Applications of USP Apparatus 3: Reciprocating Cylinder

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Development of USP Apparatus 3

While traditional paddle and basket apparatus offered a convenient means to evaluate most oral drug formulations with multiple pH over extended periods, it was difficult to change pH during the test and changes in agitation rates during the in-vitro test were seldom noted.

In the 1970s, Professor A.H. Beckett and other researchers in the field used the rotating bottle method (NF XII 1965-XIV 1975) which provided sound agitation but was labor intensive and difficult to automate. The rotating bottle method was never adopted by USP.

Development of USP Apparatus 3

A presentation at the 1980 federation Internationale Pharmaceutique (F.I.P.) drew attention to acute problems associated with USP Apparatus 1 and 2 dissolution results. The conference inspired the concept for the USP Apparatus 3.

As research progressed it became apparent that a system should be able to change media composition, agitation rate and resident time to achieve IVIVC.

Development of USP Apparatus 3

VanKel worked with Professor Arnold Beckett to develop the Bio-Dis (Bio-relevant Dissolution) which was eventually adopted in USP XXII (1991) as USP Apparatus 3

Due to ICH, USP Apparatus 3 – Reciprocating Cylinder and Apparatus 4 – Flow Thru Cell were moved to <711> Dissolution

Apparatus 3 is harmonized with the European Pharmacopeia in 2.9.3 Dissolution Test for Solid Dosage Forms*

*European Pharmacopoeia 8.0; Methods of Analysis 2.9.3 Dissolution test for solid dosage forms; The European Directorate for the Quality of Medicines and HealthCare; 8th Edition, 2014

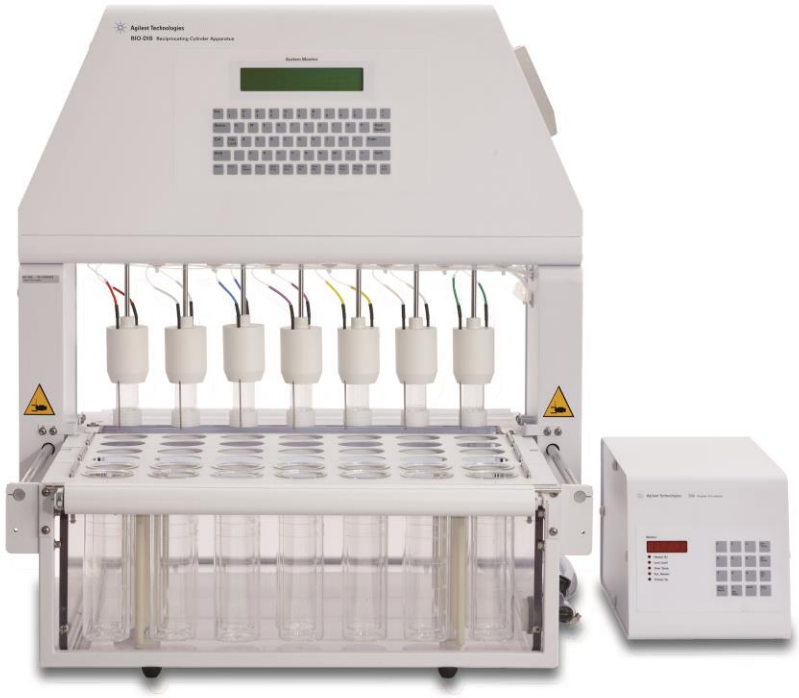
USP Apparatus 3 Overview

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 physiochemical 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.

USP Apparatus 3 Overview

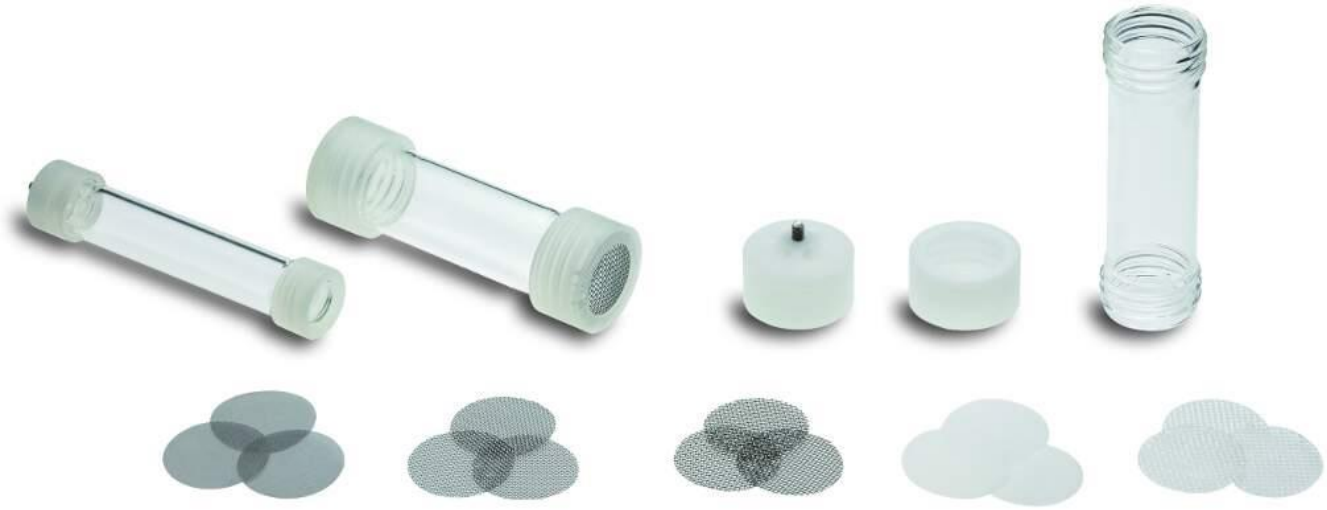


USP <711> Apparatus 3

- 300 mL Vessel
- Normally 200 mL to 275 mL vessel volume
- Operational minimum – 150 mL vessel volume
- Extended release tablets, capsules, beads
- pH profile determination in multiple media
- Harmonized between USP and EP
- Not presently recognized by Japanese Pharmacopeoia16; 6.10 Dissolution Test

