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BRYAN CRIST, SCIENTIFIC AFFAIRS MANAGER, AGILENT TECHNOLOGIES, INC.

INTRINSIC DISSOLUTION – THE ROTATING DISK METHOD

Through the pharmaceutical drug development process, whether innovative or generic in design, intrinsic dissolution gives us key information about the active pharmaceutical ingredient (API) in terms of the rate of dissolution with respect to constant media pH, temperature, and surface area. Although the Biopharmaceutical Classification System (BCS)[1] provides vital information on the solubility and permeation characteristics of the drug, the intrinsic dissolution rate helps us further characterize drug solubility with respect to its surface area. Dissolution rate is generally expressed as the mass of solute appearing in the dissolution medium per unit time. This is also described as dissolution flux, because the rate is normalized for surface area of the pure drug substance, which ultimately provides the dissolution rate constant (expressed as mg/min/cm^2).

This information about the API assists the product development process with justification for optimizing the dissolution process for instance, by altering the surface area in various ways to achieve the optimum physiological effectiveness of the dosage form. Typically, drug substances with intrinsic rates of less than 0.1 mg/min/cm^2 may be dissolution rate limited, while intrinsic rates of greater than 1 mg/min/cm^2 are most likely free of dissolution rate problems.

The intrinsic dissolution rate is generally determined by compressing pure API using a specially constructed punch and die system under high pressure to obtain a non-disintegrating disk. This is performed without the addition of any excipient such as a binder or lubricant, in order to avoid external interference in the intrinsic dissolution profile. The disk/die assembly is then transferred to a special receptor shaft that holds the die containing the drug substance within the dissolution vessel. The disk is then rotated at high speed in media that is consistent with in vivo gastrointestinal conditions for solubilizing the drug product. Samples are taken periodically during the test to demonstrate a linear release of drug, due to its constant surface area, and the slope of the linear function of release is the actual dissolution rate constant expressed as mg/min/cm^2.

The intrinsic rate constant also provides physical characterization knowledge about the consistency of API manufacture in addition to information about the physical state of the API such as crystallinity, polymorphism, hydration, and solvation, and their effects on the intended dosage form.

The following information provides a practical approach to performing the intrinsic dissolution test as described in the US Pharmacopeia <1087> Apparent Intrinsic Dissolution[2] chapter and demonstrates the hands-on portion of the intrinsic dissolution test with the rotating disk method (formerly known as the Woods Apparatus).

Preparation

To perform the intrinsic test, the apparatus components should be accounted for as shown in Figure 1. The surface plate should be polished for best results to avoid pitting of the compact surface. The punch/surface plate is constructed from hardened steel, not stainless steel, and is usually stored with a film of oil to protect it from rust. The oil must be removed prior to the test. The die has a hole for removing the punch if it is difficult to remove after the test.

In addition to the dissolution apparatus, the analyst will require a benchtop press with an accurate pressure gauge, as well as safety glasses, an analytical balance, and weighing accessories.

Figure 1. Intrinsic dissolution rotating disk components.

Prior to preparation of the compact (the compressed API pellet within the die cavity), it is wise to preheat the die, punch and shaft to 37.0 °C for best results to avoid a temperature drop when it is placed into the dissolution media. Next, bolt the die onto the surface plate with the three stainless screws and weigh an amount of API. It is not necessary for all of the drug to be dissolved during the test; in fact, we are only looking for the first 10% of the drug to be dissolved to maintain linearity through the test. Beyond this the release rate becomes non-linear due to wicking of media into the compact and the eventual depletion of the drug substance. So if we are looking for linear release of 20 mg, we will add 200 mg of API to the die cavity.

