

The dissolution media consisted of Gamble's solution as simulated lung fluid (SLF) in this study. Tween 80 was added to modify the SLF for a surfactant concentration of 0.2 v/v %. The drug-laden enhancer cell was placed into the 200 mL vessel containing 50 mL of media with a miniature paddle placed 1.0 cm above the surface and rotated at 50 rpm. Testing was conducted at 37 °C, and 2 mL samples were withdrawn at each timepoint replaced with fresh media.

The drug release profiles obtained between various drugs exhibited a logarithmic function for sustained release. The more poorly soluble formulations and very rapid burst phase dissolution profiles for high solubility drugs were also identified.

In summary, the truncated ACI demonstrated that it could collect the entire FPF into a single stage for analysis. The study also introduced a robust and reproducible dissolution method using the enhancer cell with small volume vessel and miniature paddle setup within the traditional dissolution apparatus.

For additional information on the specific products tested and HPLC analysis of the fine particle fractions from the orally inhaled products, please reference the article featured in this review:

www.ncbi.nlm.nih.gov/pubmed/29689370

We would like to acknowledge Justin Tay of NUS for his work; GEA-NUS PPRL, which provided a grant for the study; and Dr. Paul Heng for his guidance and incorporating the Agilent Enhancer Cell throughout this study.

References

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When It's Time to Calibrate Your Agilent 280-DS Instrument

Karen Krauel-Goellner, Product Manager, Dissolution Systems

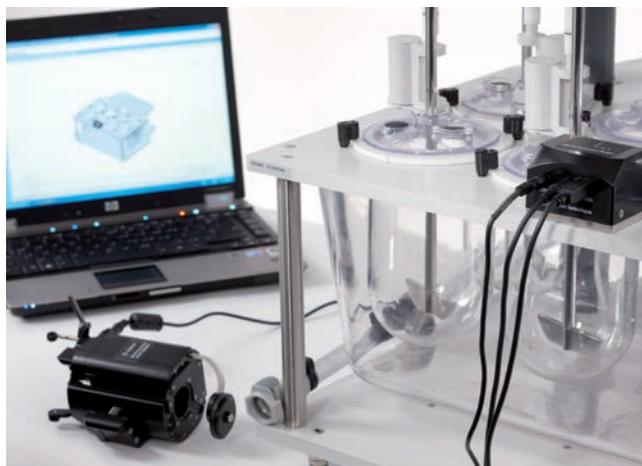
Is it time to calibrate your 280-DS Mechanical Qualification System? If this is the first round of calibrations for the instrument (or maybe you inherited the task from your colleague), then you may be wondering: How do I go about getting the instrument qualified?

It's quite simple, really. Just contact the Agilent Customer Care Center in your country and let them know that you would like to send in your 280-DS for a calibration service. An Agilent representative will then send you a quote and all the necessary details about the shipping process, including the address for the nearest Agilent calibration center. This might be in Little Falls, USA; Chengdu, China; or Waldbronn, Germany.

Some important details to keep in mind:

- We recommend calibrating your instrument in six-month intervals to provide absolute peace of mind on the quality of your mechanical qualifications.
- Always use an appropriate shipping box for the 280-DS. This is a highly sensitive instrument. Shipping the instrument in just the black storage case is not sufficient. Ideally, you still have the box your 280-DS originally came in.
- Your local account manager cannot issue you a quote for the calibration. This can only be handled by your local Customer Care Center.

By the way, calibration of the instrument can only be carried out by Agilent Technologies. The calibration of the 280-DS requires about 50 custom fixtures and special calibration software.



Agilent 280-DS Mechanical Qualification System

Learn more

To find your regional Agilent Customer Care Center, please visit www.agilent.com/chem/contactus and select your country.

Questions You Asked

Q. We have been successfully using a product called Clear Bath Algaecide from Spectrum for many years, and I now understand that the product is no longer available. Is there a substitute that you could recommend?

A. The key to an algaecide is that it is safe for heater-circulator systems and the acrylic bath material. There are many things that can kill algae but a number of these solutions may also damage the heater-circulator systems in most water baths. Additionally, harsh chemicals may cause a failure with acrylic materials commonly used in water bath construction. Currently there appear to be two alternative products that are safe for heater-circulator water bath systems:

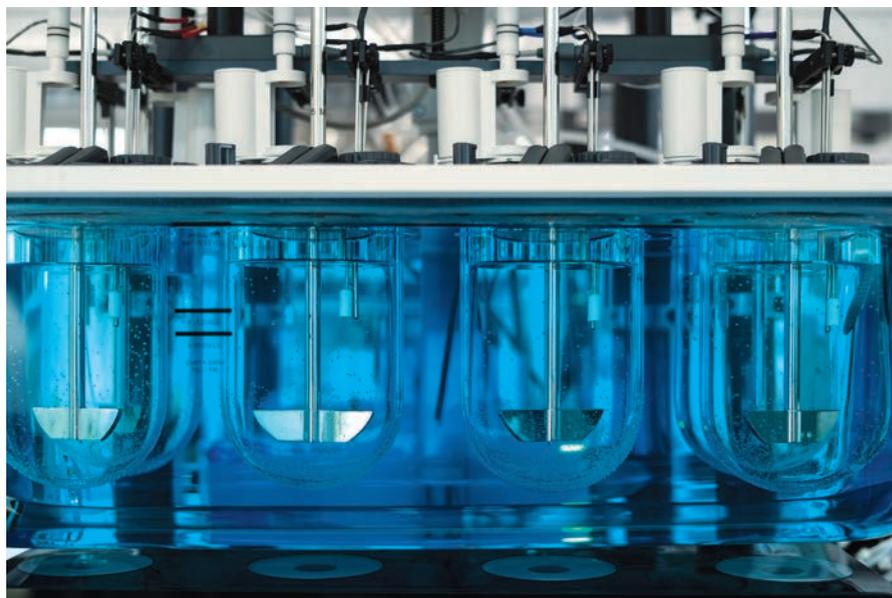
Learn more

Aqua-Clear from Bel-Art:

www.belart.com/bel-art-f17093-0000-cleanware-aqua-clear-water-conditioner-100ml.html

Aqua Stabil from Julabo (Sigma Aldrich):

www.sigmaaldrich.com/catalog/product/aldrich/z611662?lang=en®ion=US



Water bath from Agilent 708-DS Dissolution Apparatus

Learn more:

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