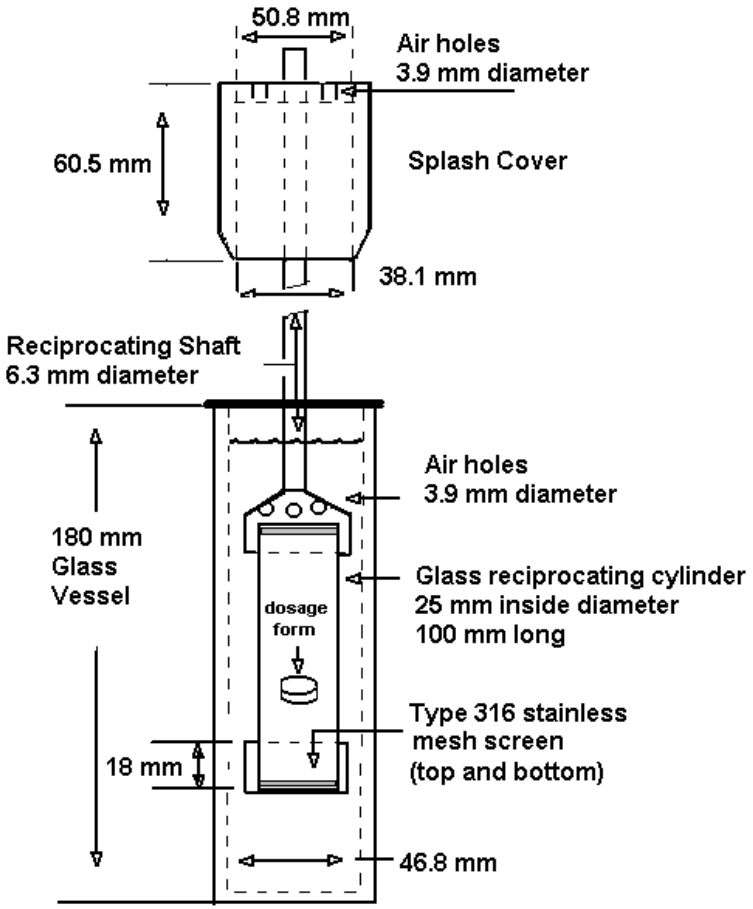
USP Apparatus 3 Overview

Reciprocating Cylinder - USP Apparatus 3 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. This cylinder may also be referred to as the inner tube.



USP Apparatus 3 Overview

Vessels – 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. The vessels may also be referred to as the outer tubes.



USP Apparatus 3 Overview

A motor and drive assembly reciprocates the cylinders vertically inside the vessels.

The cylinders are allowed to 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.

