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Enhanced Mechanical Qualification of the Dissolution Apparatus and the Chinese Pharmacopeia

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Mechanical qualification overview

Mechanical parameters crucial to maintaining the standard dissolution apparatus have had specifications and tolerances contained in the world's pharmacopeias since their inception as an official test method for the performance of drug products in terms of their dissolution and drug release rates. While these parameters and their tolerances have remained relatively unchanged over many years, the US FDA, in January of 2010, introduced an alternative enhanced mechanical qualification (eMQ) approach for qualifying the dissolution apparatus relative to the historic USP Performance Verification Test (PVT) with the prednisone calibrator tablets.

The eMQ specifications and tolerances offer a refinement of specifications for some parameters (speed, basket wobble, vessel-shaft centering) and new specifications for other critical parameters (shaft wobble, shaft verticality, vessel verticality). The eMQ approach also requires that the dimensions of dedicated components, which have been verified with calibrated tools, meet

the ICH harmonized dimensions contained in the USP. The alternative approach also requires scheduled preventive maintenance at suitable intervals and lastly, observational checks to be performed by the analyst prior to each test. The observational checks are critical for inspecting and documenting the condition of all components in terms of cleanliness and defects. If a defective component is found, it must be removed from service and replaced with a certified component, whereupon the related physical parameters are reverified and the apparatus may continue to be used.

This process has allowed the apparatus to be evaluated more often to keep the apparatus in a calibrated state instead of relying on a test with calibration tablets once every six months to determine if the apparatus has remained, or unfortunately not remained, in a calibrated state.

US FDA Guidance for Industry has also suggested that regardless of which procedure is used, the USP PVT or the eMQ procedure, three significant sources of variability in the dissolution apparatus must be controlled in terms of vessel quality, vibration, and dissolved gasses.

Mechanical qualification and the Chinese Pharmacopeia

The Chinese Pharmacopeia (CP) contains the dissolution chapter 0931 for dissolution apparatus 1 (basket) and 2 (paddle), which has historically had specifications similar to the USP. Since 2015, the CP has revised the list of physical parameters in addition to several tightened physical parameters similar to the US FDA eMQ procedures. The CP also included a few additional parameters not found in the harmonized USP <711> Dissolution chapter or eMQ procedures. The three areas of refinement over the USP or FDA proposed specifications and tolerances include: vessel plate level (≤ 0.5 mm from horizontal), vibration tolerance (≤ 0.1 mil of displacement), and a performance verification test with salicylic acid tablets. The accompanying table shows a summary of the CP dissolution test physical parameters compared to the ICH harmonized dissolution chapter and the eMQ requirements stated in the FDA and ASTM procedures.

Agilent 708-DS Dissolution Apparatus

The Agilent 708-DS Dissolution Apparatus was built specifically with enhanced mechanical qualification in mind. It provides a platform that is well within the compliance requirements contained in the Chinese Pharmacopeia in terms of physical parameter specifications and tolerances.

Parameter	ICH Harmonized (USP, JP, EP)	FDA DPA-LOP.002 and ASTM E2503-13	Chinese Pharmacopeia CFDA	USP Toolkit Ver 2.0
Basket and paddle depth	25 ± 2 mm	25 ± 2 mm or < 8 % (ASTM)	25 ± 2 mm	23–27 mm
Rotational speed	± 4 % of specified rate	± 2 rpm of target or 2 % of target (ASTM)	± 4 rpm at 50 rpm	±1 rpm of target
Shaft wobble	No significant wobble	≤ 1.0 mm total runout	≤1.0 mm total runout at 50 rpm	≤1.0 mm total wobble
Shaft verticality	Not measured	≤ 0.5 ° from vertical or within bubble (ASTM)	≤ 0.5 ° from vertical	Not measured
Basket wobble	± 1.0 mm	≤ 1.0 mm total runout	≤ 1.0 mm total runout at 50 rpm	≤1.0 mm total wobble
Vessel/shaft centering	NMT 2 mm from center axis	≤ 1.0 mm from center line (upper and lower)	≤ 1.0 mm from center line (upper and lower)	NMT 2.0 mm difference (four 90° positions)
Vessel verticality	Not measured	≤ 1.0 ° from vertical (two 90 ° positions)	≤ 1.0 ° from vertical (two 90 ° positions)	NMT 0.5° from vertical
Vessel plate level	Not measured	Not measured	≤ 0.5 mm from horizontal	NMT 0.5° from horizontal
Performance verification test (PVT)	USP prednisone tablets RS	Not measured	CP instrument performance test with salicylic acid tablets	USP prednisone tablets RS
Temperature	37 ± 0.5 °C	± 0.5 °C of the target temperature	37 ± 0.5 °C	
Vibration	No perceptible vibration (no specification)	Vibration must be controlled (no specification)	≤ 0.1 mil of displacement	

Considerations for Dissolution Testing of Suspensions

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Interestingly, suspensions are mentioned in every route of administration according to products listed in the USP <1151> Pharmaceutical Dosage Forms. These include injections and implanted drugs, oral drug products, topical drug products, mucosal drug products, as well as inhalation and nasal drug products. Although dosage forms intended for oral administration will be the focus of this topic, many suspensions for injection, mucosal, inhalation, and nasal administration require very small volumes for dissolution and drug release testing, which may be covered as a future topic in *Practical Solutions*.

