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Compendial and Regulatory Updates for Dissolution and Drug Release Testing

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This article provides a summary of compendial general chapters and regulatory guidance related to dissolution and drug release activities. The Compendial Updates section pertains to chapters within the US Pharmacopeia that are new, under revision, or recently revised. The Regulatory Updates include recent or draft guidance from the US FDA. This summary is intended to keep end users, involved in pharmaceutical disciplines of dissolution and drug release, up-to-date with new developments in the United States Pharmacopeia (USP) and the United States Food and Drug Administration (US FDA).

Compendial updates

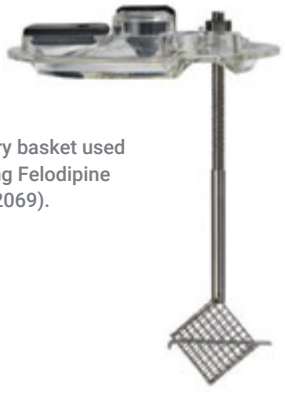
Documents in the USP Pharmacopeial Forum are not official. Proposed dates for official status are typically included at the end of the documents under revision along with the USP liaison contact information. Comments may be sent to the USP at any time; however, comments specific to revisions contained in the USP Pharmacopeial Forum must be received during the 90-day public comment period for consideration in the finalization of the chapter. While the following proposed guidance from the USP Pharmacopeial Forum is provided here as a reference, the subheading indicates the distinction between USP official information and suggested USP Pharmacopeial Forum guidance.

USP <711> Dissolution

Pharmacopeial Forum 46(6) Nov-Dec 2020, Official 01 May 2022

This in-process revision of the Dissolution general chapter focuses primarily on a stationary basket that has appeared in USP Monographs for Felodipine and Lamotrigine Extended-Release Tablets. This appears as USP national text because this chapter is partially harmonized with the European and Japanese Pharmacopoeias.

Although the stationary basket is listed in the chapter as an alternative to sinkers for USP Apparatus 2 (Rotating Paddles), it has been utilized for products requiring higher tangential flow to dissolve certain solid oral dosage forms. The basket shaft is attached to an evaporation cover so when it is in place during the test, the bottom of the quadrangular shaped basket is 1 cm from the top of the paddle blade. The dosage form is inserted through the opening in the top of the basket and the cover is inserted horizontally in the basket to keep it in the lower portion of the basket. When lowered into the vessel at the beginning of the test, the long face of the side of the basket is in a vertical plane perpendicular to the radius of the cylinder of the vessel.[1]



Stationary basket used for testing Felodipine (p/n 12-2069).

USP <1001> In Vitro Release Test Methods for Parenteral Drug Preparations

USP New Information Chapter, Pharmacopeial Forum 46(3) May-June 2020

This proposed informational chapter was developed by the USP Dosage Forms Expert Committee to support performance testing for injections and implanted drug products, generally known as parenterals. The chapter includes a table for known examples of apparatus used for in vitro release of parenteral formulations including: nonaqueous solution/oily preparations, suspensions, nanosuspensions, liposomes, microparticles, powders for suspension, emulsions, implants, drug-eluting stents (DES), and in situ forming preparations.

USP <1002> Filters and Membranes

USP New Information Chapter under development, proposed to appear in the Pharmacopeial Forum in 2022

This new General Information chapter, currently in development, will focus on synthetic membranes and skin used for testing in analytical procedures including dissolution.

1. USP Pharmacopeial Forum 46(6) Nov-Dec 2020. USP, 12601 Twinbrook Parkway, Rockville, MD 20852
2. USP Update on Performance Tests, Margareth R.C. Marques, Principal Scientist General Chapters, August 2021

This chapter is closely linked with the in-process revision of General Information chapter <1724> Semisolid Drug Products – Performance Tests. The new chapter is intended to include information on filtration procedures, material of construction, pore size, adsorption, leachable and extractable substances, and selection process, as well as filter validation, quality, and integrity.[2]

USP <1711> Oral Dosage Forms – Performance Tests

USP Official, 01 May 2021

This general information chapter lists performance tests for a variety of dosage forms that are not specifically covered in other dissolution-related USP General Chapters. These include effervescent, chewable, sublingual, orally disintegrating, and gastroretentive tablets, as well as delayed-release dosage forms, granules or pellets, suspensions, powders, lozenges, oral pastes, oral gels, chewable gels, and medicated feeds and drug products in animal/veterinary feeds.[3]

References are included in this chapter for pertinent FDA guidance, issued for many of the dosage forms listed above. References are also provided for the FDA Dissolution Methods Database on the US FDA website.