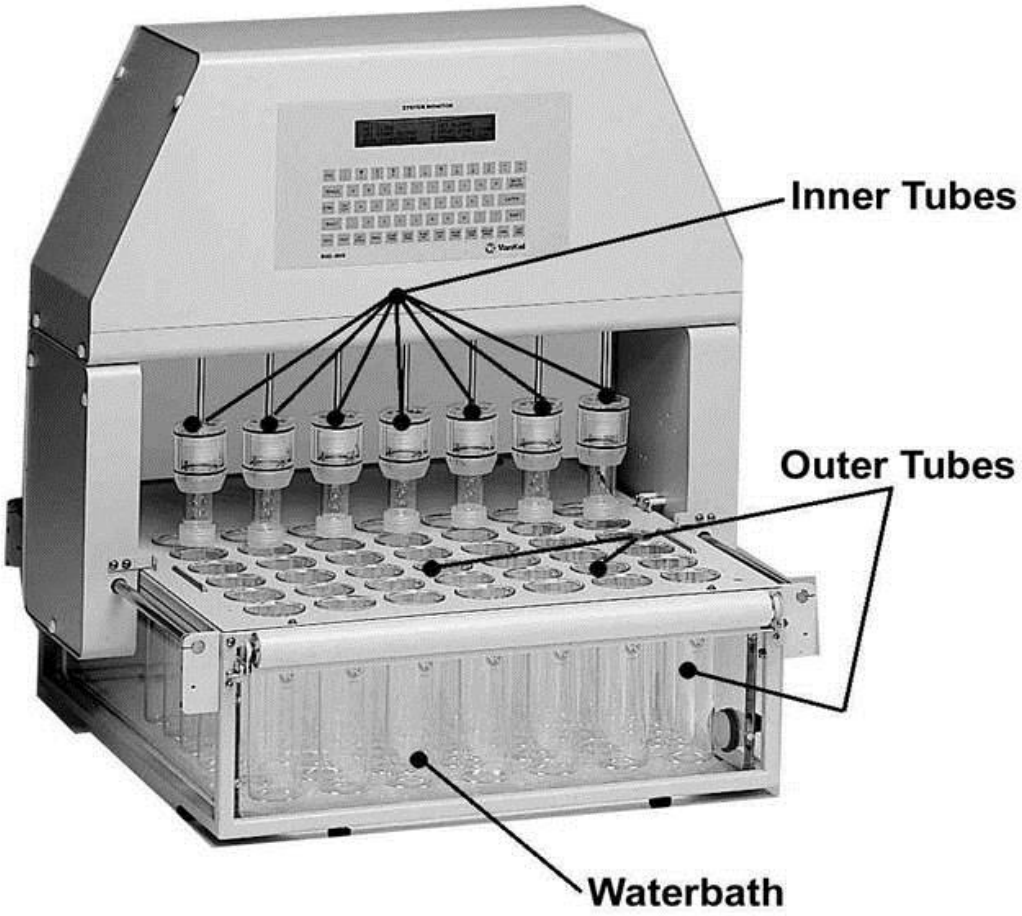
USP Apparatus 3 Overview

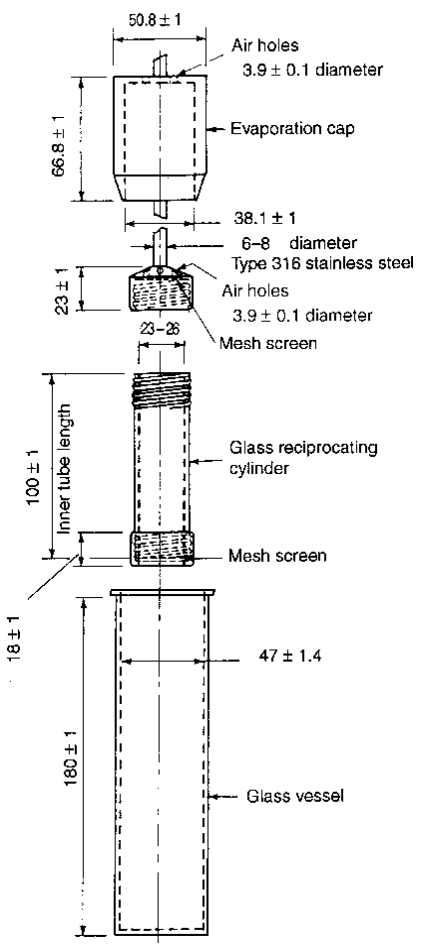
When the test begins, the reciprocating cylinders descend slowly into the first row of the vessels. Then the reciprocating motion starts.

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 3
Reciprocating Cylinder





USP Apparatus 3

Current Physical Parameters and Tolerances

Temperature	37 ± 0.5 °C
Dip rate (DPM)	± 5% of set speed
Stroke Distance	10.0 ± 0.1 cm
Bottom screen	Method specific
Top screen	Method specific (optional)

Media Volume Considerations

- Each of the outer tubes is usually filled with 250 mL of medium.
- Because there are 6 rows of outer tubes, 6 x 250 mL or 1500 mL of medium can be used in a single dissolution test.
- If the proper conditions are not achieved with 1500 mL of medium, rows can be refilled and the tester can be programmed to return to the first row and continue.

Mesh Size Considerations

Mesh size should be chosen in the same way a basket is selected:

- Retain undissolved API product
- Allow for maximum flow

Media Considerations - Surfactants

- If surfactants are used, regardless of speed, foam will occur and lead to lost volume and a mess
- Use of an anti-foaming agent such as simethicone is recommended
- Infant gas drops can be an inexpensive early check of feasibility

Background of Apparatus 3 Qualification

Similar to Dissolution Apparatus 1 and 2, the qualification of USP Apparatus 3 had consisted of a combination of:

- Physical parameter verification
- PVT with USP Chlorpheniramine Maleate ER Tablets.

Effective February 1, 2012, USP has removed the requirement for Apparatus 3 Performance Verification Test Apparatus Suitability section of General Chapter <711> Dissolution.

The change was necessary because the supply of current lot G1J218 has been depleted and no suitable replacement has been found.

Notification Letter from USP, Dec 20, 2011

Current State of USP Apparatus 3 Qualification

Similar to requirements for Enhanced Mechanical Qualification, the absence of PVT should require additional steps to assure the apparatus is suitable for its intended use.

<u>Current State of Qualification:</u>

- Certification of Components
- Documentation of Preventative Maintenance
- Mechanical Qualification Parameters
- Operational Checks

Current State of USP Apparatus 3 Qualification

Operational Checks: Before each run with the USP apparatus 3 system, the analyst should perform the following checks on the apparatus to ensure integrity:

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

Applications for USP Apparatus 3

Applications For USP Apparatus 3

Immediate release

- Metoprolol
- Ranitidine

Testing products with the addition of beads.

- Extended Release
- Chewable Tablets

Controlled Release – Site specific

Microparticles

Regulatory Expectation for Drug Release Methods

Method and specifications should provide:

- Characterization of release
- 80% release or asymptote
- Evaluate release with various conditions: agitation, media composition, pH, temp, etc…
- Discrimination by process validation samples
- Consistent performance lot-to-lot
- Must show failure and ability to reject a batch

In general, methods must be:

