USP Apparatus 3 – Reciprocating Cylinder

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Description of subject matter

Traditional paddle and basket apparatus offer a convenient means to evaluate most oral drug formulations over extended periods of time. If, however, a more representative drug release method including changes in pH, agitation and resident time were required to characterize the release profile, it was difficult to accommodate these variables during a dissolution test with the basket and paddle apparatus. In the 1970s, researchers in the field of extended and controlled release formulations used the rotating bottle method established in the US National Formulary (NF XII 1965 - XIV 1975) which provided sound agitation but was labor-intensive and difficult to automate which was probably the reason that the USP never adopted the rotating bottle method.

A presentation at the 1980 Federation Internationale Pharmaceutique (F.I.P.) meeting in Europe drew attention to acute problems associated with USP Apparatus 1 and 2 dissolution results. The conference inspired the concept for the USP Apparatus 3 based partially on the increased agitation characteristics found in the rotating bottle apparatus. As research progressed it became apparent that a system should be able to change media composition, agitation rate and resident time to achieve in vitro-in vivo correlation (IVIVC). The inspiration led to the design of the BIO-DIS during the 1980s which was an abbreviation for biorelevant dissolution. Due to promising research, the apparatus was eventually adopted in USP XXII in 1991 as USP Apparatus 3 – Reciprocating Cylinder Apparatus in the USP Chapter <724> Drug Release. Due to harmonization of the dissolution pharmacopeial text through the International Conference on Harmonization (ICH), USP Apparatus 3 – Reciprocating Cylinder was moved to USP Chapter <711> Dissolution. Apparatus 3 is also harmonized with the European Pharmacopeia in 2.9.3 Dissolution Test for Solid Dosage Forms.

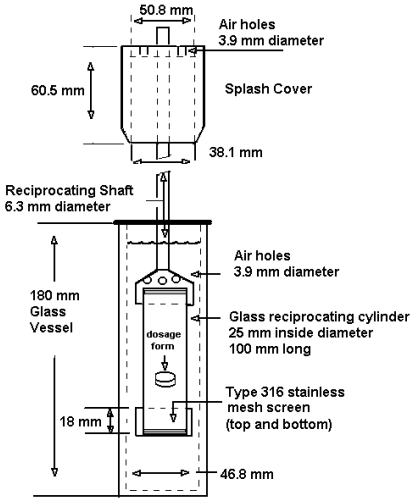
The USP Apparatus 3 – Reciprocating Cylinder (BIO-DIS) is an apparatus utilized for drug release profiling from extended release products because it can quickly and easily expose products to mechanical and physio-chemical conditions which may influence the release of the products in the GI tract. The Extended Release Apparatus was designed to test the dissolution rates of extended release products or any dosage form requiring release profiling at multiple pH levels. The ability to transfer the product from one pH to another makes it an excellent candidate for delayed release products.

Technical details

Apparatus Description: The reciprocating cylinder apparatus has seven reciprocating cylinders which consist of glass tubes with threaded ends to secure an upper cap and lower cap which hold screens to contain the dosage unit. Also, this cylinder may be referred to as the inner tube.

The apparatus consists of up to six sets of cylindrical, flat bottom 300 mL glass vessels which are filled with media and held in a water bath with a vessel rack. Also, the vessels may be referred to as the outer tubes.

A motor and drive assembly reciprocate the cylinders vertically inside the vessels. The cylinders move from row to row, to expose the undissolved drug product to various pH levels. As the cylinder reciprocates vertically, the drug product is constantly exposed to media contained in the vessel.



The apparatus' 300 mL vessels typically contain a working volume of 200 to 275 mL vessel volume, avoiding overflowing of the media during periods of higher reciprocation rate. The operational minimum is about 150 mL vessel volume. A wide range of products may be tested in the apparatus

from immediate release to extended and sustained release products. Formulations can include tablets, capsules, gel caps, beads, chewable tablets, delayed release and formulations with site-specific properties.

The key feature is its ability to accurately profile drug release through various pH, agitation rates, and residence times. The apparatus is harmonized between the USP and EP however, it is not presently recognized by the JP 16 dissolution test chapter 6.10.

