Dispelling the Myth: 6 versus 12 Position Dissolution Apparatus

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The dissolution test is based on 6 results. The apparatus has been typically built with a minimum of 6 positions to accommodate enough vessels to run a complete test. The number of units to evaluate appears in the USP General Chapter <711> Dissolution, Acceptance Criteria tables for each type of dosage. This number and configuration can be found in the literature beginning in the 1950s. It officially appeared in the US Pharmacopeial Forum in 1970. Often the acceptance criteria or comparison data requires several sets of 6 to obtain 12 or 18 results which have historically been tested on 6-position apparatus. Interestingly, the number of tablets to be tested in the ICH Harmonized Pharmacopeia (EP, USP, and JP) is described as an assembly in the singular throughout the harmonized dissolution chapter. For instance, place the stated volume of dissolution media in the vessel…place one dosage unit in the apparatus, etc.

In terms or regulatory requirements for dissolution testing, FDA guidance suggests that marketed dosage forms are tested for specification setting with 12 units. This number also correlates with the FDA's required number of tests on human subjects ($n \geq 12$) to determine the bioavailability of products and in vitro-in vivo relationships. Specifications (Q) are based on twelve units and expressed as the percentage of labeled required for demonstrating a therapeutic effect. However, this *does not imply or intend for this testing to be done at the same time or on a single dissolution apparatus with 12-positions*. 6-Position dissolution apparatus utilized for testing products whether they are used for specification setting (testing a total of 12 dosage units) or routine quality and conformance testing which is based on sets of 6 units with tighter limits (Q+5%). FDA Guidance also requires testing a total of 12-units each for demonstrating bioequivalence between reference and generic products – but they do not require all 12 units to be tested simultaneously.

In summary, the number "12" is only a reference point of a minimum number of units to be tested to adequately set specifications and ensure bioequivalence between generic and reference drug products; it is not an apparatus requirement. More units (18 or 24) may be tested to assure higher accuracy and precision in statistical comparison methods such as f_2. Dissolution apparatuses are developed and used worldwide based on 6-positions for matter of convenience and conformance. 12 units are routinely tested on a single 6-position apparatus performing the method twice.

Why is it more advantageous to use two 6 or 8 place units versus one with 12 or 14 positions?

1. Regulatory. Although it is a requirement for f2 comparison to utilize a minimum of 12 units, it is *not* a regulatory requirement to perform dissolution on a single 12-position system. There is no regulatory requirement to perform all numbers required for comparison at the same time.
2. Compendial requirement #1 – Samples are withdrawn only at specific times within 2% of the time they were dropped. You do not have a sample until it has been filtered to stop the dissolution process. This equates to pulling and filtering 6 samples in ± 36 seconds but this

has to be done at the proper position. If a 12-position apparatus is used, 12 samples will need to be collected and filtered within ± 36 seconds; this is only 3 seconds per position.

3. Compendial requirement #2. Because of the previous requirement, dosage forms may be introduced at consecutive intervals (for instance every 30 seconds) to allow time to sample. Tablets may be staggered however; dosage forms are required to be dropped into nonrotating medium. If someone starts the apparatus by introducing a tablet to the first vessel and starts the apparatus, all positions will rotate. The 12-position apparatus must be able to keep media from moving until each dose is introduced.
4. Flexibility. Two 6-position units allow you to start and stop two independent tests at different times. With a single unit, you must run the same method speed and test length for both batches. You can start and stop two apparatus independent of one another with 6-position systems.
5. Failure investigation. Two 6-position apparatus will require less investigation and retesting if there is a failure. If one tablet among the 12 fails due to a mechanical issue, do both batches need retested? With two independent apparatus there is less ambiguity if a failure occurs since a single test is associated with a single apparatus.
6. Adherence to stricter Enhanced MQ guidelines. The tighter specifications required by the ASTM and FDA MQ procedures will be more difficult to meet. We suggest you receive assurances that any 12- or 14-place system will pass the new MQ physical parameters. Vessel/shaft centering is now only 1.0 mm; if one position is off by more than 1.0 mm in the upper and lower portion of the vessel the entire unit should be taken out of service until repaired, or readjusted and re-qualified.
7. Less downtime. If a single 12 or 14 place unit is removed from service for a mechanical or repair issue, you've lost the productivity of two systems. If a problem occurs with one of two dissolution apparatus, you can still operate the other system.
8. Automation flexibility. Whether it is automated sampling, media replacement, or online UV or LC measurement; there are a multitude of automation solutions available for 6 or 8 place systems. If your testing needs change, the more independent approach can accommodate pathways for automation. 8-position apparatus allow easy online UV integration since the spare vessels are used for blank and standard solutions during the test.

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