

# Practical Aspects of Dissolution Instrument Qualification—a European Perspective

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## INTRODUCTION

**D**issolution testing is an important tool to characterize the in vitro performance of dosage forms. It is not an absolute method; strictly speaking, equipment cannot be calibrated. Instead, from the perspective of a quality control (QC) laboratory, reliable instrument qualification is one of the most important requirements of cGMP. While harmonization efforts for qualification strategies of standard laboratory equipment lead, in most cases, to clear and undisputed approaches, the standardization of dissolution apparatus qualification procedures is still ongoing.

The most common USP Apparatus 1 and 2 are used in pharmaceutical laboratories worldwide to perform quality control analyses either during the manufacturing process (PAT) or as part of release testing. Moreover, they are used to monitor formulations throughout pharmaceutical development. Drug candidate selection for clinical studies is based on differences attributed to manufacturing variables during a Quality by Design (QbD) oriented development, whereas the release of marketed products relies on the dissolution similarity of manufactured batches in comparison to the models described in the dossiers for registration. This underlines the need for reliable dissolution data.

A study of the relevant rules and procedures reveals that dissolution apparatus qualification consists of two parts: a mechanical qualification and a performance test with a reference standard. In detail, the leading documents concerning dissolution apparatus qualification [e.g., *United States Pharmacopoeia (USP)* and the *European Pharmacopoeia (EP)* on the one hand and ASTM E2503-07 and FDA Guidance for Industry (1) on the other hand] do not advise identical procedures and specifications. Proposals were made for procedures to match the so-called “chemical” and “mechanical” qualification (2) but are still leaving some uncertainty at QC testing labs.

In the past, harmonization efforts like ICH Q4B took effect and harmonized the respective chapters of the *USP* and the *EP*. One remaining difference is the *EP* nonmandatory recommendation of the use of a reference product that is sensitive to hydrodynamic conditions for performance testing, while *USP* requires the use of its reference tablet.

This article describes the authors’ strategy and observations when performing “mechanical” and “chemical” qualification of dissolution Apparatus 1 und 2 in a typical QC laboratory that has to follow both United States and European requirements.

## SOURCES OF VARIABILITY FOR DISSOLUTION TESTING

Proper QC testing targets the accurate and precise characterization of product in vitro performance. The principal goal of a QC testing laboratory is therefore to minimize the artifacts that may potentially increase both patient and pharmaceutical manufacturer risk. General sources of variability may arise from the testing procedure, the instrument, and the analyst in addition to the inherent properties of the drug product. Relevant sources of variability are listed in Table 1.

Modern dissolution testing mostly uses automated systems consisting of the dissolution apparatus, a sampling and processing unit, and an instrument for quantification. For each testing run, the operational variables are adjusted because they may influence the results. These are the stirring rate, the temperature, the medium volume, and the sampling schedule. They are not part of the qualification process. These factors are individually programmed and are thus subject to random errors. In addition to the factors mentioned above, permanent and systematic errors leading to highly biased data may be generated by the apparatus itself. Inherent instrument-related sources of variation that may influence the dissolution results (e.g., by altering fluid dynamics) are listed in Table 2.

The primary goal of routine qualification and re-qualification is to prove that each individual parameter is within the specifications set by the pharmacopoeias and, importantly, that the sum of all tolerable deviations has no relevant impact on the results.

## ENHANCED MECHANICAL QUALIFICATION—IQ AND OQ CHECKPOINTS AND LIMITATIONS

We developed our standard operating procedure (SOP) for the qualification of dissolution apparatus used for QC testing based on a risk analysis. The concept of this SOP is an enhanced mechanical qualification in line with pharmacopeial requirements. This SOP contains specifications that, in some cases, may be more stringent than *USP* or *EP* recommendations. The SOP only allows performance

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**Table 1. Sources of Variability in Dissolution Testing**

Lab environment
Medium preparation
Dissolution testing apparatus
Sampling, transfer, processing (filtration, dilution, storage) of solutions
Analytical instruments and the method used for quantification
Testing procedure
Analyst

verification testing (PVT) after successful mechanical qualification. Selected IQ and OQ checkpoints as well as the specifications of our internal SOP are given in Table 3.