A suspension typically consists of two components: a liquid vehicle with solid particles including the API dispersed throughout. Some suspensions may be formulated as ready-to-use while others may require reconstitution of a powder or granular mixture with water by the pharmacist prior to dispensing. The latter typically carries a product designation of “for oral suspension”

(Left to right) Electropolished stainless steel paddle, PTFE-coated paddle, PEEK paddle, electropolished mini paddle, and PTFE-coated mini paddle

which generally provides physical and chemical stability of the preformulated suspension in a dehydrated state to ensure a suitable shelf life of the drug product.

Typical oral suspensions work well in USP Apparatus 2 paddle in traditional 1000 mL vessels with 500 to 900 mL volume used for most methods. The speeds that must be justified and validated during method development range between 25 and 50 rpm for most products to allow for suitable discrimination of dissolution method. Since a suspension is primarily dosed as a liquid preparation containing solid particles dispersed in the liquid, dissolution offers several challenges that must be considered in the dissolution method. These considerations and points of discussion include:

- Sample preparation (reconstitution and mixing)
- Density determination (ensuring dose accuracy)
- Sample measurement (accountability)
- Sample introduction (technique)

Sample preparation

If testing a product labeled "for oral suspension," the product must be reconstituted with purified water according to the labeled instructions. The product must then be properly mixed and the analyst must follow the required means of shaking (manual or mechanical) for the required length of time needed to disperse the preformulation into a homogeneous suspension. Mechanical shakers are preferred over manual means because of the variability that may be introduced analyst-to-analyst by "hand shaking" the suspension. Although, even mechanical shakers should have a fixed arc of rotation because the distance from the shaft of the mixer can also increase or decrease the mixing capability of the shaker. Most important is that the suspension is shaken for a fixed time, which must be stated in the method and documented by the analyst.

After shaking, a waiting period of typically five minutes should be implemented. During mixing, air bubbles will be introduced into the suspension and these need to have adequate time to surface. Second and equally important, the waiting time ensures that the suspension is actually "suspended." Performance testing of a suspension must challenge that the suspending agents are working to keep the product in a homogenous state and allow proper dosing. In other words, a seemingly harmless suspension of ibuprofen could have serious dosing consequences if the active drug floated to the top of the bottle immediately after shaking due to the failure or absence of suspending agents. This could allow an overpotent dose to be administered to an infant causing toxic levels in the serum, which may trigger a potentially life-threatening situation. After settling, the dose should be withdrawn from the middle of the container.

Density determination

The suggestion for sample introduction will be given in the next section but it will include a verification that the proper sample amount was delivered to the media in the vessel. A typical means of determining density is with a pycnometer, however, suspended particles may block the overflow tube. A simpler way may be to utilize a tared 50 mL volumetric flask to contain the suspension that was shaken as above to ensure homogeneity. Allow it to stand to allow bubbles to escape and implement tapping on a surface to assist with the removal of air bubbles. Clean the exposed surfaces of the glass volumetric and reweigh to determine the density in grams per mL of the oral suspension contained in the flask. The process should be repeated several times to ensure an accurate density determination.

Sample measurement

The most technique-dependent portion of the test is measuring a sample aliquot and introducing the aliquot into the dissolution media accurately and precisely. While most solid oral dosages are simply introduced into a basket or dropped into nonrotating media for the paddle apparatus, suspensions take considerably more technique, which should be well described so trained analysts can repeatedly and consistently introduce an accurate dose.

The preferred method of measurement is with a tared 5 mL syringe fitted with a cannula or large bore needle. After shaking and allowing to settle:

- Slowly draw sample from the midpoint of the container. The validation phase of method development should draw from the top, middle, and bottom. Withdraw an excess into the syringe.
- Remove the syringe and cannula and dispense excess sample to waste until the plunger reads 5 mL, then wipe the tip and set aside. Prepare all six samples prior to moving on to introduction in the next step.

Sample introduction

Sample must be introduced into the vessel based on the method that should state whether the sample is to be delivered to or under the surface of the media. After measurement:

- Introduce the sample into nonrotating medium. If variability occurs during development due to the pooling of a viscous sample in the bottom of the vessel, it may be justified to introduce the sample into rotating media. The method needs to state whether the media is rotating or not.
- After sample introduction, place the empty syringe with cannula on a balance to determine the weight of sample introduced, corrected for the tare weight, to ensure that the sample weight is within the acceptance criteria based on the density determination.
- Withdraw dissolution samples from the vessel at the halfway point and at the appropriate times within the ±2 % of the time requirement stated in the USP.