- Relevant
- Predictable
- Specific
- Discernable

Apparatus 3 for Immediate Release

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
- Ranitidine, 300 mg

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

Apparatus 3 and Immediate Release - Metoprolol

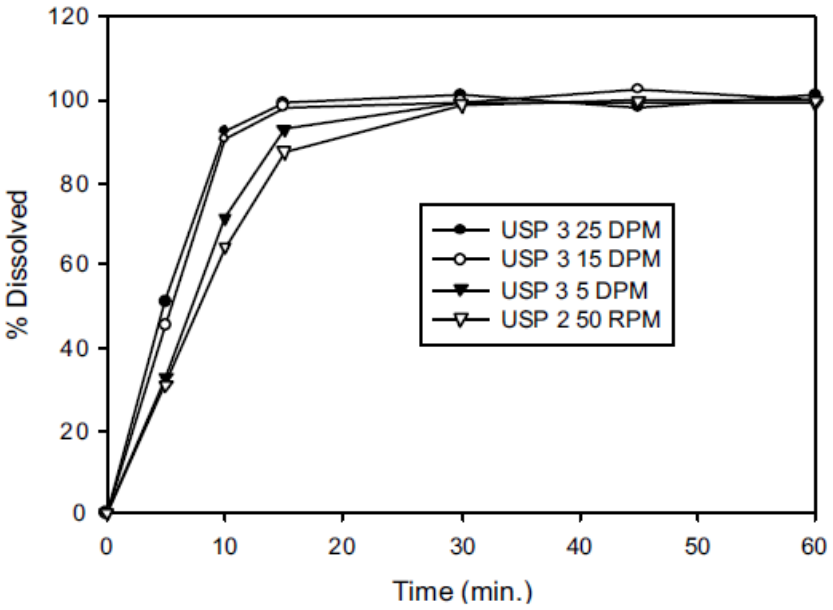


Figure 1. Dissolution profiles of metoprolol tartrate tablets of innovator's product.

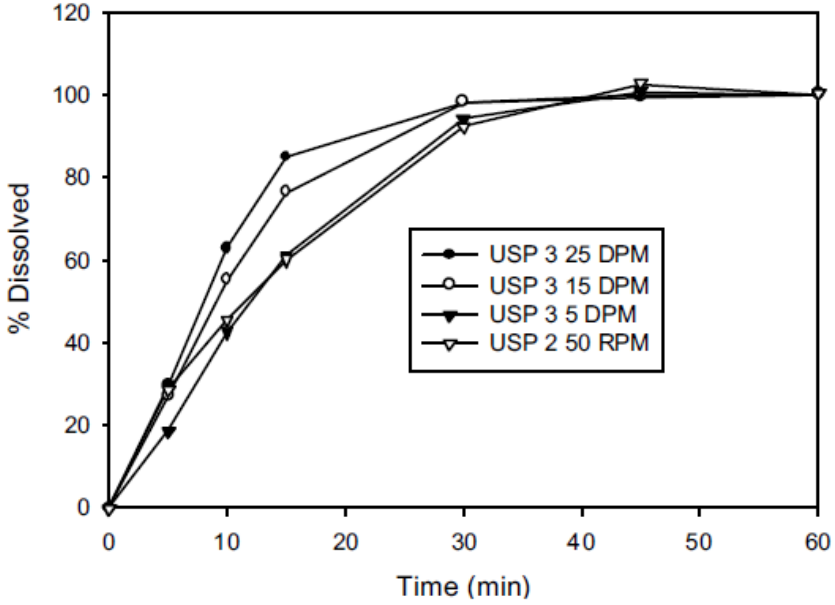
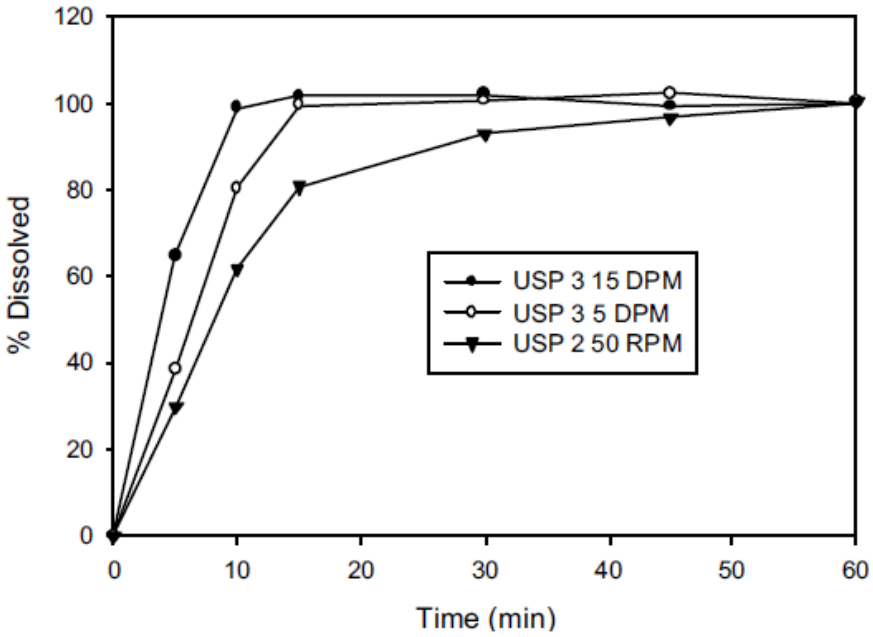


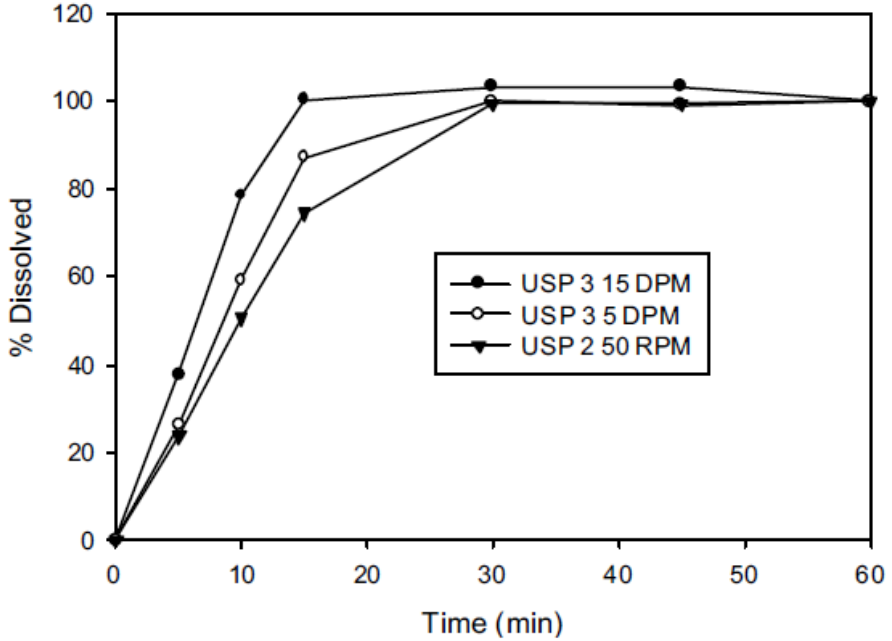
Figure 2. Dissolution profiles of metoprolol tartrate tablets of generic product A.