After weighing, insert the punch into the die cavity and place the surface plate containing the die cavity, API, and punch into a suitable laboratory press equipped with a pressure gauge. For initial testing, USP recommends applying a pressure of 15 MPa (Megapascals) equivalent to 2,175 PSI (150 Bar). Hold the pressure constant for about 1 minute to set the compact density. Note that excessive pressure could cause changes in crystalline state and should be avoided. All API have different physical qualities, and alternative pressures need to be evaluated to ensure consistent results. Once the compression is complete, remove the assembly from the press, unbolt the die cavity from the surface plate and assemble into the holder (shaft), leaving the punch in place. The components of the intrinsic device are shown in Figure 2.

To prepare the test, we must set up the dissolution apparatus with the USP basket or paddle shafts removed. Heights need to be preset at a height of 3.8 cm (1.5 inches) from the bottom of the vessel with an intrinsic height setting gauge. Media must be thoroughly deaerated and preheated 37.0 °C.

Once the shaft holders with intrinsic dies are in place and raised out of the vessels, introduce the required amount of media, typically between 500 and 1000 mL. Once the media has stabilized at 37.0 °C, lower the intrinsic devices into the media, start the timer, and begin rotation immediately, typically at 250 rpm. Check that no bubbles have formed on the compact surface; if bubbles are present, tap on the shaft to remove them.

Continue the test and pull samples accordingly with a minimum of about 5 samples through the run. When conducting initial trials, numerous points may be pulled until the intrinsic rate is ultimately determined, but subsequent runs only need to allow the first 10% of the drug substance to be dissolved.

Samples should be withdrawn according to USP <711> sampling guidelines and filtered. Once the samples are obtained, they may be measured with UV or HPLC methods consistent for the analytical determination established for the drug product. Results are calculated and corrected for analyte and volume loss in previous samples. Sample concentrations are plotted against time and surface area, to be reported as mg/min/cm^2. The slope of the line is the intrinsic dissolution rate constant.

After the test, remove the device from media and clean immediately in fresh water. Remove the punch from the die, with the aid of a rod through the hole if necessary, and rinse thoroughly. Dry immediately and coat the punch and surface plate with light machine oil to prevent rust. Store all components in a clean, protected dry area.

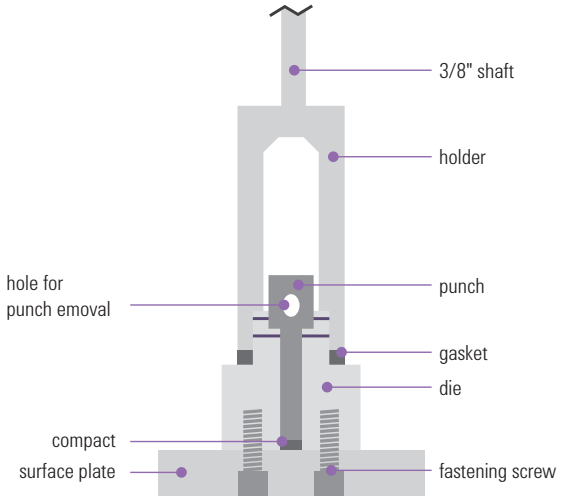

Figure 2. Components of the intrinsic device.

Agilent has also provided a video of the intrinsic method, which may be found at: https://www.agilent.com/en-us/products/dissolution/accessories/intrinsic-dissolution-accessory/intrinsic-dissolution-video

References

1. Amidon, G.L.; Lennernas, H.; Shah, V.P.;Crison, J.R., A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability, Pharmaceutical Research 1995, Vol. 12, No. 3.
2. USP <1087> Apparent Intrinsic Dissolution – Dissolution Procedures for Rotating Disk and Stationary Disk, US Pharmacopeia 38, Rockville, MD, 2015.

Intrinsic Dissolution Apparatus

Description	Part Number
Intrinsic Dissolution Apparatus, 0.5 cm² exposed surface area, with punch, shaft and holder, for 7000E/7010, 708-DS, 705-DS*	12-4101
Intrinsic Dissolution Apparatus, 0.125 cm² exposed surface area*	12-4110
Intrinsic die, 0.5 cm² exposed surface area	12-4120
Punch	12-4140
Shaft and die holder only, for intrinsic dissolution	12-4150
Surface plate, for intrinsic dissolution	12-4130

*Surface plate sold separately. Only one plate required for testing.

