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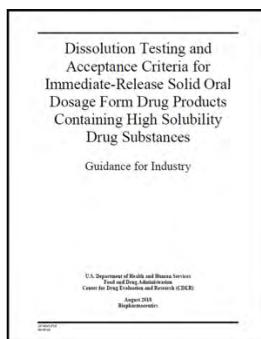
Questions You Asked

A Summary of FDA Guidance for Industry

Bryan Crist, Scientific Affairs Manager, Dissolution

Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

This Final FDA Guidance was published in August 2018 to finalize the Draft FDA Guidance on the subject issued August 2015. This final guidance may be found at the [US FDA site](#)*.



This guidance establishes standard dissolution methodology and acceptance criteria that are appropriate for highly soluble drug substances that are formulated in immediate-release (IR) dosage forms. The availability of this standard will facilitate the rapid development of dissolution methodology during drug product development. In addition, these standards will facilitate

FDA's evaluation of the data submitted in the application. This finalized guidance supersedes the guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997) for biopharmaceutics classification system (BCS) class 1 and 3 drug substances in IR drug products. For drug products not meeting the eligibility requirements or conditions of this guidance, the recommendations of the August 1997 guidance should be followed.

*US FDA site
(<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM456594.pdf>)

Eligible drug products

Eligible drug products pertaining to this guidance are based on:

- **The dosage form.** Applies to solid orally-administered IR drug products meant to be swallowed, not orally disintegrating tablets.
- **Solubility.** To be considered BCS class 1 or 3, the drug substance should be considered highly soluble with the highest dose strength soluble in 250 mL or less of aqueous media over the pH range of 1 to 6.8 at 37 ± 1 °C.
- **Therapeutic index.** Does not apply to drugs with narrow therapeutic index (nicotine).
- **Time to maximum plasma concentration.** Does not apply to drugs when maximum plasma concentration is critical to the intended use, such as a sublingual tablet (nitroglycerine).
- **Manufacturing and testing history.** Stability throughout shelf life is to be demonstrated by the standard dissolution testing conditions contained in this guidance.
- **Excipients.** Need to be consistent with the design of IR drug products; not excessive amounts which may affect drug absorption or performance.

For high solubility products, these recommendations will supersede those in the Dissolution Methods Database for high solubility products. For products where the method described in a United States Pharmacopeia (USP) drug product monograph differs from the recommendations of this guidance, ANDA applicants may propose to use the approaches in this guidance as an alternative method and seek revision of the relevant monograph.

Standard dissolution test conditions

The GI tract is quite complex and although the agitation characteristics may be different for the USP basket and paddle methods, the following standard conditions are recommended for meeting the specifications in this guidance if the drug product meets the six eligibility requirements above. The dissolution apparatus should also be qualified before use.

Basket method (USP Apparatus 1)

- Stirring rate 100 RPM
- 500 mL of 0.1M HCl aqueous media
- No surfactant in media
- 37 ± 0.5 °C

Note: a rotation speed of 100 RPM has been found to be discriminatory for the basket method.

Paddle method (USP Apparatus 2)

- Stirring rate 50 (75 RPM with the appropriate justification)
- 500 mL of 0.1 M HCl aqueous media
- No surfactant in media
- 37 ± 0.5 °C

Note: 75 RPM paddle speed can be discriminatory while minimizing coning effects seen with lower rates. Wire helix sinkers may be used to ensure that capsules are fully immersed in the paddle dissolution apparatus.

Rationale

The acid conditions of the media reflect the conditions of the stomach whose volume is estimated at 250 mL when a glass of water is co-ingested with the oral dosage form. However, this volume is too low for the operation of the basket and paddle apparatus. Therefore, 500 mL of media should be sufficient volume to meet sink conditions for highly soluble rapidly dissolving drug product.

Appropriate justification should be provided if 900 mL volume of the medium is used or if alternative dissolution media within the physiological pH range are used over the recommended 0.1 M HCl aqueous medium.

In terms of specification setting for IR solid oral drug products containing a high-solubility drug substance, a single point dissolution specification of $Q = 80\%$ in 30 minutes is recommended.

In support of any scale-up and postapproval changes, SUPAC-IR Guidance from FDA should be followed.