USP 3 at 5 DPM appears equivalent with USP 2 at 50 RPM

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

Apparatus 3 and Immediate Release - Ranitidine





Release profiles for 2 of 6 generic ranitidine products failed to pass f2 although they were all bioequivalent *in vivo*

In this case, USP apparatus 2 seems over discriminating.

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

Apparatus 3 and Immediate Release

Although this apparatus was developed for extended release products, App 3 may be used for testing IR products with high solubility.

Apparatus 3 can produce similar dissolution profiles to Apparatus 2 paddle and certainly avoids the coning issues associated with the axis of rotation from the paddle.

Apparatus 3 uses is capable of using 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.

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Lawrence X. Yu, Jin T. Wang and Ajaz S. Hussain; US Food and Drug Administration, Office of Pharmaceutical Science, Rockville, MD; AAPS PharmSci 2002

Apparatus 3 with Beads for Better IVIVC

Case Study 1

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.

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

Apparatus 3 with Beads for Better IVIVC

Case Study 1

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 they sank to the bottom of the cylinder and did not exert the desired mechanical forces required even with higher DPM.

Test conditions:

- Beads filled about 1/4th (8 g) of the cylinder
- Media: 250 mL of water at 37ºC
- Polypropylene screens top and bottom, 840 µm
- Test length, 14 hours
- Reciprocation: 20 DPM (1 hour), 40 DPM (15 min.), 25 DPM (remainder of test)

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

Apparatus 3 with Beads for Better IVIVC

Case Study 1 - 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.

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.

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

Apparatus 3 with Beads for Chewable Tablets

Beads Case Study 2

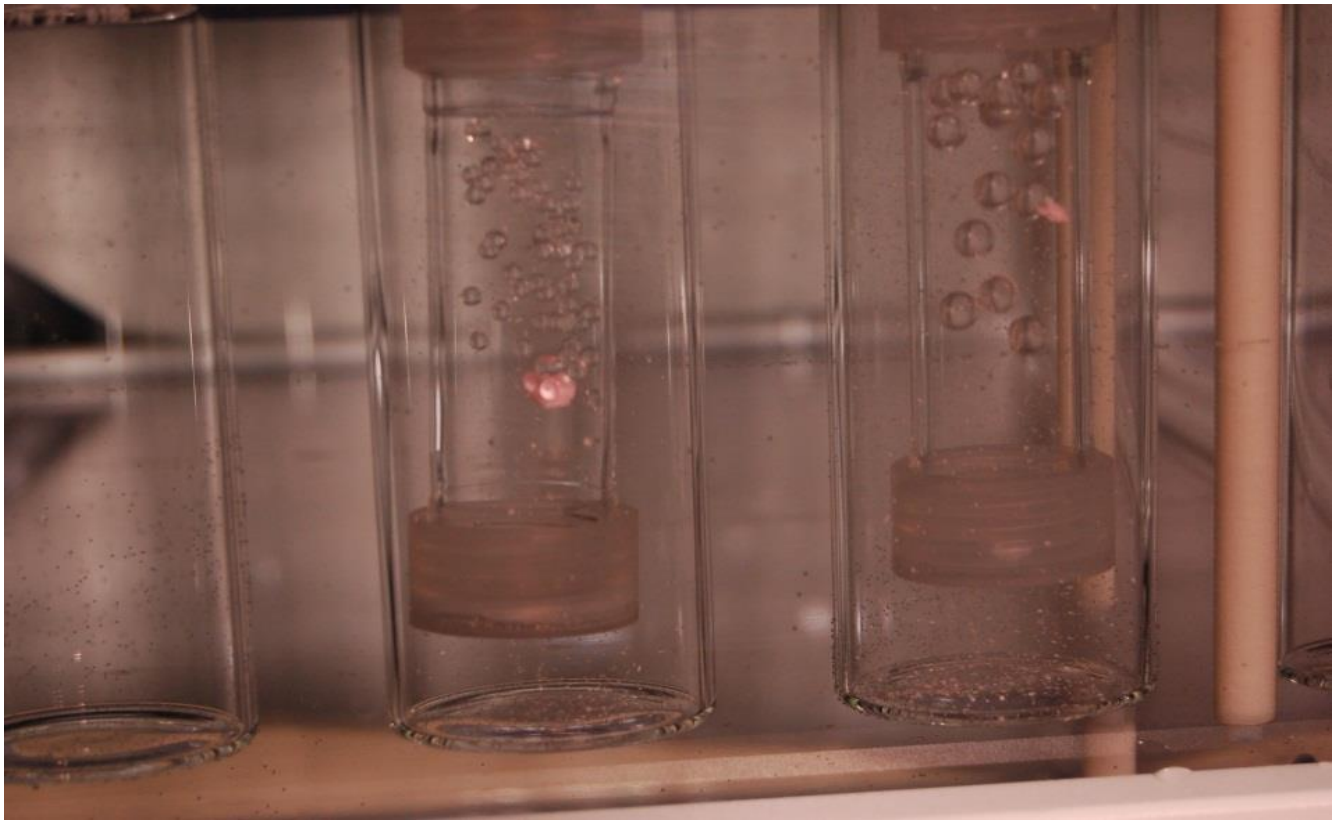
Workshops held by FIP and AAPS have outlined guidelines for the dissolution and drug release testing of novel dosage forms indicating that the reciprocating cylinder apparatus may be suitable for testing of chewable tablets.