BRYAN CRIST, SCIENTIFIC AFFAIRS MANAGER, AGILENT TECHNOLOGIES, INC.

DEAERATED DISSOLUTION MEDIA: WHAT'S ALL THE HOT AIR ABOUT?

Deaeration is the controlled process of removing excess dissolved gases, primarily air, from dissolution media. Gas laws dictate that air is less soluble in aqueous solutions at 37.0 °C than at room temperature, so a common occurrence when media is heated is that bubbles may be observed on surfaces in the dissolution environment as air comes out of solution upon heating. If air is removed from the media prior to the dissolution test, the bubble phenomenon is not observed during the test, and the dissolution environment is preserved and free from influences that bubbles have on the dissolution process.

Bubbles forming in the media may affect products immensely or not at all. How do we know which products are sensitive to dissolved gasses? This has to be evaluated during dissolution method development and validation on a product-by-product basis. Some paddle methods may exhibit faster dissolution rates due to increased turbulence; conversely, baskets may occasionally exhibit lower dissolution rates due to blockages in flow through the basket. These are typically due to the physical impact that the bubbles have within the dissolution environment, and effects may only be understood through study.

Most monographs do not specifically call for deaeration of the media, even for products that are affected by dissolved gasses. Why? For the same reason monographs do not list the brand of filter, HPLC columns, amount of media to waste, etc. – namely, because these are part of the method development and validation process, and USP methods should still be validated in the end-user environment to verify that the method is suitable for its intended purpose.

The responsibility to evaluate this effect is found in USP <711> Dissolution chapter, where a note on dissolution media reads, "dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gasses influence the dissolution results, dissolved gases should be removed prior to testing."[1]

The immediate dissolution environment consists of only three things: a vessel, media, and an agitating element. The interior surface of the glass vessel has a uniform smooth finish. During a normal dissolution test with a disintegrating formulation in the paddle apparatus, undissolved drug product typically circulates around the vessel in a centrifugal motion, sliding along the glass surface and occasionally settling to the bottom of the vessel in the center of rotation to form a cone. This may be easily observed in the early stages of dissolution by looking down into the vessel and seeing particles near the interior surface of the vessel. If the interior surface of the vessel is coated with bubbles, a tremendous amount of turbulence exists at the interface with the glass, which erodes the surface of the active drug particles more quickly as it moves through a virtual obstacle course of bubbles. To compound this problem, a paddle that is covered with bubbles may impart significantly more agitation due to the increase in its surface area. These two physical forces are enough to increase the overall agitation in a vessel and to increase the dissolution rate significantly. The consequences of this may be easily understood in a dissolution test for an immediate release dosage form with a single limit of ≥ 85% dissolved in 30 minutes: if a sub-performing product is manufactured and tested in a vessel covered with bubbles it could appear to pass and be released into distribution.

Our job as chemists is to test with validated and approved methods and procedures and ultimately to prevent products that do not conform to specification from being released. In short, our job is not to help products to pass but to ensure the quality of a product – and this can only be done if our methods are carried out correctly.

Simple Deaeration Procedure

With the aid of a Millipore Sterivac™ GP20 Vacuum Filtration Unit,[2] deaeration of dissolution media by the USP recommended technique may be accomplished in minutes. This filter will require the use of a heating stir plate, a vacuum source with moisture trap, two preparation bottles built to withstand low pressure vacuum, and of course the Sterivac™ Filter. Deaeration techniques should be performed within the safety of a laboratory fume hood with the sash lowered.

The vacuum filter setup should provide the vacuum moisture trap closest to the vacuum source followed upstream to the Sterivac™ filter, which will have the inlet connected to the source media and the outlet connected to the moisture trap. The bottom of the filter has a gasket that should fit the top of the vacuum-resistant receiving bottle. If the opening of the receiving bottle is too large, you can attach it to a small funnel within a stopper.

