Developing Methods for Apparatus 3 and 7

Ken Boda
Applications Engineer

Apparatus 3 and 7

Apparatus 3 and 7 are both reciprocating systems and allow for the testing of samples in multiple vessels.

This ability allows for:

- pH profiling
- Programmable dip speeds at each interval
- Programmable interval time

Flexibility allows for closest in vivo/in vitro modeling

Agitation

Agitation in these systems comes from dipping within the vessel, rather than through a stirred media approach.

Apparatus 3 and 7 look very similar

Apparatus 3

Apparatus 7

Comparison of Systems

	Apparatus 3 (Bio-Dis)	Apparatus 7
Stroke Length	10cm	2cm
Dips per Minute (DPM)	5-60 dpm	5-60 dpm
Vessel Volumes	100mL, 300mL, 1L	5mL, 10mL, 20mL, 50mL, 100mL, 300mL, 1L
Holders	Reciprocating Cylinders, baskets (non-compendial)	Pointed rod, various transdermal and medical device holders
Applications	Tablets, capsules, beads, chewables	Osmotic tablets, transdermals, medical devices

Apparatus 3

History of the USP Apparatus 3

As knowledge of therapeutic performance of drugs increased, more sophisticated formulations became available.

Modified Release :

- Timed Release
- Extended Release
- Positioned Release
- Controlled Release
- Delayed Release

History of the USP Apparatus 3

In the 1970s, Professor Arnold Beckett and many workers in the field used the rotating bottle method (NF XII 1965-XIV 1975) to evaluate pellets and other solid dosage forms.

Rotating Bottle Apparatus

History of the USP Apparatus 3

The rotating bottle method created a sound hydrodynamic system.

- The dosage form moves freely through the dissolution medium as the bottle is rotated.
- This free movement contrasts the movement in USP 1 and 2 where various portions of the bulk medium move at different rates.

History of the USP Apparatus 3

Despite the proven pH profiling capability and highly reproducible dissolution profiles of the rotating bottle method, there were downfalls associated with the process.

- Labor intensive
- Difficult to automate

These shortcomings were deemed too important for official acceptance as a viable method by the USP.

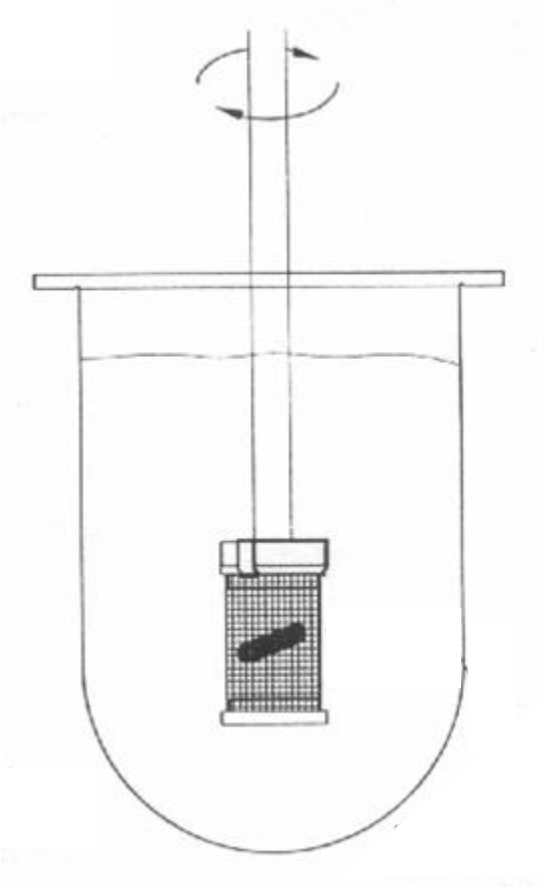
History of the USP Apparatus 3

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.

Participants at the conference also agreed that physical, mechanical, and hydrodynamic variations in Apparatus 1 and 2 could jeopardize the international acceptance of high-quality pharmaceuticals.

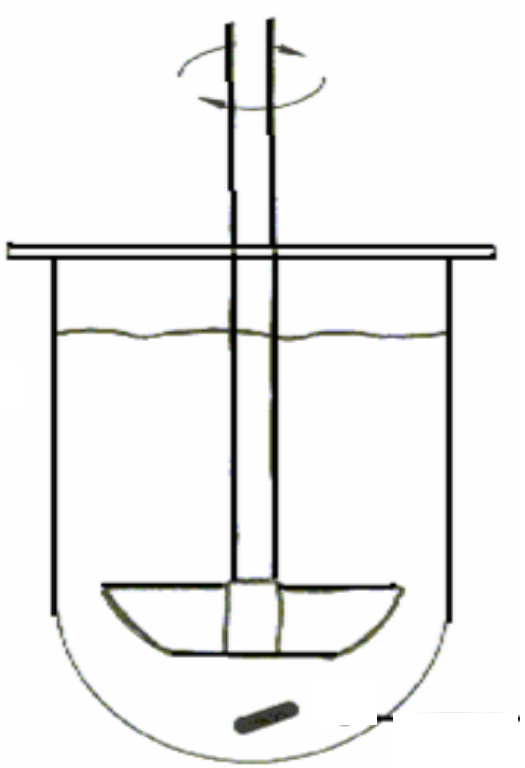
USP Apparatus 1

- Dosage form contained within basket
- Dissolution should occur within basket
- Useful for :
  - Tablets
  - Capsules
  - Beads
  - Floaters
- pH change by media exchange



USP Apparatus 2

- Dosage form should remain at the bottom center of the vessel
- Sinkers used for floaters
- Useful for :
  - Tablets
  - Capsules
  - Suspensions
- pH change by media addition



USP Apparatus 2

The most distinct disadvantage of USP 2 is its coning problem :

History of the USP Apparatus 3

As research progressed, it became apparent that a system would have to sequentially alter a variety of dissolution conditions in order to achieve an in vitro – in vivo correlation.