However, not all potential factors of influence, such as the inner surface of the vessel, vibration, or their combination, may be covered by a qualification strategy limited solely to mechanical qualification.

The design of most modern dissolution testers incorporates precisely controlled physical parameters, test conditions, and alignment to ensure that the release of drug from a dosage form will be determined consistently from one tester to another and from one laboratory to another. However, apparatus performance may contribute to interlaboratory variability as demonstrated from the results generated in laboratories that participated in global collaborative trials (3).

In addition to these arguments for a staggered use of USP Prednisone Tablets RS, the following example shows that isolated physical-parameter checking is not a substitute for the performance verification test of the instrument run under operational conditions. Because of design features, physical checkpoints may not be accessible during operation. The results depicted in Figure 1 show the malfunction of an autocentering lid after mechanical qualification successfully passed.

**Table 2. Instrument-Related Sources of Variability for Dissolution Results**

Levelness of plate and lid
Vessel dimensions, asymmetry and surface irregularities
Instrument vibrations
Verticality of vessel and/or stirrer shaft
Rotation speed variations
Wobble, height and centering of stirring elements
Paddle or basket dimensions including irregularities
Sampling probes and positioning

**Table 3. IQ and OQ Checkpoints Taken from PHAST SOP for Mechanical Qualification**

Part	Checkpoint	Specification
Dissolution apparatus	Installation location	Installation on a leveled and stable workbench
	Vibration	No additional sources of vibration in the work environment
	Work environment	Constant conditions, no direct ventilation
Vessels	Dimensions	Conform to USP <711> / Ph. Eur. all vessels from the same vendor
	Centering	Maximal deviation from vertical axis of the shaft 1.0 mm
	Assignment	Vessels are clearly assigned to test centers
Shafts	Dimensions	Conform to USP <711> / Ph. Eur.
	Wobble	$\leq \pm 1.0$ mm
	Assignment	Shafts are clearly assigned to test centers
Paddles	Dimensions	Conform to USP <711> / Ph. Eur.
	Wobble	$\leq \pm 1.0$ mm
	Height	Distance to the bottom of the vessel 25 mm $\pm$ 2 mm
Baskets	Dimensions	Conform to USP <711> / Ph. Eur.
	Mesh size	
	Wobble at the lower rim	$\leq \pm 1.0$ mm
	Height	Distance to the bottom of the vessel 25 $\pm$ 2 mm
Test centers	Assignment	Clearly assigned
	Rotation Speed	50 rpm $\pm$ 2 rpm ( $\pm 4\%$ ) 100 rpm $\pm$ 4 rpm ( $\pm 4\%$ )
Thermostat	Temperature accuracy	Adjustment to 37.0 $\pm$ 0.5°C, temperature check before and after a dissolution run
	Temperature stability	
Sampling unit	Positioning	Conform to USP <711> / Ph. Eur.

### SOURCES OF ERROR ON VERIFICATION TESTING WITH THE USP PREDNISONE TABLETS RS

The use of a qualified tablet formulation is well accepted in a laboratory designed for routine tablet testing. However, the USP Prednisone Tablets RS are not optimized for fast and complete dissolution like a conventional oral immediate-release drug product. Instead, slow dissolution within a reasonable time is needed for a qualification product to detect instrument