References throughout

FDA Guidance for Industry; Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs; August 2015

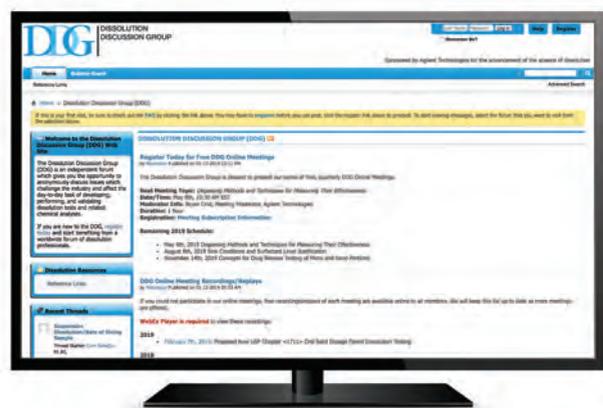
When Was the Last Time You Visited the Dissolution Discussion Group?

Allan Little, Director of Marketing, Dissolution

The DDG is a community of dissolution users and experts from around the world. Our bulletin board contains over 20 years of questions and answers in a convenient, searchable database. If you have a question, check out the DDG (www.dissolution.com). There's a good chance someone else may have already answered a similar question.

What has made the DDG work for two decades is the willingness of users to help others. Please visit the DDG regularly and assist your fellow dissolution scientists.

Membership in the DDG is free. Register today and tap into the knowledge of dissolution professionals worldwide.



Mixing It Up: 850-DS Firmware Update and Accessory Addition

Dan Spisak, Product Manager, Dissolution

An updated version of the 850-DS sampling station firmware is available for all existing systems. This release includes several key benefits to enhance your laboratory performance. A short summary is provided in the following table:



850-DS Dissolution Sampling Station

| Feature | Benefit |
|---|---|
| Added Volume Calibration guide | Screens have been added to conveniently step the user through the volume calibration process that should be completed periodically according to internal SOPs. |
| Added Volume Calibration history | A historical log of the previous 10 calibration events is now maintained in the firmware that includes date/time, user, and pump speed. |
| Auto-calculate feature | When enabled, this option automatically determines the vessel volume based on the media removed at previous timepoints; this prevents any errors and adjusts the 708-DS manifold depth as well. |
| Cleaning cycle parameters added | The system now includes optional rinsing of the media and waste reservoirs as part of the automated cleaning cycle to further flush the internal system and extend the life of key components. |
| USP Apparatus 5 test start sequence | Improvements have been made to simplify the test start sequence when using the Paddle over Disk feature. |
| User-level customization | An administrator of the 850-DS can now select specific functions for all user levels based on exact internal requirements. |
| Initial temperature for USP Apparatus 1 tests | Initial vessel temperatures can now be recorded for tests using baskets with the addition of this option to the firmware as well as three-fin baskets to the 708-DS accessory kit (continue reading below). |



A complete set of three-fin baskets (pictured left) are now included with all 708-DS systems that include standard USP 40-mesh baskets. The baskets are installed prior to beginning the actual test and gently mix the dissolution media to equilibrate each vessel for accurate temperature measurements. Once the values are recorded, the system prompts the user to install the dosage-filled baskets for testing. This accessory speeds up the pre-test process and prevents the test from starting with wet baskets. To add these baskets to any existing system, you can simply order them from Agilent using part number 12-1049.

This 850-DS firmware (version 3.07) is compatible with current versions of the following key instrumentation and software with which it is commonly paired:

- 708-DS dissolution apparatus—version 2.07
- Dissolution workstation software—version A.01.05
- Cary WinUV dissolution software (Multicell)—version 5.2.1

For additional details, or to schedule your system upgrade, please contact your local Agilent representative. You may also contact the Dissolution Hotline at dissolution.hotline@agilent.com for more information.

Dissolution Media Addition Tips for Enteric-Coated Products

Bryan Crist, Scientific Affairs Manager, Dissolution



Media addition is performed for several reasons. It is the more popular of the two options for evaluating enteric-coated products designed for gastric environments. These delayed-release products require methods allowing for pH change to occur from a typical gastric pH between 1.2 and 2.0 to a buffered media capable of dissolving the coating and allowing the product to disintegrate and dissolve. Reasons for this are:

- To protect the gastric lining from an API that may be irritating (acetylsalicylic acid is a good example),
- To protect the API from the acidic gastric fluids that may degrade the API, or
- To allow a site-specific drug to release the API at a specific pH associated with a section of the intestinal tract where the dissolved API can provide a local effect in the intestinal wall.

Regardless of the reason, the USP <711> Dissolution chapter outlines the two primary methods for evaluating dissolution of delayed-release products: Method A, which is a media addition method, and Method B, which is a media exchange method. Each has advantages and disadvantages. For this discussion, we will focus on the Method A—Media Addition process.