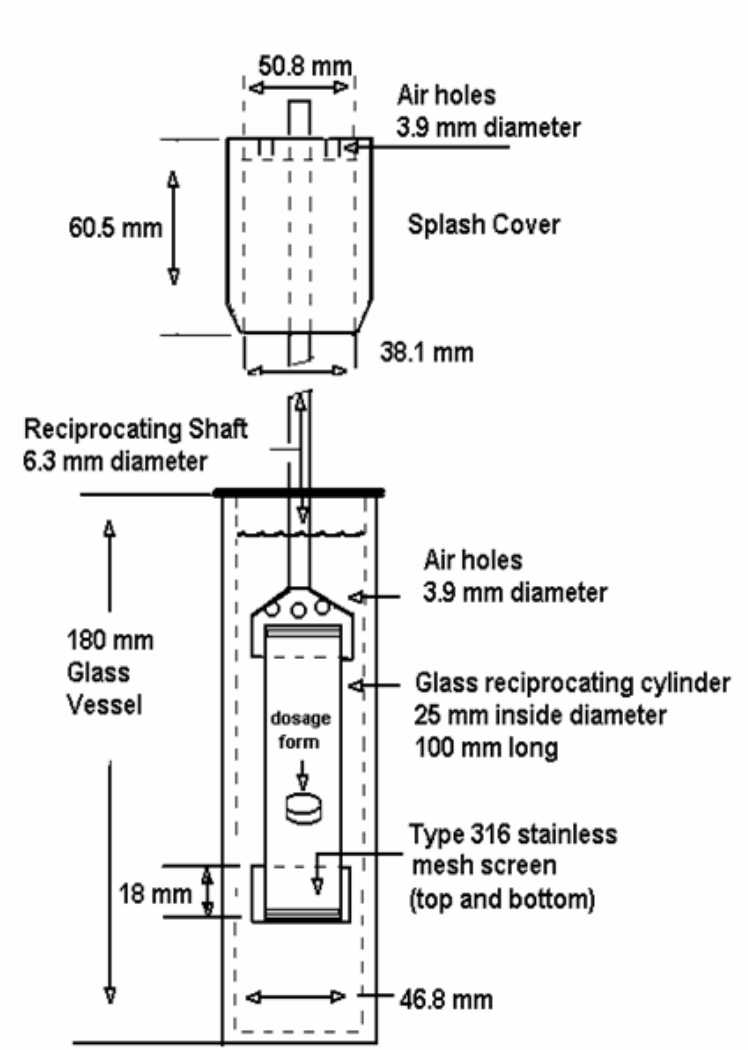
- pH
- Molarity
- Anions
- Cations
- Viscosity
- Buffers
- Surface Active Agents
- Degree of Agitation

USP Apparatus 3

Reciprocating Cylinder

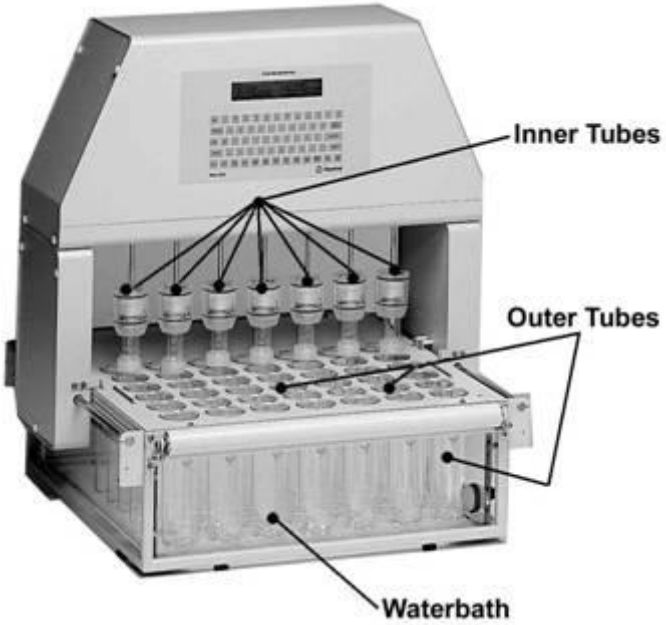
Useful for :

- Extended release testing
- Tablets
- Capsules
- Beads
- pH change in different rows



Basic Components of the Reciprocating Cylinder Apparatus

The Reciprocating Cylinder Apparatus has 6 or 7 inner sample tubes, which mechanically traverse six rows of corresponding, media-filled outer tubes.



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)

Reciprocating Cylinder

USP Apparatus 3

The Reciprocating Cylinder Apparatus Creates a Moving Medium

- When you operate the Reciprocating Cylinder Apparatus you program the agitation rate as dips per minute (DPM) for the inner tubes.
- When the inner tube elevates, the bottom mesh moves upward to make contact with the sample.
- When the inner tube lowers, the sample leaves the mesh and floats freely within the tube.
- The resulting agitation creates a moving medium.