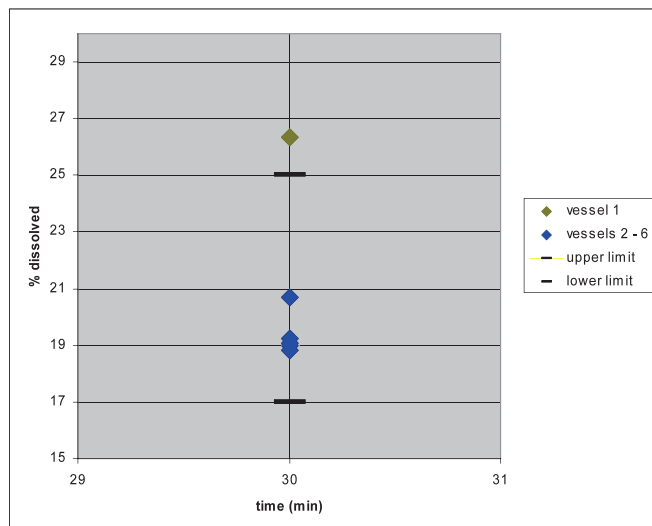


Figure 1. PVT of USP Apparatus 2 with an autocentering malfunction at vessel 1.

impact on the rate. A typical slow-release product would not be suitable because one of the goals of slow-release products is robustness against physiological and mechanical impact. This may not match the need of sensitivity to mechanical deficiencies. Moreover, this product must be qualified by collaborative trials of laboratories that need clear qualification themselves. Only after independent qualification is the product considered suitable. From the European perspective, the USP Prednisone Tablets RS may be such a product. They are used in our laboratory following successful mechanical qualification to prove the performance of the apparatus. Examples are taken from real-life performance verification tests according to USP (USP Prednisone Tablets RS, 500 mL water, 50 rpm, 30-min sampling).

Some remarkable observations were made in the course of numerous qualification runs. The manual and staggered sample insertion process is mentioned as one example of a constructional deficiency in some instruments. USP <711> requires application of the tablet before the start of stirring. Autosampling devices are disconnected for qualification of the bath. This requires a staggered start to leave time for sampling. With a particular apparatus, all spindles are driven by a belt that is connected to the central motor via a clutch. This does not allow a properly staggered start. After application of the first USP Prednisone Tablets RS, a staggered immersion of rotating spindles is required. While manually lowering the individual spindle to the final position previously adjusted to 25 mm, rotation may be hindered. The clutch compensates for the friction, which has an effect on all spindles. Thus, the rotation speed may be slightly higher for a limited time after release. The sum of all individual rotation-speed discontinuities is greatest for the first, and lowest for the last, USP Prednisone Tablets RS applied. The exposure time to the initially increased hydrodynamic

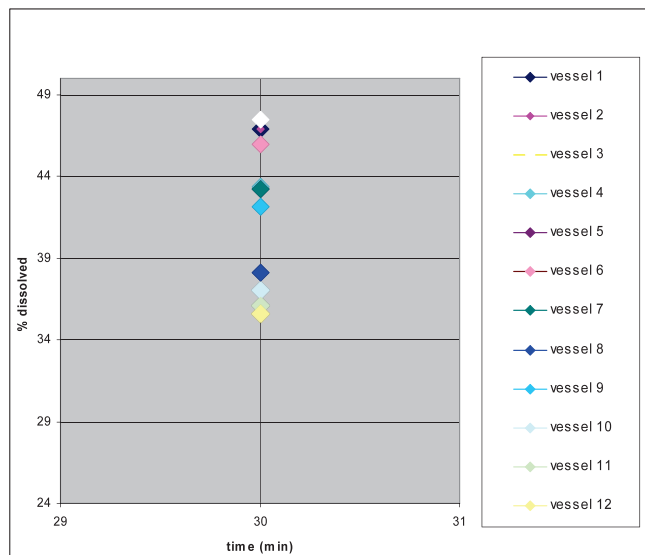


Figure 2. PVT of USP Apparatus 2. Relation of initial clutch compensation after staggered insertion of connected spindles. The latest insertion has the lowest dissolution rate. Application sampling times corrected for delay.

forces is related to the amount dissolved after 30 min. This relation is depicted in Figure 2.