The addition of glass beads would be required to provide more intensive agitation to the in vitro dissolution test.*

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

Apparatus 3 with Beads for Chewable Tablets

Beads Case Study 2



1.5 mm Beads (left) 6.0 mm Beads (right)

Apparatus 3 with Beads for Chewable Tablets

Beads Case Study 2 – Summary

Chewable tablets often contain highly soluble API but they are very difficult to disintegrate and eventually solubilize in traditional Apparatus 1 basket or Apparatus 2 Paddle due to the lack of mechanical shear.

Chewable formulations require additional mechanical forces similar to poorly soluble compounds.

Such dosage forms requiring mastication to initiate 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.

Apparatus 3 Characterizing Drug Release at Specific Sites 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.

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

Apparatus 3 Characterizing Drug Release at Specific Sites in the GI Tract

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

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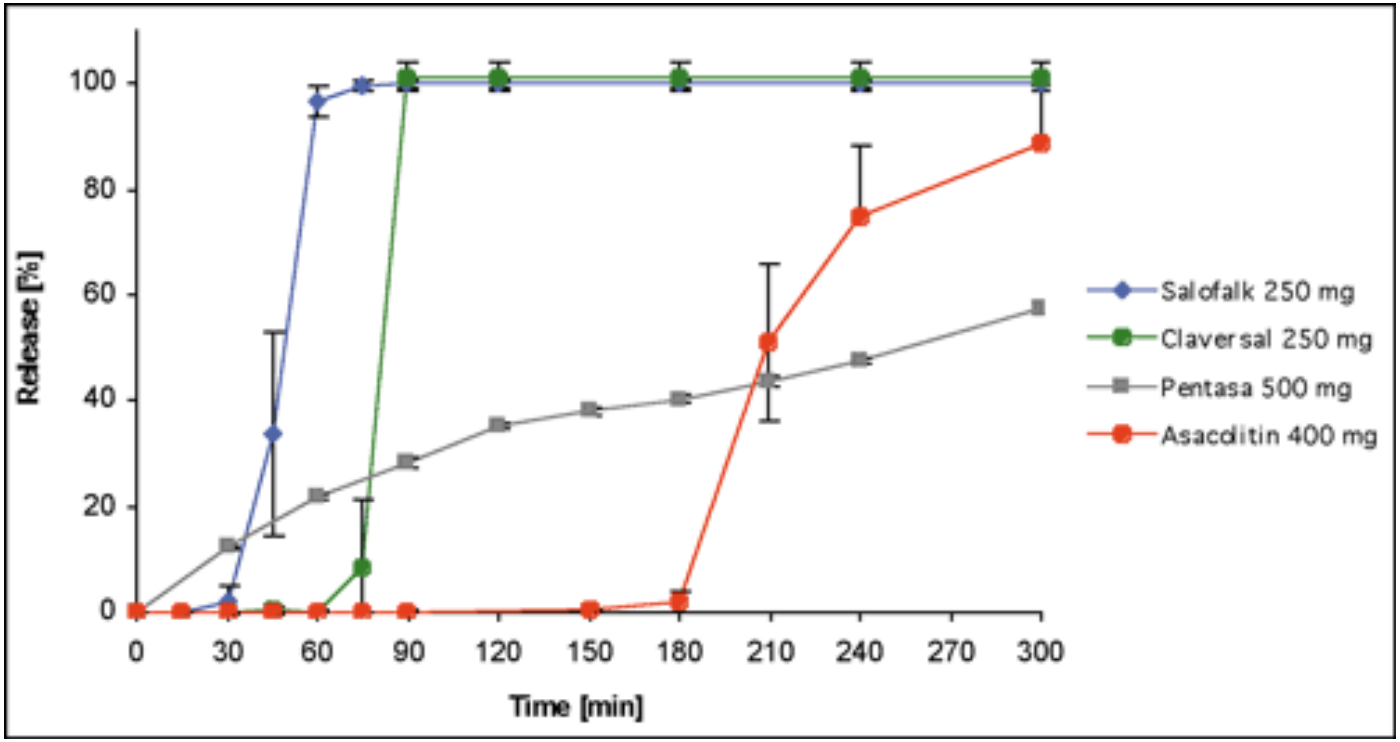
Apparatus 3 Characterizing Drug Release at Specific Sites in the GI Tract

Dissolution behavior of different mesalazine dosage forms in Phosphate Buffer pH 7.2 Ph. Eur., expressed as mean + SD.



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Case Study #2 – University of Bath, UK

The Impact of Float-A-Lyzer (Spectrum Labs) Dialysis Membranes for the Dissolution of Particles

- Naeema Jafar Malik, MPharm4
- Dr. Nikoletta Fotaki, Associate Professor,

University of Bath, Department of Pharmacy and Pharmacology, School of Pharmacy, Bath, United Kingdom

Case Study #2 – University of Bath, UK

Project focused on the surrogate testing of paracetamol, ibuprofen and carbamazepine oral suspensions with the use of several Float-A-Lyzer (Spectrum Labs) membranes:

- 0.1-0.5 kD
- 0.5-1.0 kD
- 3.5-5.0 kD

to determine the feasibility of utilizing dialysis membranes in traditional dissolution apparatus to study drug release from micro/nanoparticles.

Microparticles are often not at sink condition in vivo so the restricted sink conditions could theoretically be replicated in the Float-A-Lyzer cell.