Performing the test: When the test begins, the reciprocating cylinders descend slowly into the first row of the vessels. Then the reciprocating motion starts. After the programmed time for this row expires, the reciprocating cylinders rise above the vessels to drain for a programmed time, and automatically move to the next row. Then the reciprocating process is repeated in the vessel containing the next media.

Apparatus Qualification: Similar to Dissolution Apparatus 1 and 2, the qualification of USP Apparatus 3 had consisted of a combination of physical parameter verification and the PVT with USP Chlorpheniramine Maleate ER Tablets. Effective February 1, 2012, USP removed the requirement for Apparatus 3 Performance Verification Test Apparatus Suitability section of General Chapter <711> Dissolution. Although an alternative process was under investigation, no replacement PVT test has emerged at the time.

As an alternative to the PVT, some quality programs have adopted a similar transition to enhanced mechanical qualification and these additional steps should ensure the suitability of the apparatus under guidelines of analytical instrument qualification (AIQ). These steps should include certification of components, documentation of preventative maintenance, mechanical parameters, verification and operational checks performed at time of use.

The current physical parameters and tolerances stated in USP <711> Dissolution are:

Physical Parameter	Specification and tolerance
Vessel Temperature	37 ± 0.5 °C
Dip rate (DPM)	± 5% of set speed
Stroke Distance	10.0 cm ± 0.1 cm
Bottom screen	Per method, subject to ASTM or ISO
Top screen	Per method (optional), subject to ASTM or ISO
Time points	± 2% of specified time

Operational checks at time of use should include:

- Reciprocating cylinder glass tubes are free from residue, scratches and cracks
- Screens of appropriate dimension required in the method are used and are not damaged, frayed, misshapen or corroded
- Vessels are clean and free from residue, scratches and cracks
- Upper and lower caps are clean and free from residue
- Vessel temperature is maintained at 37.0 ± 0.5°C
- Evaporation covers (2) for the vessels are installed with the proper tension to retract and move freely during the test

Calculations: The calculations for Apparatus 3, which utilizes separate rows during a test, differ slightly from traditional Apparatus 1 and Apparatus 2 methods. When multiple rows of media are used, add the amount of drug from previous rows to the amount of release in the current row. This is most easily done by calculating the mg of drug released in each row, adding them, and then comparing that to the total label claim of the drug. For example:

- mg dissolved row 1 = (sample absorbance row 1/standard absorbance) x (standard weight/standard volume) x vessel volume

- mg dissolved row 2 = mg dissolved row 1 + [(sample absorbance row 2/standard absorbance) x (standard weight/standard volume) x vessel volume]

- mg dissolved row 3 = mg dissolved row 1 + mg dissolved row 2 + [(sample absorbance row 3/standard absorbance) x (standard weight/standard volume) x vessel volume]

- Note: mg dissolved divided by the label claim will be the % dissolved for each time point

Example Applications for USP Apparatus 3:

Immediate Release Testing: FDA published the "Evaluation of USP Apparatus 3 for Dissolution Testing of Immediate Release Products. When Apparatus 3 is reciprocated at the extreme low end of the agitation range, such as 5 DPM, hydrodynamic conditions equivalent to Apparatus 2 at 50 rpm were achieved when compared with the f_2 similarity test. Two products were tested with high solubility: Metoprolol, 100 mg, and Ranitidine, 300 mg. Although this apparatus was developed for extended release products, App 3 may be used for testing IR products with high solubility.

The study showed that Apparatus 3 can produce similar dissolution profiles to Apparatus 2 paddle and avoids the coning issues associated with the axis of rotation from the paddle. Apparatus 3 uses much less media and chemicals for soluble products. Enteric-coated products utilize the ability to reciprocate in simulated gastric fluid then move to simulated intestinal fluid without intervention.

Better IVIVC over USP 1 and 2: A USP 3 Reciprocating Cylinder Apparatus was used for the testing of HPMC extended release matrix tablets. Traditional testing with Basket and Paddle apparatus provided low discrimination between various tablet formulations.

Plastic beads were utilized within the reciprocating cylinder to better mimic the mechanical forces that occur *in vivo*. Results showed that sufficiently high mechanical stress was achieved with up to 40 dips per minute (DPM) which was needed to obtain *in vitro* discriminatory results that were in line with the *in vivo* data.