### PVT "FAILURE" DUE TO PRECISE RESULTS AFTER HEIGHT MANIPULATION OF PADDLES

During one root-cause analysis, we also investigated the impact of small deviations from the physical specifications. We used an apparatus with 12 positions. The first six paddles (1–6) were adjusted to exactly 25 mm from the center of the hemispherical bottom. The other positions (7–12) were adjusted to 24 mm, which is still in specification. The geometric mean (GM) of the first six vessels differed by 3% from the GM of vessels 7–12. This

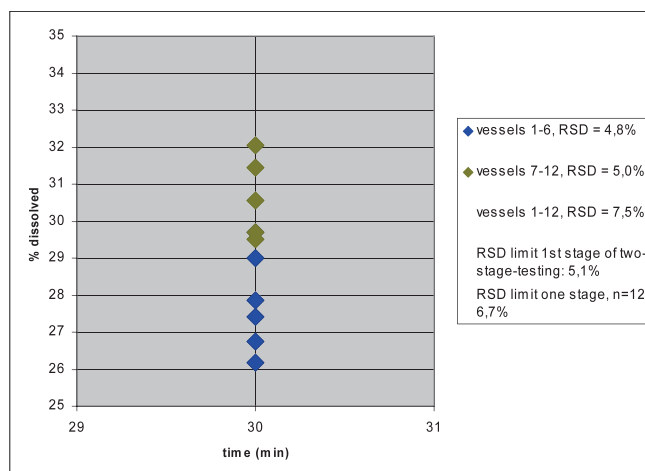


Figure 3. PVT of USP Apparatus 2 showing sensitivity of PVT toward height adjustment. Distance for vessels 1–6 was 25 mm and for vessels 7–12, the distance was 24 mm.

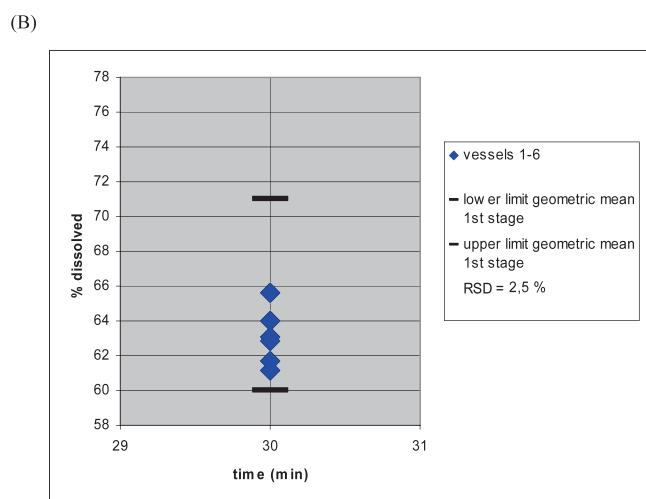
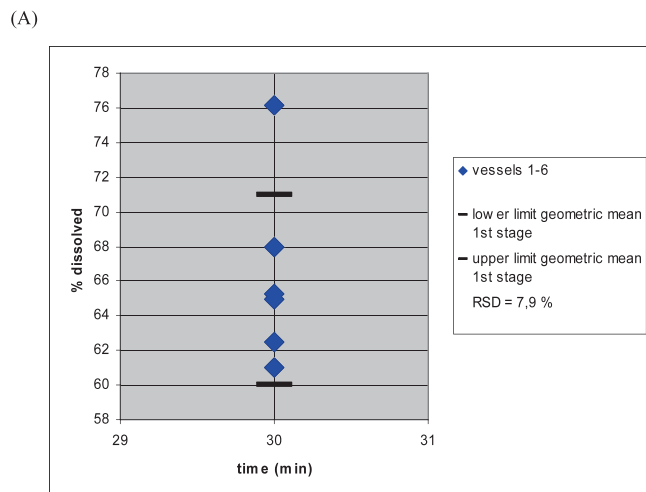


Figure 4. PVT testing of USP Apparatus 1. (A) Floating USP Prednisone Tablets RS. (B) USP Prednisone Tablets RS sitting at the lower bottom mesh of the basket.

demonstrates precision and sensitivity of the USP Prednisone Tablets RS to minor changes in hydrodynamic conditions.

While the separate analyses of vessels 1–6 and 7–12 met the stringent first-stage criteria of the two-stage procedure, the entire data set did not meet the specifications for the one-stage procedure with twelve vessels. These findings, depicted in Figure 3, may lead to further harmonization of mechanical and PVT procedures.