Factors for USP Apparatus 3

- Type of product
- Volume of medium
- Number of rows
- Mesh size
- Medium in each row
- Dip speed per row
- Residence time per row

Typical Products Tested

- Tablets
- Capsules
- Beads
- Chewable Products
- Animal Feeds

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.

Media Volume Considerations

- Traditionally, after the required time interval, the medium in each tube was made up to volume and then analyzed giving one result per row.
- Today, automation of the sampling and/or analysis is common so that multiple measurements can be made in each row.

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

- Media usually related to in vivo fluids, and will range in pH from pH 1.1 – pH 7.5 in early method development work
- Delayed Release may utilize 2 different media (pH ~1.1 and pH 6.8 – 7.5)

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

Typical Conditions for Extended Release Testing

Row	GI Position	pH	Speed - DPM	Time - Hours
1	Stomach - fed	1.2	20	2
2	Duodenum	4.5	20	1
3	Small Intestine - Proximal	6.4	15	3
4	Small Intestine - Medial	6.8	10	3
5	Small Intestine - Distal	7.2	8	3
6	Colon	7.4	5	4

Achieving Fasted and Fed States

- To simulate a fasted state, dip the product in the first row for one hour.
- To simulate a fed state, dip the product in the first row for four hours and for one hour in the second row.
- The appropriate dipping times for the other rows depends on whether a 12 or 24 hour product is being analyzed.
- The dip speeds for each row should be set to 10 or 15 DPM except in the fed state (first row pH 1.5 for four hours) when the dipping rate should be increased to 30 or 40 DPM to simulate stomach turbulence.
- The fed state can also include inert beads of mixed density to represent moving particles of food.