The method-addition technique is perhaps the easier of the two methods. Because *the dose is introduced as typically required for immediate release products, a sample is pulled at the end of the gastric period, buffered media is added, pH is checked, and the run continues until the remaining timepoints are pulled*. There are two sets of acceptance criteria that are applied; one for the acid stage and one for the buffer stage. The acid stage is supposed to demonstrate a limited release of the drug in the gastric region. The buffer stage should demonstrate that sufficient drug is released in buffered media, representing the targeted area of the intestinal tract, and is available in sufficient quantity to provide the intended therapeutic effect according to the acceptance criteria for each stage.

Key points to be considered during the Delayed-Release, Method A, media addition test:

- **Introduction:** The dose must be introduced into nonrotating media for the paddle method. This is a special consideration if a staggered start is used to allow an analyst enough time to pull and filter samples and to add media within the 2% time tolerance. It is important to maintain the requirements for dose introduction as described in the <711> Dissolution chapter. Typically paddle methods are used for most enteric coated methods because the enteric coating for some products may be damaged by the rotating basket method due to contact abrasion with the screen surface.
- **Time:** The clock never stops, and all test times and actions must conform to the $\pm 2\%$ time tolerance. For manual testing, this may best be accomplished by staggering the start to allow the analyst sufficient time to perform the italicized steps above. The 2% rule applies not only to pulling a sample but also filtering it. In other words, you don't have a sample until it is filtered, and this is true for all timepoints. For automated methods of analysis, the sample may be automatically collected and filtered but remember the volume correction for the remaining timepoints if the sample volume is not replaced.
- **Media:** Only preheated media is added. Typical media addition methods begin with around 750 mL of gastric media. After the gastric sample is pulled, buffered media preheated to 37.0 ± 0.5 °C is added to each vessel. The analyst will have to ensure that the media is added, the pH is checked and adjusted if necessary within five minutes of the gastric time point; the clock never stops. The method should be developed and validated to ensure the proper pH is obtained after the buffered media is added. Also, the temperature of the buffered media must be recorded to ensure that the test conditions were maintained.

Attention to these steps and details will ensure that the delayed-release testing for enteric-coated products is performed as intended with the USP <711> Dissolution chapter for the Method A, media addition method.

Questions You Asked

- Q.** I have a problem with a capsule product which contains pellets that float. Unfortunately, some of the pellets float out of the hole in the USP Apparatus 1 Basket. What can be done to eliminate this problem?
- A.** The hole in the basket shaft disk was designed to allow an air bubble, which may form on the bottom of the disk while immersing, to escape through the hole as the assembly is lowered into position. Other than this, it doesn't serve any other purpose. I believe the first place to look is whether the media for the method requires deaeration. Dissolved gasses can sometimes form on small pellets as bubbles which may become buoyant.

This is probably rare and if you are seeing variability from this issue due to the dosage form you may be able to justify a slight modification by blocking the hole in the top of the basket disk. I remember someone moving the clip over the hole and another had custom made and placed a tiny stainless steel "nail" in the hole. It may also be possible to temporarily place a small ball of parafilm in the hole to prevent particles from leaving the basket. Whatever is used, it needs to be properly justified, validated, and reflected in the method so the analysts are consistent in performing the test. Any modification must also be removed immediately after the test restore the basket shaft to its proper compendial configuration with the hole open. For compliance related issues, it is best to consult USP directly.

- Q.** How can I determine the proper level of n-octanol or antifoam to use in my surfactant containing dissolution medium for USP Apparatus 3?
- A.** Some methods may require only a single drop of simethicone (20 drops equal about 1.0 mL, 1 drop equals about 0.05 mL) for use with low volumes of sodium lauryl sulfate but the levels of surfactant, volume of media and types of surfactant vary a lot in dissolution methods. Just as the level of surfactants must be justified to reach sink conditions (three times the amount of volume at saturation of the highest dose strength), the level of antifoam should also be justified to reduce the foaming.

Although I would suggest simethicone over n-octanol, due to the potential increased solubility with an organic solvent, the amount of n-octanol must be justified relative to the amount and type of surfactant used in a specific volume of media. So, I would start with a single drop and increase dropwise to determine the amount of antifoam required to reduce the foaming of the surfactant required for the dissolution method in USP Apparatus 3.



Basket shafts with visible holes to accommodate air bubbles



BIO-DIS Apparatus 3

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