First, prepare media as required by the test method and adjust pH if necessary. As directed in USP, heat media to 41.0 °C then vacuum filter the media through the filter. The filter unit houses up to 8 individual filters, which increases the surface area of filtration tremendously. Once the media has passed through the filter, continue vacuum for 5 additional minutes. Remove the filter and recheck the pH of the media, and adjust volume if necessary. It is now thoroughly degassed and ready to use.

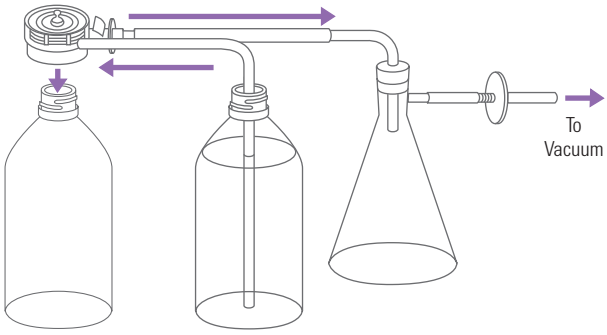

Figure 3. Set up your vacuum line. You may want to use an in-line filter (Millex®-FG_{50} device) and vacuum trap to protect against water intrusion. Attach end of vacuum tubing to blue tubing adapter. Turn on the vacuum. The vacuum must remain on until all liquids have been processsed.

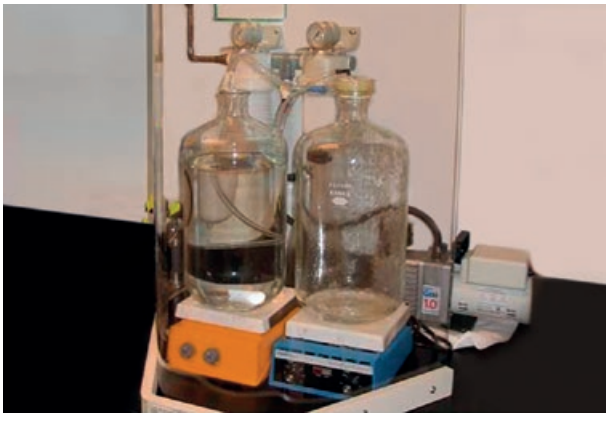

Figure 4. Typical laboratory deaeration setup according to the USP.

References

1. US Pharmacopeia Physical Test <711> Dissolution, USP 38, 2015
2. Millipore Technical Publication P35904, Rev. D, 5/2003; Sterivac™ is a registered trademark of Millipore Corporation.

DAN SPISAK, DISSOLUTION PRODUCT MANAGER, AGILENT TECHNOLOGIES, INC.

DISSOGUARD PROVIDES THE IDEAL PERSPECTIVE FOR LIGHT-SENSITIVE SAMPLES

"Visual observations are often helpful for understanding the source of the variability and whether the dissolution test itself is contributing to the variability." -Excerpt from USP <1092>

Figure 5. The dissoGUARD sits conveniently beneath the 708-DS, providing a view of each individual vessel.

Although the above statement from the USP General Chapter <1092> makes perfect sense, who has the time to sit in front of the dissolution apparatus and view the entire test? Even for immediate release products, this is a bit impractical; for extended release methods, it's totally out of the question. For most products, the predictable moments are easily observed, such as dosage introduction or sampling.

Other moments, however, are a bit less foreseeable and could occur at different times during the run. These include abnormal release patterns or disintegration, opening of capsule shells, etc. Photosensitive products that require additional protection or special lighting – those that exhibit degradation when exposed to light – further prohibit proper viewing of the dissolution vessel.