Effects of Geometry

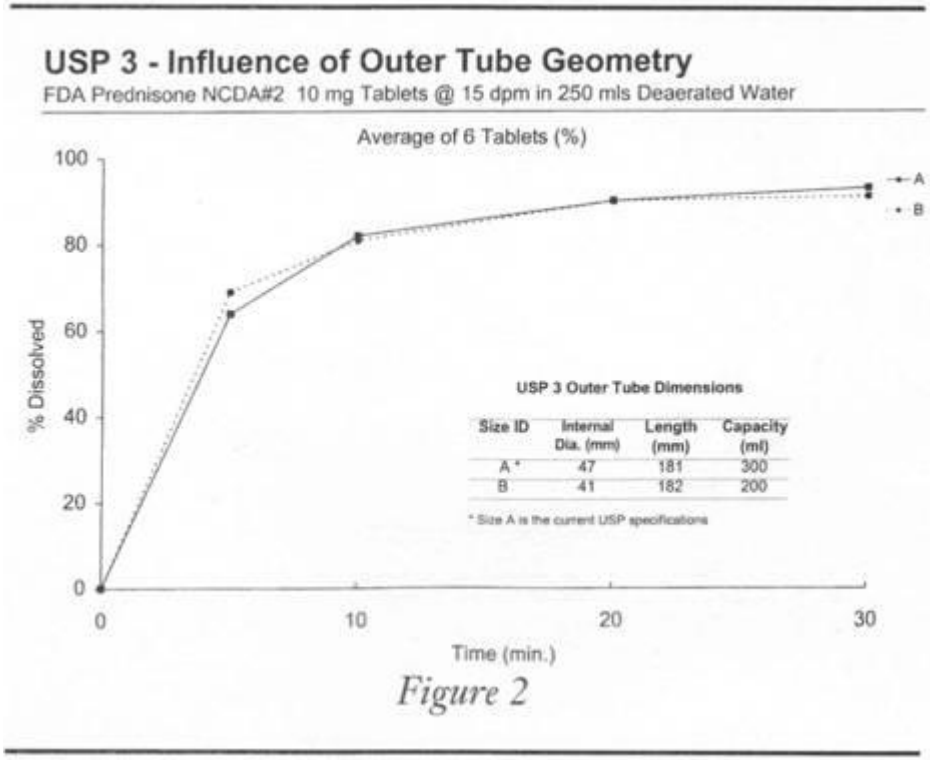


Figure 2

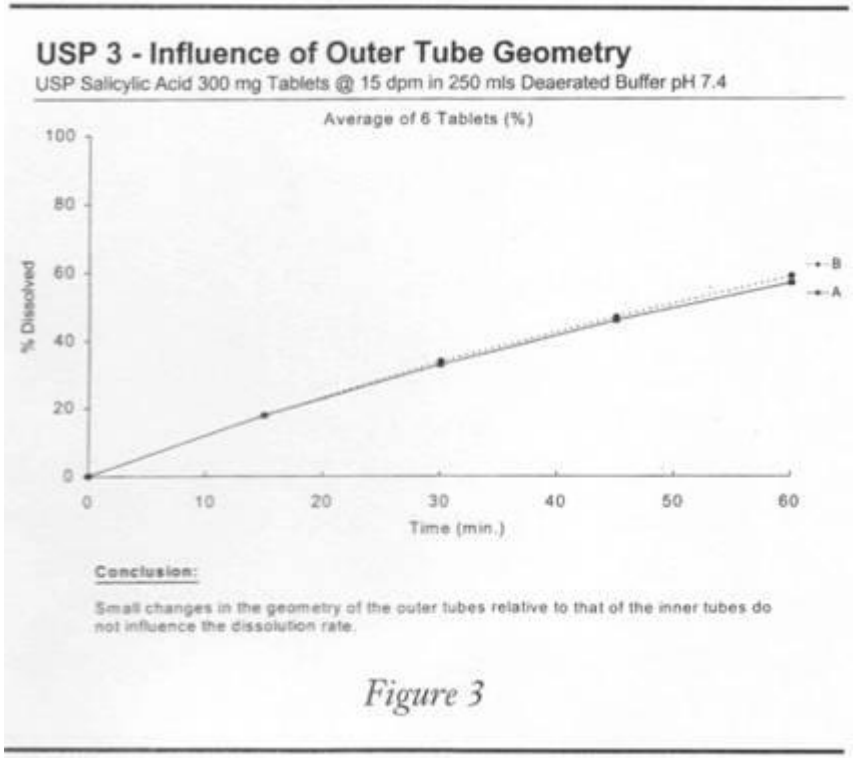
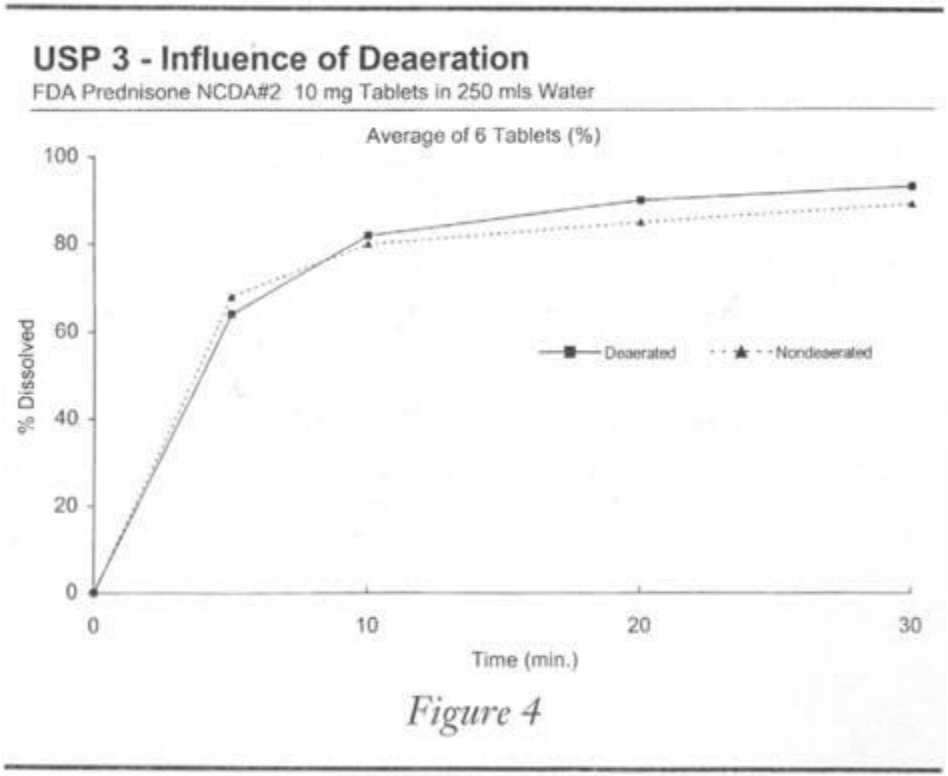
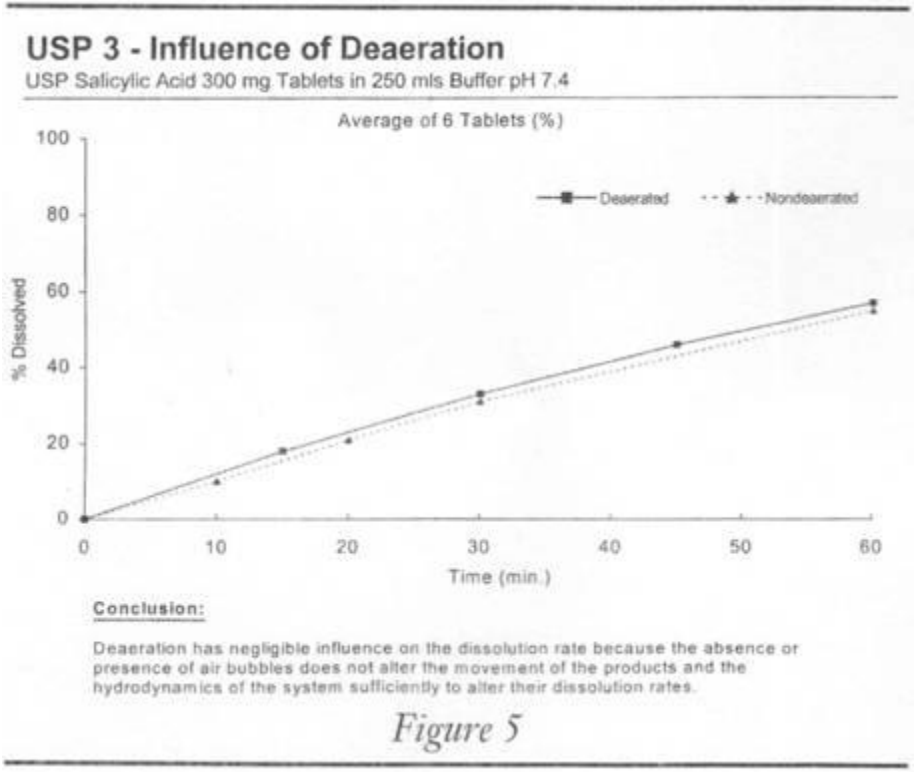