Read more

USP <1087> Intrinsic Dissolution

Dissolution Testing Procedures for Rotating Disk and Stationary Disk – USP National Formulary (NF) Official 01 Dec 2020

Review of this chapter by the USP Expert Panel determined that the content is complete and current. However, it was decided that the original title "Apparent Intrinsic Dissolution" was misleading. This revision includes a change in title and minor corrections.

USP <1088> In Vitro and In Vivo Evaluation of Oral Dosage Forms

USP NF Official 01 May 2021

This chapter underwent numerous changes in content and organization and included the concept of in vitro – in vivo relationship (IVIVR) if the preferred in vitro – in vivo correlation (IVIVC) is not possible.

The chapter also provides an expanded definition of IVIVC and IVIVR, as well as the following revisions:

- Revision of the title to include "Oral" Dosage Forms
- Replaced "In Vitro Evaluation" section with a new section on "In Vitro Characterization" including technical requirements for dissolution testing
- Revised "In Vivo Evaluation of Dosage Forms" section including pharmacokinetic profiling and characterization
- Removed "Characterization of Drug Substance" as not necessary for IVIVC
- Revised the "Characterization of the Oral Dosage Form" section on IVIVC to give examples of correlation
- Added Glossary for terms used in connection with the development of an IVIVC[4]

USP <1724> Semisolid Drug Products

Performance Tests – In Process Revision

The USP Expert Panel is in the process of revising General Information chapter <1724>. The current version primarily discusses in vitro release testing (IVRT) requirements utilizing synthetic membranes.

The revision will include in vitro permeation testing (IVPT) requirements utilizing skin, and also includes chapter reorganization.

3. USP NF Official 01 May 2021. USP NF 2021, 12601 Twinbrook Parkway, Rockville, MD 20852
4. USP NF Official 01 May 2021. USP, 12601 Twinbrook Parkway, Rockville, MD 20852

Regulatory updates

While regulatory guidance from the US FDA represents the current thinking of the Agency, they do not establish legally-enforceable responsibilities. The legal aspects are contained in the US Code of Federal Regulations (CFR 21) Parts 210 and 211 for the pharmaceutical industry. Guidance documents provide recommendations and information to meet legal requirements in the referenced CFR.

Level 2 Q2(R1) Validation of Analytical Procedures: Text and Methodology Guidance for Industry

September 2021; Final

This regulatory guidance combines previously-published FDA guidance and elements of the International Council for Harmonization (ICH) Q2A and Q2B guidelines in a single document.

The objective of the validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. Validation procedures are not only for the analytical finish procedures for drug formulations, but also apply to assays associated with other analytical procedures such as dissolution.[5]

For additional detail, refer to USP <1092> The Dissolution Procedure which recommends several parameters to be evaluated for dissolution methods: media composition, surfactant concentration pH, deaeration, volume agitation rate, sampling time, and temperature.[6]

Read more

Level 1 Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations

June 2021; Draft

The dosage forms mentioned in this guidance for enteral feeding tubes cover a wide range of oral dosage forms including pellets, powders, granules, suspensions, capsules, and tablets. The guidance covers the selection of media, as well as recommendations for dissolution testing of modified- and extended-release drug products.

Read more

Level 1 Transdermal and Topical Delivery Systems Product Development and Quality Considerations

November 2019; Draft

This guidance contains recommendations for manufacturers of transdermal and topical delivery systems (TDS) in line with quality-by-design (QBD) principles. Although the two systems have many similarities, transdermal systems deliver the active pharmaceutical ingredient (API) across the skin and into systemic circulation, while topical formulations are designed to deliver the API into local tissue.

Among the drug product characterization studies is in vitro permeation testing (IVPT) which generally involves the use of skin to characterize the rate and extent of transdermal or topical drug delivery. Routine quality control with transdermal systems utilizes USP Apparatus 5 (Paddle Over Disk), Apparatus 6 (Rotating Cylinder), and Apparatus 7 (Reciprocating Disk), while topical semisolids use the vertical diffusion cell, immersion or enhancer cells, or the flow-through cell with synthetic membranes.