Summary

The rotating paddle method is typically used for dissolution testing of suspensions. Standardized methods of preparation based on shaking, settling, sample measurement, and introduction should be written into the method, and analysts should be trained in the dissolution testing of suspensions. Other methods of sample introduction have been employed such as re-pipetting, however, a positive displacement of the suspension with a syringe is recommended to minimize variability. Due to the possibility that air may be trapped in the suspension due to its viscosity, gravimetric introduction methods are preferred. Although numerous suspension methods are contained in the USP, which mention the apparatus type, media and volume, sampling times, and acceptance criteria, the analytical method should be validated to ensure that the above techniques are written into the method used by the laboratory to ensure accuracy and precision for testing from day-to-day, lab-to-lab, and analyst-to-analyst.

References:
- *US Pharmacopeia, USP 41, NF 36 Information Chapter <1151> Dosage Forms, 2018; USP Rockville, MD, USA*
- *FIP/AAPS Guidelines for Dissolution In Vitro Release Testing of Novel/Special Dosage Forms, Dissolution Technologies, February 2003*
- *Dissolution Discussion Group www.dissolution.com*

Are You Missing Out? Stay Current with Dissolution Product Updates

Dan Spisak, Product Manager, Dissolution Systems

Things move fast in today's world and it seems like every few weeks there's a new iOS, Android, or Windows update. Although the 708-DS and similar Agilent Dissolution instrumentation are not yet equipped to manage over-the-network firmware updates, we have other ways to keep you informed. This would be difficult to implement in a regulated environment such as Pharma, where dissolution testing is traditionally performed. For now, it's up to a variety of channels to communicate when updated firmware or software is available; one of them being the *Practical Solutions* newsletter you're reading right now.

Product and software improvements are being continuously developed at Agilent. Keeping up with these updates provides your laboratory with the latest features and compatibility offered for each system. Here are some ways that you can make sure you're taking full advantage of your Agilent dissolution investments:

- **Visit the Agilent Community** (https://community.agilent.com/). This online resource contains a wealth of product support information, including revision history for firmware and software products from Agilent.
- **Email the Dissolution Hotline.** You can always request this information by contacting the Dissolution Hotline at dissolution.hotline@agilent.com. It would be beneficial to review what updates are available prior to a regularly scheduled service (e.g., PM) or qualification (e.g., PQ/MQ) of your dissolution system.
- **Review the following table.** You can find the current (or soon to be released) versions of firmware or software for most Agilent dissolution products below.

Dissolution Product / Software	Current Version of Firmware (FW) / Software (SW)
708-DS Dissolution Apparatus	2.07 (main) / 2.02 (LCD)
850-DS Sampling Station	3.07 (main) / 3.0 (LCD)
Apparatus 3 (BIO-DIS) / Apparatus 7	5.08 (FW)
400-DS Apparatus 7	1.10 (FW) / A.01.05 (SW)
280-DS Mechanical Qualification System	A.01.05 (SW)
Dissolution Workstation Software	A.01.05 (SW)
Cary WinUV Dissolution Software	5.2.1 (SW)

Keep in mind that this information is always changing, so be sure to remain in touch with an Agilent representative or the Dissolution Hotline for the latest information.

Questions You Asked

Q. Referring to the USP Chapter <1724> Semisolid Drug Product – Performance Tests, what is the selection criteria for using various surface areas stated for the Immersion Cell – Model A specifically, Cell Area 4.0, 2.0, and 0.5 cm^2?

A. The Immersion Cell – Model A is based on the Agilent Enhancer Cell for drug release testing of ointments, creams, and gels. Regarding surface area, testing with an immersion cell is a bit different than typical dissolution testing because it provides a drug release rate relative to the surface area of the skin. In other words, dissolution testing provides a release rate (mg/min) for the active releasing from the dosage form, while a diffusion cell provides the release rate as related to a specific surface area (mg/min/cm^2). So, the variable surface area options with the Enhancer Cell (Immersion Cell – Model A) relate to controlling the release rate within the required 250 mL vessel.

The second issue with diffusion testing of an ointment, cream, or gel is that *there is no dose*. This means that the acceptance criteria is expressed as the rate of drug release with respect to a specific surface area (mg/min/cm^2). Traditional oral dose dissolution testing acceptance criteria is based on % of drug release comparable to its "Label Claim" so if a drug has 200 mg per tablet, the results are expressed as % of label claim. So, if 190 mg are found in the last sample, it is 95% of Label Claim.

The dissolution testing of an ointment, or gel, is relative to surface area of the membrane with respect to the 250 mL vessel volume for the Enhancer Cell. So the variable surface area options for the Enhancer Cell can restrict the rate with a smaller surface area since the volume is limited to 250 mL. This is helpful for a product that has a large amount of active drug that may quickly diffuse with respect to the limited volume in the dissolution vessel. Typically, the larger 4 cm^2 surface area is preferred for most compounds, but the smaller sizes are available as needed depending on release criteria of the formulation.

Immersion Cell – Model A is based on this Agilent Enhancer Cell

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