Figure 3

New and Extended Applications for USP Drug Release Apparatus 3; available at: http://www.dissolutiontech.com/DTresour/1997Articles/DT199702_A02.pdf

Effects of Bubbles





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Modified End Cap

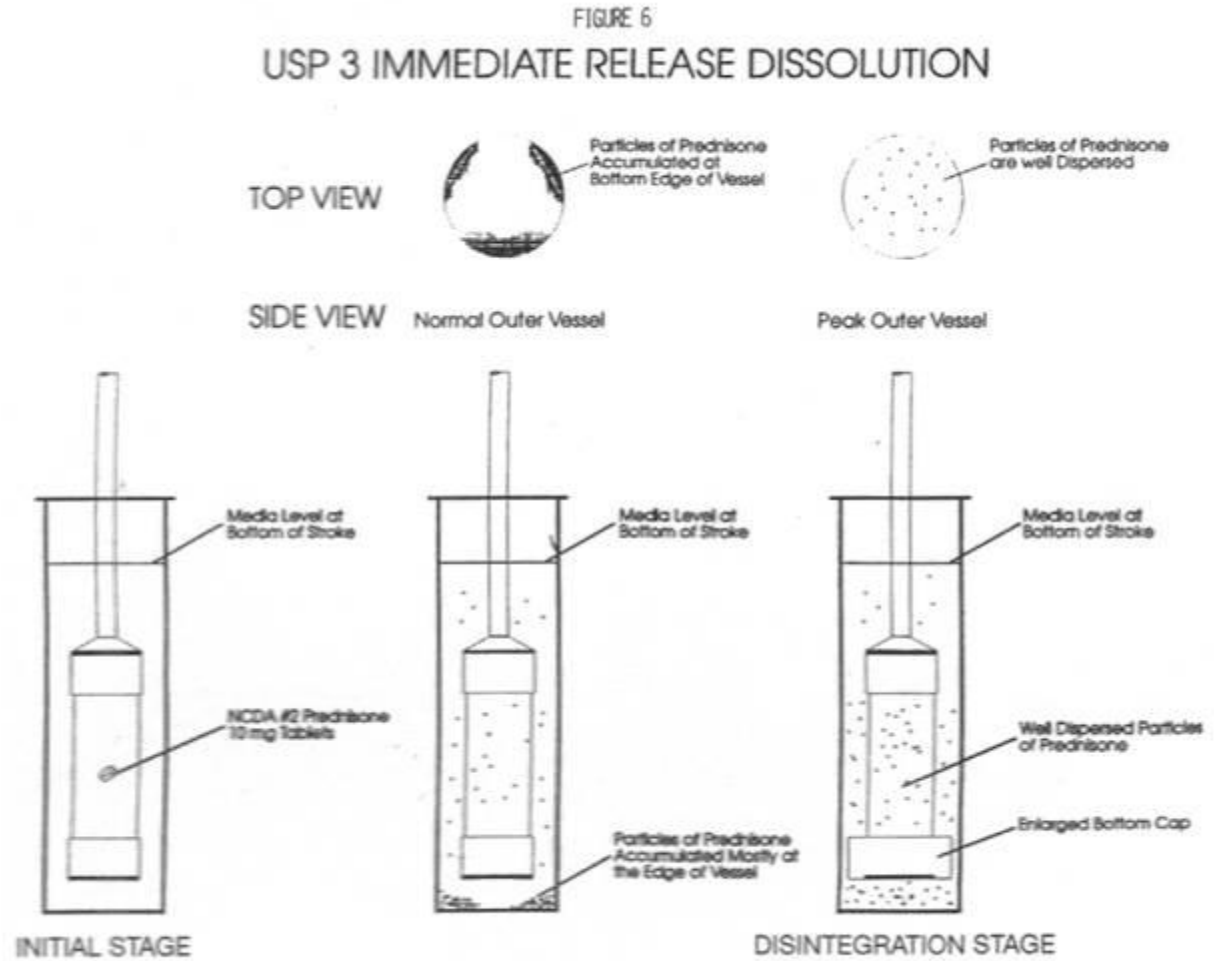
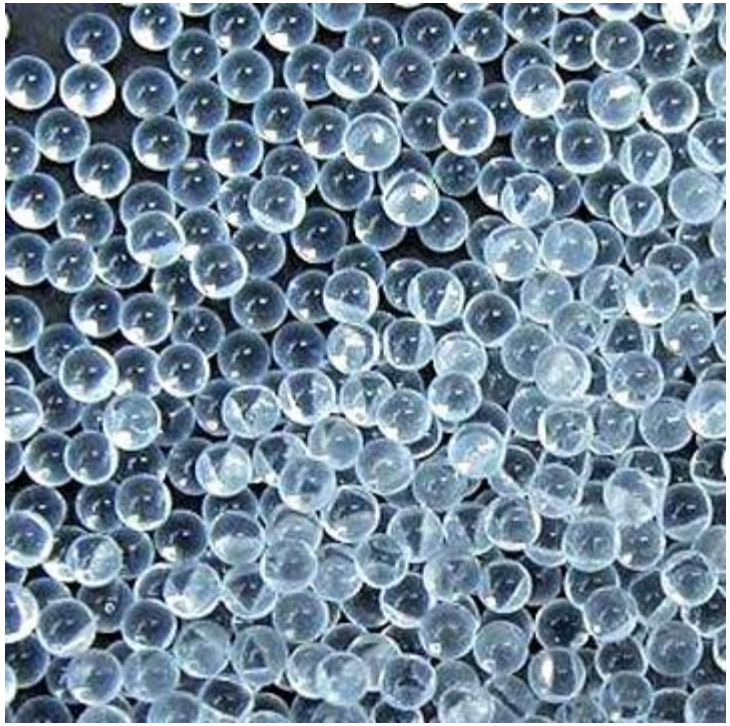