### IMMERSION OF BASKETS

The sample insertion process appears to be critical for Apparatus 1. Even after proper degassing, air may be entrapped in the basket depending on the lowering speed of the basket. Air bubbles may adhere to USP Prednisone Tablets RS as well as to particles after disintegration, causing floatation. Particles inside the basket are exposed to higher shear forces than particles settled on top or throughout the meshes into zones of lower hydrodynamic

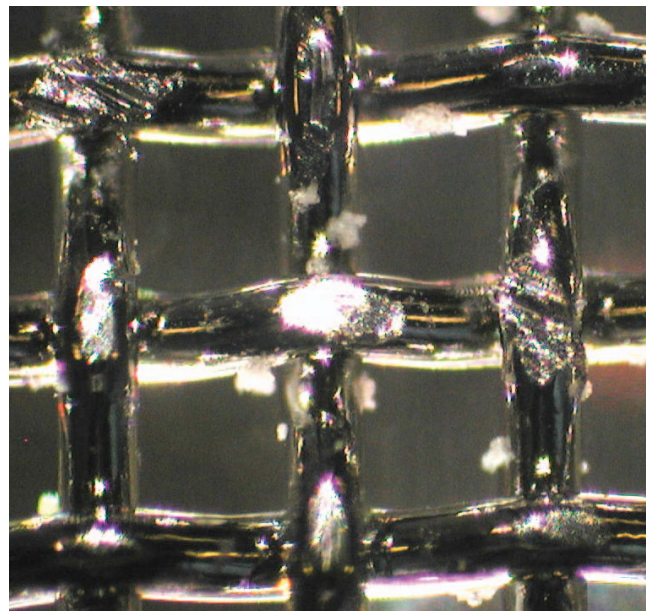


Figure 5. Deposits on basket wires.

activity. Hence, floating particles and tablets are often the cause of higher dissolution results for the PVT. The effect of floating tablets is shown in Figure 4. Floating USP Prednisone Tablets RS dissolved with an RSD of 7.9%, whereas PVT sitting on the bottom mesh of the basket dissolved with an RSD of 2.5%. This meets the specification of 7.7% for lot P11300 in the first stage of the two-stage-testing procedure.

### INSUFFICIENT BASKET CLEANING

Other issues that have been identified through the PVT are basket deficiencies and basket meshes clogged by air bubbles even after proper degassing. The effect of insufficient cleaning is shown in Figure 5.

Air bubbles adhered to an unclean wire surface when baskets were immersed. Mesh openings tended to be partly or completely clogged by bubbles. Particles were retained longer in an environment of higher hydrodynamic activity leading to high results. These observations were made after several out-of-calibration results were obtained, and resulted in a revised cleaning procedure for the baskets.

### WISH LIST FOR IMPROVED USP PREDNISONE TABLETS RS

Although the practical experiences with the PVT lead to improved preconditions in dissolution testing, not all sources of failure could be eliminated. Due to stability effects of properly stored USP Prednisone Tablets RS, paddle apparatus qualification in the past failed reproducibly with results that were too low. The effect, which was known to the USP, led to a resetting of specifications. More stable USP Prednisone Tablets RS, preferably with a shelf-life specification, are desired in the future.

## SUMMARY AND CONCLUSION

An extensive qualification strategy for dissolution Apparatus 1 and 2 may combine meaningful mechanical qualification with the use of reliable standard tablets like the USP Prednisone Tablets RS. Instrument quality has largely improved over the last decades. Vessel quality and mounting provide room for further improvement as shown by Marc Liddell (4).

The USP Prednisone Tablets RS may need to be improved as well. Reformulation with ongoing stability studies is desired. This may not be an easy task because sensitivity to the combination of factors, each individually not violating the specifications of mechanical qualification, would have to go in line with greatest robustness of use. Finally, both similarities and differences between the USP Prednisone Tablets RS and any pharmaceutical tablet product may need to be explained to users.

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