The dissoGUARD dissolution surveillance system possesses key features to help gather critical evidence in these situations. Not only do the individual cameras capture video and monitor key parameters, dynamic LEDs illuminate the individual vessels. This adaptive control is programmable using white or red lighting. An optional, easy-to-install bath shield delivers the perfect solution for light-sensitive applications. You are now able to completely conceal the apparatus, yet have recorded video of every second of every vessel.

Figure 6. dissoGUARD Bath Shield

Learn more about dissoGUARD and its full spectrum of capabilities in Agilent Dissolution's Digital Source Book. For a personalized demonstration of the system, contact the Dissolution Hotline at dissolution.hotline@agilent.com. Put dissoGUARD to work in your laboratory today and see what you've been missing!

BRYAN CRIST, SCIENTIFIC AFFAIRS MANAGER,
AGILENT TECHNOLOGIES, INC.

DISSOLUTION DISCUSSION GROUP (DDG) ONLINE MEETINGS

The DDG Online Meetings have occurred quarterly since 2011, with 22 meetings already held. They are an extension of the popular DDG site, which maintains a bulletin board for dissolution analysts worldwide. The DDG provides a free forum for analysts to discuss the practical issues that challenge the pharmaceutical industry day-to-day in terms of developing, validating, and performing dissolution tests and related chemical analyses.

The DDG online topics generally follow hot trends in drug release and dissolution testing throughout the year. Some examples of popular topics include: *Deaeration of Dissolution Media: What's All the Hot Air About?*, *Dissolution SOPs: Do What You Say and Say What You Do*, and most recently, *USP <1092> and its Impact on Dissolution Automation*.

All 22 sessions are recorded sessions with invited panelists joining Agilent moderator Bryan Crist. Registrations for upcoming meetings and for access to recorded sessions can be accessed directly on the DDG site at www.dissolution.com; the DDG may also be accessed while visiting the Agilent Dissolution Exchange at http://dissolution.chem.agilent.com/. The DDG is sponsored by Agilent Technologies, Inc. – we hope to see you there soon!

QUESTIONS YOU ASKED

We are routinely asked for input on applications or our instruments. The following are excerpts we thought you'd find interesting.

Question: I understand that the USP Standard disintegration basket may also be used with a stainless steel cover. What is the purpose of the cover, and can you test any product with the cover over the basket?
Answer: The SS wire cover is mentioned for the disintegration of hard gelatin capsules in the USP <701> Disintegration chapter. It is there because disks are not commonly used with capsules, and this cover keeps the capsules from floating out in the event the top of the basket becomes submerged.

Question: I am curious about long-term storage requirements for dissolution equipment, since we are relocating a laboratory. Is there a specific procedure for this?
Answer: In addition to draining the bath, the surfaces of the dissolution apparatus and any associated sampling equipment should be wiped with a clean, damp cloth and dried. This should ensure that no buffer reagents or acids remain, which could cause corrosion upon prolonged storage.

All sampling lines should be well rinsed with purified water and purged of the rinse. Full Flow Filters should be removed from the sampling cannulas. The tubes connecting the apparatus to the sample collector should be disconnected after purging to allow them to dry and not retain moisture, which could promote algae or mold growth. Keep all of the tubing and components together for reassembly.

The water bath should also be rinsed and drained, and circulator tubing may be disconnected and allowed to dry. Ensure all vessels, shafts, and baskets are clean and dry. Instruments should be stored in controlled temperature and humidity and should be wrapped with a barrier to keep out moisture and dust.

Correction to 16.2 article ADDRESSING DISSOLUTION COMPLIANCE THROUGH AGILENT LEARNING RESOURCES

Under the section: FDA Draft Guidance for Industry: Dissolution Testing and Specification Setting for BCS Class 1 and 3 Drugs

Original Text:
We will also address the possibility of utilizing the disintegration test for some products where greater than 85% release is achieved in 85 minutes or less.

Correction:
We will also address the possibility of utilizing the disintegration test for some products where greater than 85% release is achieved in 15 minutes or less.

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dissolution.hotline@agilent.com

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