Figure 6

Chewable products

- Chewables and veterinary products may benefit with addition of glass beads into the inner tubes
- Act as abrasive agents (teeth)



Variations

- 1 litre vessels
- “Enteric” version : 300ml vessels + 1l vessels
- Double row : 2 x 6 x 3
- Immediate release
- Basket

Apparatus 3 Qualification - Background

Similar to Dissolution Apparatus 1 and 2, the qualification of USP Apparatus 3 has 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

The Future of USP Apparatus 3 PVT?

"USP remains convinced that a PVT is a critical element in the qualification of in vitro performance test equipment. USP will continue to seek a material which can serve as the PVT for Apparatus 3."

Notice of discontinuance of Chlorpheniramine Maleate ER Tablets RS, 20 Dec, 2012

http://www.usp.org/sites/default/files/usp_pdf/EN/referenceStandards/discontinuancechlorpheniraminemaleateextendedrt.pdf

Apparatus 3 Mechanical Qualification

In the absence of a PVT, and MQ could be adopted such as with Apparatus 1 and 2 including:

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

Apparatus 7 options

USP Apparatus 7

Also known as the “Alza Apparatus”, USP Apparatus 7 has evolved to handle not only transdermal apparatus but other modified release products.

USP Apparatus 7

- Typical volume is 50 mL through 75 mL
- Operational minimum around 25 mL
- Modifications have been made to accommodate 300 mL vessels.
- Extended release tablets, capsules, transdermals, osmotic pumps, beads, arterial stents.
- Small volume App 7 – 400-DS also available

USP Apparatus 7

Current Physical Parameters and Tolerances

Temperature	32 or 37 ±0.5°C
Dip rate	5 - 40 DPM
Stroke Distance	2 cm
Holder	Method specific

USP Apparatus 7 - Reciprocating Holder

Note on Apparatus 7 Holders

- Not all holders fit in all volumes
- Older methods often refer to an older App 7 model which is no longer made and had wider vessels

		Apparatus 7 – Outer Tube			
		50 mL	100 mL	300 mL (USP)	1000 mL
27-5000	Inner tube (300 mL)	-	-	◆	◆
27-5010	Inner tube (100 mL)	-	◆	◆	◆
27-2400	Durafit basket adapter	-	NR	◆	◆
27-2401	Basket adapter with clip assembly	-	NR	◆	◆
27-8620	Basket, mini, 40-mesh	◆	NR	◆	◆
27-8621	Basket, mini, 50-mesh	◆	◆	◆	◆
27-8600	Basket shaft, mini	◆	◆	◆	◆
27-8622	Basket assembly, titanium	◆	◆	◆	◆
27-3000	Pointed acrylic rod	◆	◆	◆	◆
27-3002	Replacement acrylic rod kit	◆	◆	◆	◆
27-3001	Transdermal patch holder kit	-	-	◆	◆
27-8005	1.6 cm^2 reciprocating disk	◆	◆	◆	◆
27-8010	2.5 cm^2 reciprocating disk	-	-	◆	◆
27-8015	5.0 cm^2 reciprocating disk	-	-	◆	◆
27-8020	7.0 cm^2 reciprocating disk	-	-	◆	◆
27-8025	10.0 cm^2 reciprocating disk	NR	NR	◆	◆
27-6540	Replacement stent holder	◆	◆	◆	◆
27-6541	Stent holder, 8 mm (horizontal)	◆	◆	◆	◆
27-6542	Stent holder, 18 mm (vertical)	◆	◆	◆	◆
27-6543	Stent holder, 30 mm (vertical)	◆	◆	◆	◆
27-0101	Spring holder, 1.40 in. L x 0.31 in. inner dia. x 0.040 in. wire inner dia.	◆*	◆*	◆*	◆
27-0102	Spring holder, 0.96 in. L x 0.33 in. inner dia. x 0.031 in. wire inner dia.	◆*	◆*	◆*	◆
27-0103	Spring holder, 0.60 in. L x 0.25 in. inner dia. x 0.040 in. wire inner dia.	◆*	◆*	◆*	◆
27-0104	Spring holder, 1 in. L x 0.50 in. inner dia. x 0.031 in. wire inner dia.	◆	◆	◆	◆
27-8035	Angled disk, 1.98 in.	-	-	-	◆
27-8036	Angled disk, 1.42 in.	-	-	-	◆

Diamond image (◆) = Compatible, Shaded box = Not compatible, NR = Not Recommended,
Asterisk (*) = based on dimension measurements only