The plastic beads were round synthetic polymeric material with a density of 1.1 g/cm3 and diameter of 8 mm. Glass beads, with a density of 2.5 g/cm3 were evaluated but sank to the bottom of the cylinder and did not exert the desired mechanical forces required, even with higher DPM. Test conditions included:

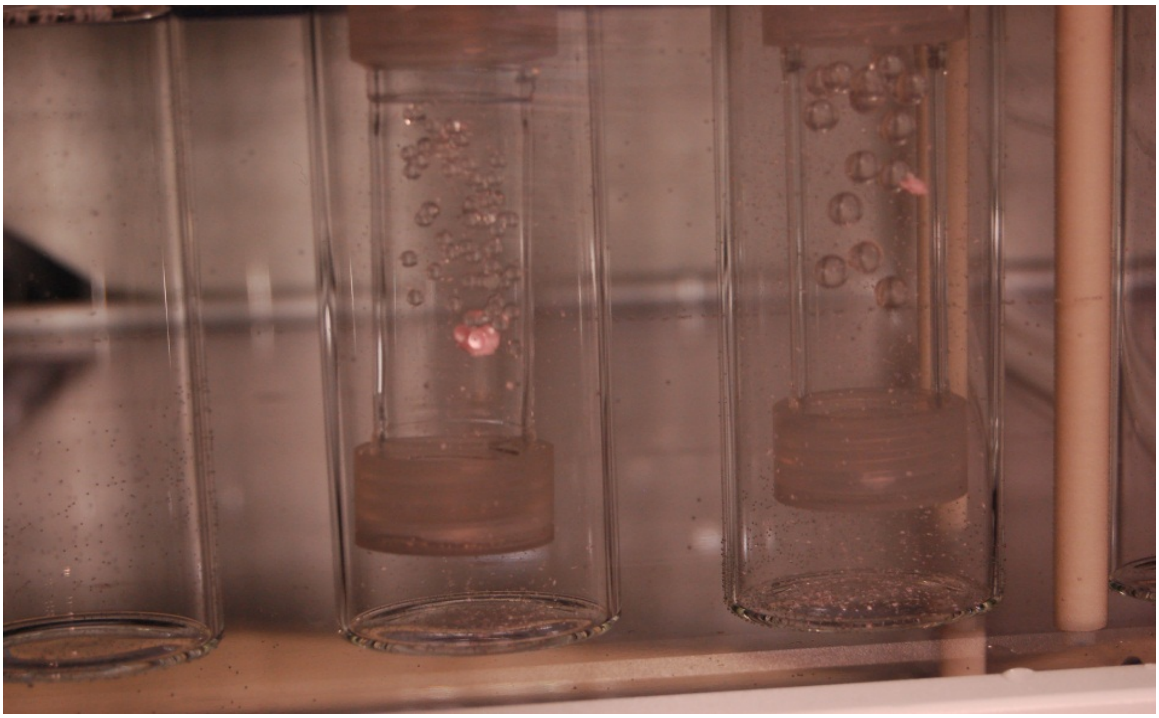
- beads filled to about one-quarter full (8 g) within the cylinder

- the media was 250 mL of water at 37 °C

- polypropylene screens were used top and bottom (840 µm)
- the test length was 14 hours
- the reciprocation rate was 20 DPM (1 hour), 40 DPM (15 min.), 25 DPM (remainder of test)

In summary, the method was able to predict *in v*ivo performance and enabled the development of a level A IVIVC. It was noted that high mechanical forces in vitro were necessary to provide a satisfactory correlation with in *vivo* data especially at the point of gastric emptying. The use of beads-based dissolution methods may be useful in the future since robust matrix formulations that are bio-equivalent to the reference product could be planned during early stages of development.

Testing chewable formulation with glass beads: Workshops held by FIP and AAPS have outlined guidelines for the dissolution and drug release testing of novel dosage forms indicating that the reciprocating cylinder apparatus may be suitable for testing of chewable tablets. The addition of glass beads was suggested to provide more intensive agitation to the in vitro dissolution test. The image following shows a chewable tablet with 1.5 mm polymeric beads on the left and 6.0 mm beads on the right.