Case Study #2 – University of Bath, UK

Drug	pKa [29]	Oral suspension strength	MW	BCS Class	MWCO membranes	Volume Size of flotalyzer	Wavelength (nm) required for testing absorbance of drug
Paracetamol	9.86	120mg/5ml	151.17	III	0.1-0.5 kD 0.5-1.0 kD 3.5-5.0 kD	5ml	243
Carbamazepine	13.94	100mg/5ml	236.27	II	0.1-0.5 kD 0.5-1.0 kD 3.5-5.0 kD	5ml	287
Ibuprofen	4.41	100mg/5ml	206.28	II	0.1-0.5 kD 0.5-1.0 kD 3.5-5.0 kD	5ml	221

Case Study #2 – University of Bath, UK

Modifications were made to USP Apparatus 3 reciprocating cylinder.

The Float-A-Lyzers were prepared

- Rinsed and soaked surfaces 10-minutes with 10% ethanol to remove glycerin on the surface.
- Rinsed and soaked in purified water for 15-20 min.
- Add 2.5mL of the suspension and attach to the appropriate apparatus.

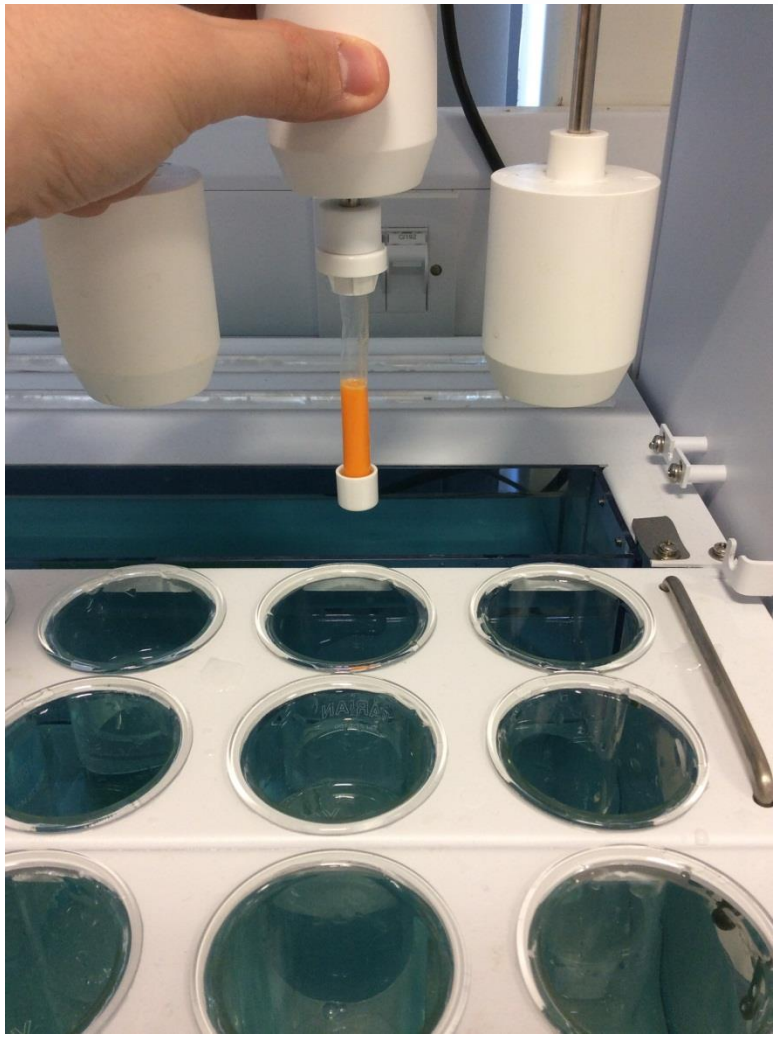
Repeated for all three MWCO's for each drug.

Case Study #2 – University of Bath, UK

USP Apparatus 3 – Modified Reciprocating Cylinder

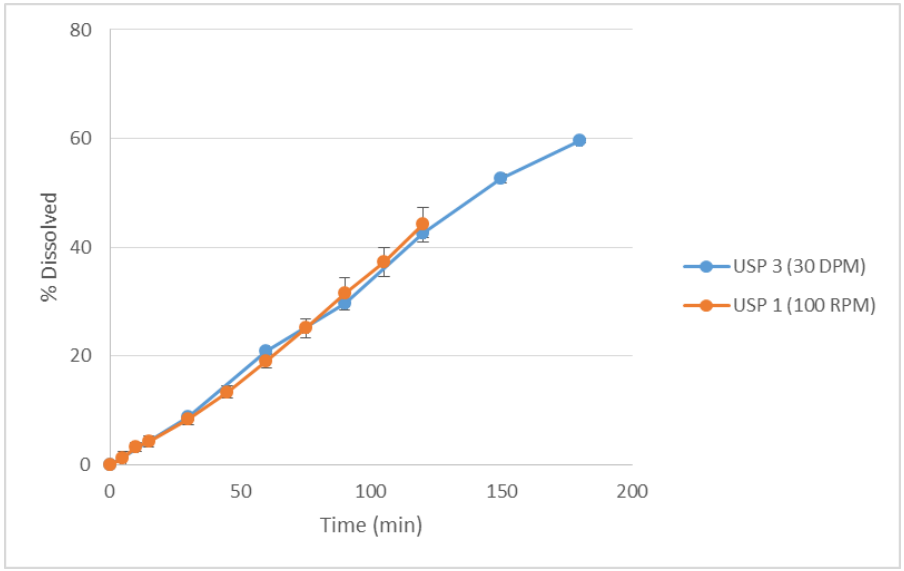
The device was placed on a modified shaft to fit in the apparatus. Each sample was reciprocated at 30 DPM (dips per minute) for typically 180 minutes and samples were taken at 30 minute intervals.