USP Apparatus 7 – Solid Oral Dosage Forms

Pointed Rod holder

- Used for osmotic dosage tablets
- Apply very small dab of cyanoacrylate glue (not on hole)

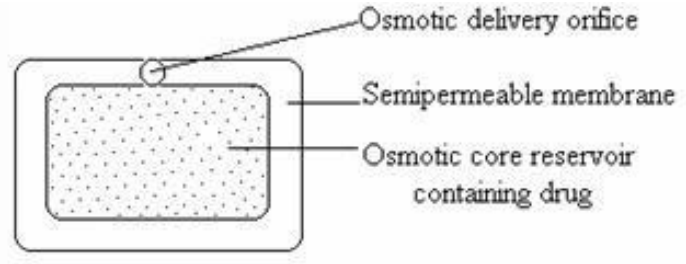
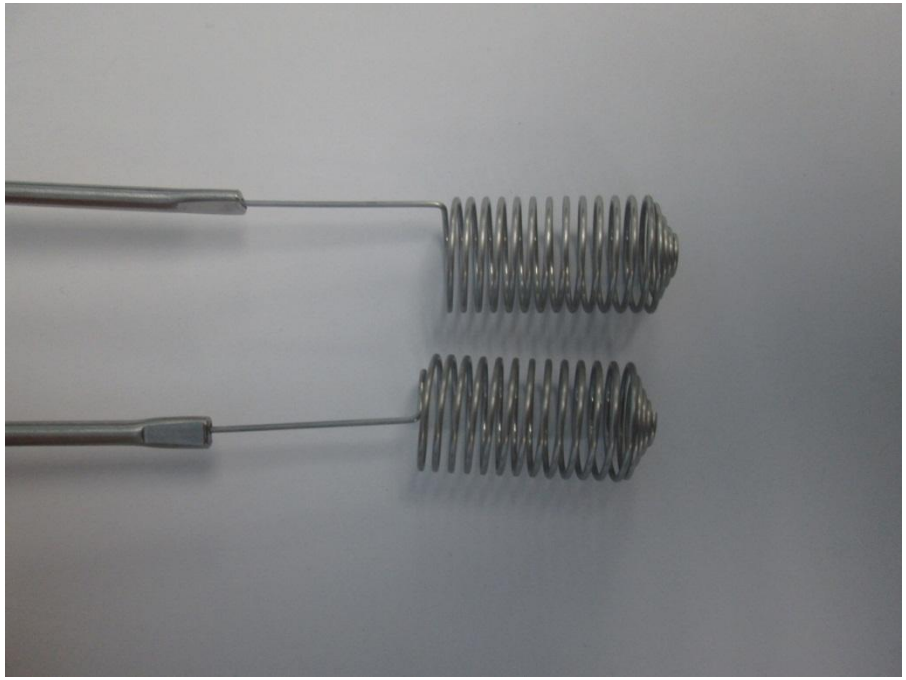


Figure 5: Elementary osmotic pump

http://www.pharmainfo.net/reviews/specialized-chronotherapeutic-drug-delivery-systems

Spring Holders

- Utilized for capsule shaped osmotics and non-disintegrating products
- Choose Spring Holder the same way you size a capsule shell
- 5 sizes, centered and off-centered
- Titanium “bird cage” basket, and 40 or 50 mesh minibaskets are also options

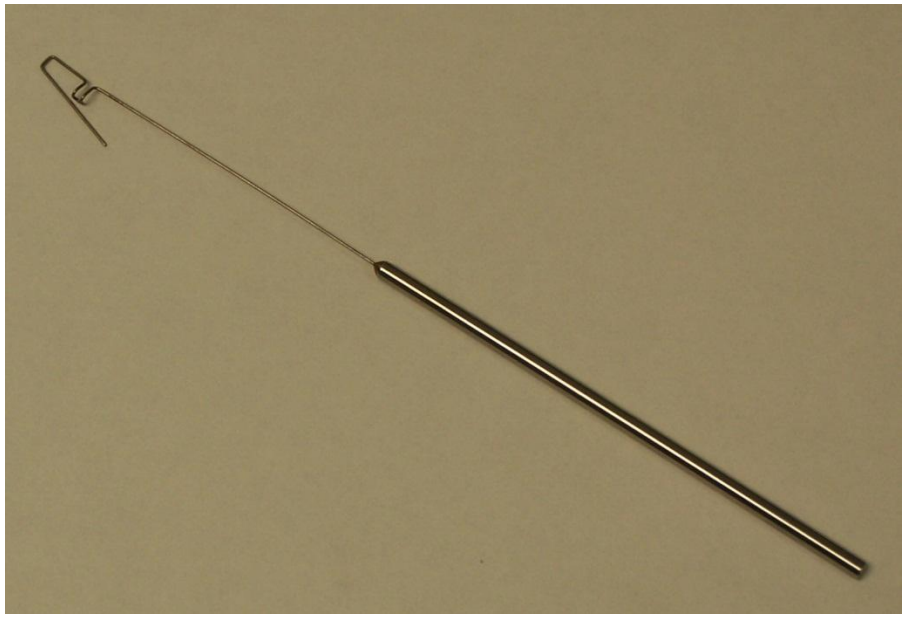


Apparatus 7 – Transdermal Holders

- Holders utilized with a patch and an appropriate membrane material
- Membrane secured by o-rings
- Cylinder accommodates largest patches
- 5 flat disk sizes available, 2 angled disks