The testing with beads addressed the fact that chewable tablets often contain highly soluble API but they are difficult to disintegrate and eventually solubilize in traditional Apparatus 1 basket or Apparatus 2 Paddle due to the lack of mechanical shear.

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Chewable formulations require more mechanical forces similar to poorly soluble compounds. Such dosage forms requiring mastication to start the disintegration process will benefit with the addition of plastic beads at up to 40 DPM, and even small glass beads if reciprocated up to 60 DPM.

Characterization of site-specific formulations in the GI tract: Studies were conducted on several Mesalazine products to evaluate the enteric coating properties of drugs for inflammatory Bowel disease (IBD). High concentrations of API are needed in the lower GI tract to treat chronic IBD. Sudden release of the drug in the stomach would deplete the drug due to absorption in the duodenum, leaving insufficient therapeutic levels in the lower small intestine and colon.

Tests were conducted at 10 DPM with 220 mL of the various media and transit times described in the table:

GI Segment	Transit time	Medium	pH value
Stomach	120 min	Simulated Gastric Fluid USP 24 sine pepsin (SGFsp)	1.2
Duodenum	10 min	Phosphate Buffer Ph Eur. 1997	6.0
Jejunum	120 min	Simulated Intestinal Fluid USP 24 sine pancreatin (SIFsp)	6.8
Proximal Ileum	30 min	Phosphate Buffer Ph Eur. 1997	7.2
Distal Ileum	30 min	Simulated Intestinal Fluid USP 23 sine pancreatin (SIFsp)	7.5

A summary of test results showed that of four Mesalazine products under study that only one released in the lower small intestine where it was present in sufficient quantity to deliver the required therapeutic effect. When the same conditions were applied to the other three formulations, their release profile indicated a substantial premature release of the API which was later absorbed leaving non-therapeutic levels in the lower GI tract to render the required therapeutic effect. In this case, in vitro drug release testing could screen formulations and precisely evaluate the site(s) of release within the GI tract for better understanding of the release mechanisms and ultimately, optimization of the formulation.

References:

- Evaluation of USP Appparatus 3 for Dissolution Testing of Immediate-Release Products Lawrence X. Yu, Jin T. Wang and Ajaz S. Hussain; US Food and Drug Administration, Office of Pharmaceutical Science, Rockville, MD; AAPS PharmSci 2002
- A Novel Beads-Based Dissolution Method for the *In Vitro* Evaluation of Extended Release HPMC Matrix tablets and the Correlation with the *In Vivo* Data, The AAPS Journal, Vol.1 5, No 1, Jan 2013
- FIP/AAPS Guidelines to Dissolution / in Vitro Release Testing of Novel / Special Dosage Forms; Martin Siewert, Jennifer Dressman, Cynthia K. Brown, and Vinod P. Shah; AAPS :PharmSciTech 2003; 4 (1) Article 7, January, 2003
- Drug Release Characteristics of Different Mesalazine Products Using USP Apparatus 3 to Simulate Passage Through the GI Tract Sandra Klein, Markus W. Rudolph, Jennifer B. Dressman;; Dissolution Technologies, Vol. 9, Issue

Agilent catalog numbers (or links to Digital Source Book)

USP Apparatus 3 Reciprocating Cylinder Ordering Information:
http://read.nxtbook.com/agilent/source_book/dissolution_systems_2017_2018/usp_apparatus_3.html

Literature/specification sheet

USP Apparatus 3 Reciprocating Cylinder Specification Sheet:
https://www.agilent.com/cs/library/datasheets/public/5990-7394EN_BIO-DIS%20Reciprocating%20Cylinder%20Apparatus.pdf

Link to video

Video of USP Apparatus 3 in Operation:
https://youtu.be/AQgW7IpXzOk

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White Papers/posters (attach files)

Poster of the Development of an IVIVC Apparatus 3 Dissolution Method for a Highly Soluble API in an Extended Release Soft Gelatin Capsule:
http://www.agilent.com/cs/library/posters/Public/App3_GelatinCapsule_AAPS_poster_M1289.pdf

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