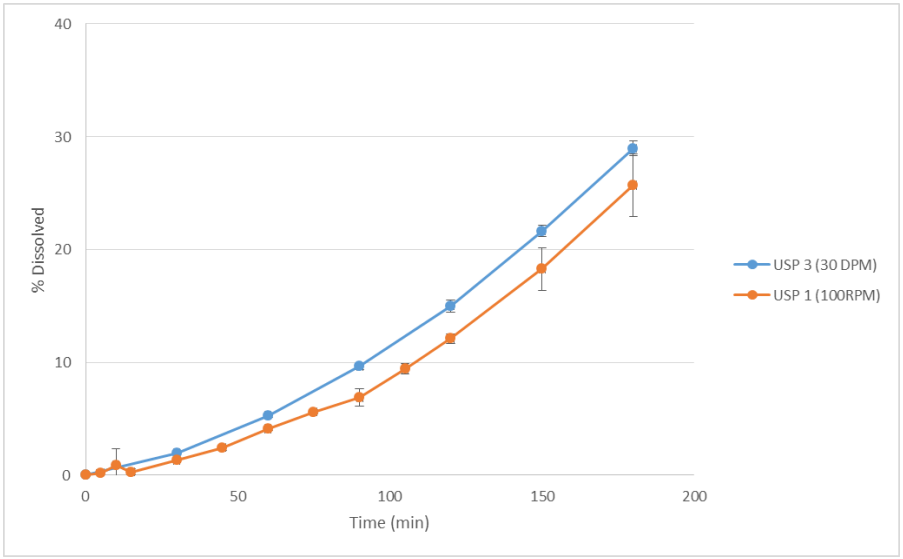
Apparatus III provides good mechanical agitation due to continuous dipping but hosts a smaller quantity of media volume than traditional dissolution apparatus.



Case Study #2 – University of Bath, UK

USP 1 vs. USP 3





Paracetamol suspension in 3.5-5.0 kD, dose 60mg (2.5mL) in phosphate buffer 6.8

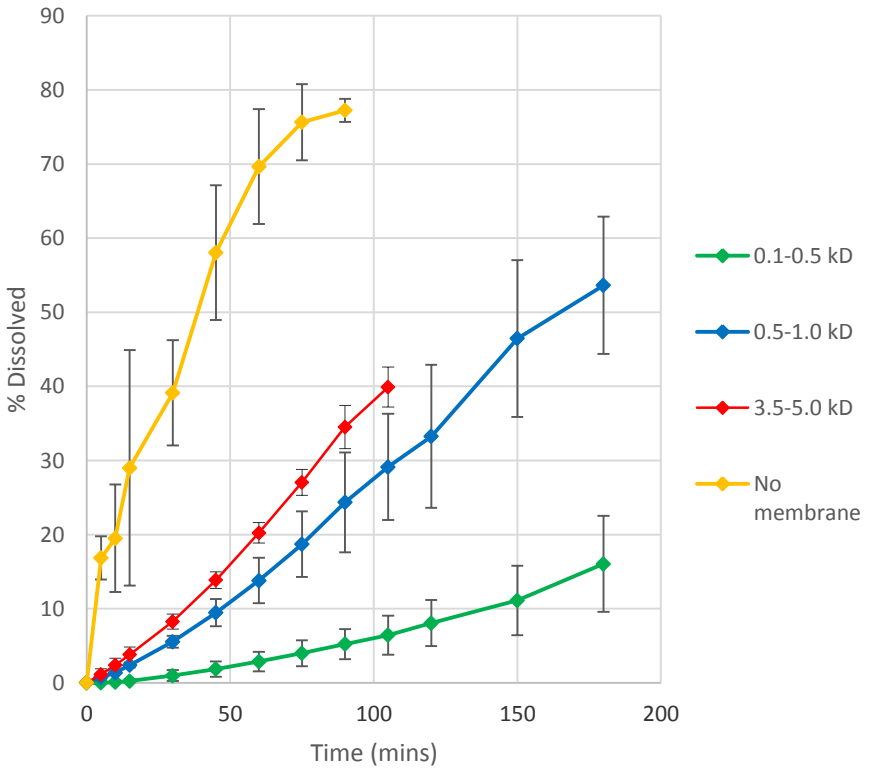
Ibuprofen suspension in 3.5-5.0 kD dose 50mg (2.5mL) in phosphate buffer 6.8

Case Study #2 – University of Bath, UK

As expected, the release through the membrane suppresses the dissolution rate since the product must first dissolve then diffuse through the membrane.

Highest drug release was observed with the largest MWCO membrane.

Summary: As presented with the suspensions it appears feasible to conduct testing of micro and nanoparticles within dialysis membranes which would simulate drug release in tissues which are not at sink.



The effect of no membrane and presence of MWCO on the dissolution profile of paracetamol suspension.

Summary

The greatest value in developing effective dissolution and drug release methods with USP Apparatus 3 is not in the fulfillment of regulatory requirements, but in providing accurate, reliable data for decision making during drug development stages and assurance of quality when the product reaches full scale production.

References

United States Pharmacopeia, Rockville, MD, USA

European Pharmacopoeia 8.0; Methods of Analysis 2.9.3 Dissolution test for solid dosage forms; The European Directorate for the Quality of Medicines and HealthCare; 8th Edition, 2014

Agilent Bio-Dis III Testing Station Operators Manual and Service Manual

USP Notice: Discontinuance of Chlorpheniramine Maleate ER Tablets RS, 20 Dec, 2012

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QUESTIONS?