Read more

Level 1 guidance: new regulatory requirements or significant changes to existing policy

Level 2 guidance: minor changes to existing policy

5. Validation of Analytical Procedures: Text and Methodology FDA Guidance for Industry (September 2021)
6. USP <1092> The Dissolution Procedure: Development and Validation, Official as of 01-Dec-2020, USP, 12601 Twinbrook Parkway, Rockville, MD 20852

The Agilent Dissolution Hub: Our Expertise at Your Fingertips

Lorraine Kay, Product Manager, Dissolution Systems

The field of dissolution can sometimes be confusing or difficult to navigate. Thankfully, your Agilent team has a long history of success from gaining knowledge, expertise, and innovation through years of sharing ideas and trialing new concepts.

Agilent gives you the latest source of information regarding dissolution testing, with the Dissolution Hub as our centralized repository to help you navigate through our resources.

Community

Visit the Agilent online community for up-to-date resources on dissolution, including a repository of videos, whitepapers, and questions asked by users of our products. Ask fellow customers and Agilent experts for help anytime, anywhere.

Dissolution Discussion Group (DDG)

The DDG is the oldest dissolution forum available on the web. Free to register and post, this forum contains information from over twenty years of conversations from people like you.

Practical Solutions

Access past copies of the Agilent Practical Solutions Newsletter, your free and quarterly dissolution newsletter that includes updates to USP, best practice advice, Q&As, firmware and software updates for Agilent Dissolution Solutions, and much more.

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Contact the Agilent Dissolution Hotline, connecting you directly to dissolution specialists when you need us.

Find resources to support your dissolution needs, including webinars, one-on-one training, and more.
Visit: www.agilent.com/chem/dissolution-hub

Advancing the Science of Dissolution

Karen Krauel-Göllner, Product Manager Dissolution

The Dissolution Discussion Group (DDG) is an independent forum which gives you the opportunity to discuss issues which challenge the industry and affect the day-to-day task of developing, performing, and validating dissolution tests and related chemical analyses.

Apart from the online forum, the Dissolution Discussion Group also runs quarterly meetings to provide you with the latest updates in the field of dissolution. The agenda includes a brief overview of the session's topic, followed by an open forum and panel discussion with leaders from the industry, academia, and/or authorities.

This format provides you with direct access to experts – you are free to ask your questions and listen as the topic is discussed.

To sign up for the free events simply go to:
https://webinars.on24.com/agilentafo/ddgonlinemeetingsFY22

We are looking forward to your contributions during the discussions.

DISSOLUTION
DISCUSSION GROUP

Meetings in 2022

17 February 2022
What You (May) Have Missed: Key Regulatory and Compendial Dissolution Updates in 2021

12 May 2022
Exploring Dissolution Techniques for Vaccines, Liposomes, and Parenterals

28 July 2022
Current Practices for the Dissolution Testing of Medical Devices, Combination Products, and Novel Dosage Forms

10 November 2022
A Trip to the Vet: Expert Advice about Dissolution Testing of Veterinary Products

Questions You Asked

Bryan Crist, DissoAssist Consulting

Getting your (sample) timing right

Q When the USP General Chapter <711> Dissolution mentions in the Procedure section that sample "specimens are to be withdrawn only at the stated times, with a tolerance of ± 2%." What does this mean exactly and how can it be applied to automated equipment?

A The ± 2% rule ensures that withdrawing sample at each individual time point is occurring precisely enough to provide an accurate assessment of the release profile for multiple samples. Since dissolution is basically a kinetic test, relying on precise timing must also be properly documented to prove that each sample was pulled within the ± 2% time window.
For example, an immediate-release product with a 30 minute sample means that each of the six samples must be pulled within 36 seconds of the time that the dosage forms were dropped.

If sampling manually, it is advantageous to stagger the dosage introduction to allow extra time to properly take the sample. It is also important to note that the sample must be filtered during this timing window to stop the dissolution process.

For automated systems, preconditioning of the tubing and filters, as well as movement of the sample, should be taken into account. It is important to ensure that the sample being collected is indeed removed from the vessels within the USP timing window.

Automation has many advantages, such as repeatability and reduced variability, but an equivalence study (versus manual sampling) should be performed to ensure results for each product are consistent.

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