Apparatus 7 – Medical Device Holders

- Medical device hook used for stents, pacemaker leads, etc.
- Basket holders also used to contain implants as well
- Other modified holders are known to exist as well



400-DS Small Volume Apparatus 7

The 400-DS was designed to meet the challenges associated with the testing of combinatorial products:

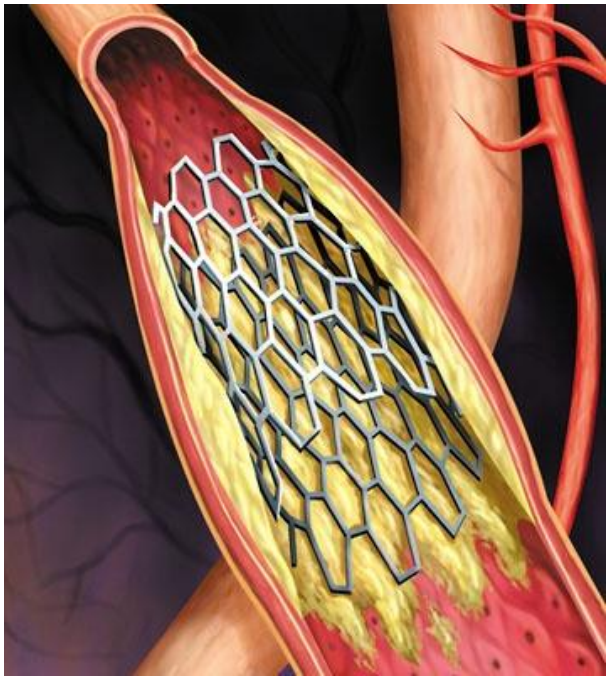
- Small Volume
- Low Evaporative Loss
- Automated Sampling
- Automated Media Replacement
- Bathless
- Regulatory Compliance
- Small footprint

400-DS Applications

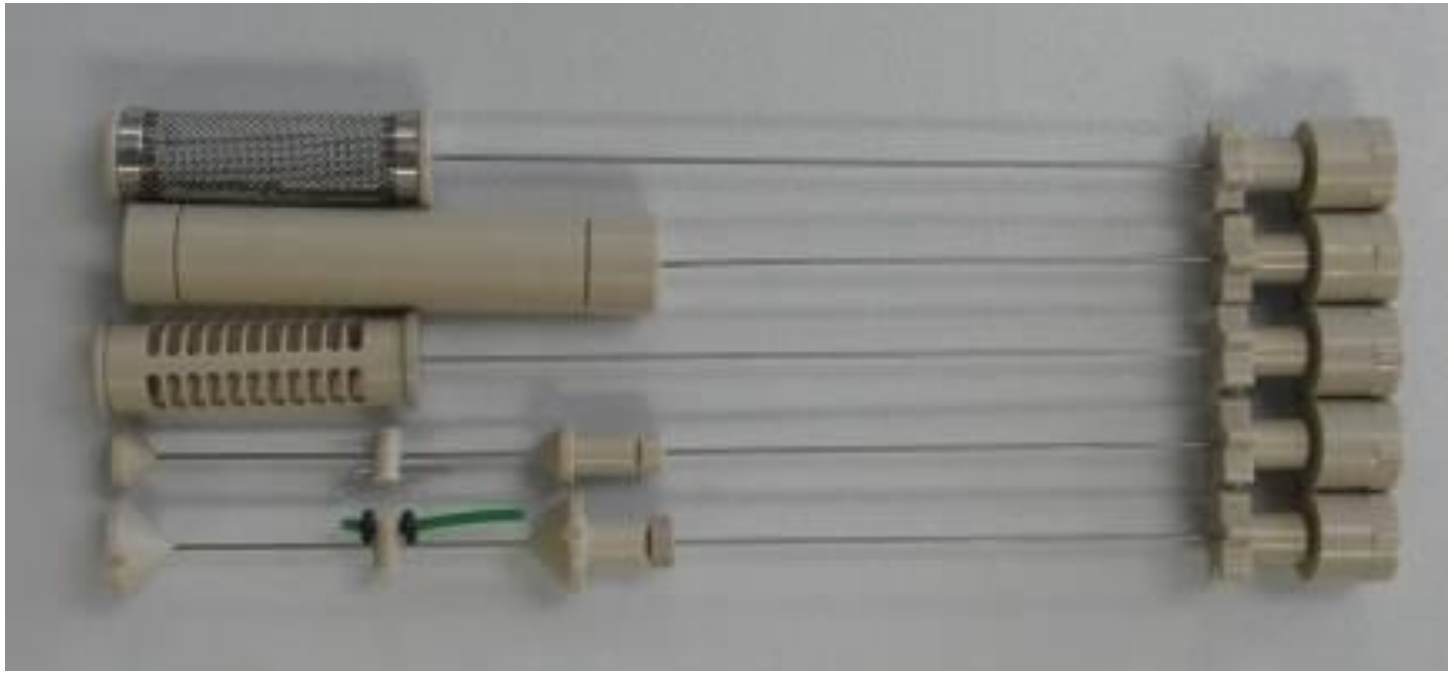
- Volumes <20mL needed
- Dissolution run times > 1 day
- Dissolution media containing alcohols/some organics
- Product is non-disintegrating

Applications of the 400-DS Apparatus 7

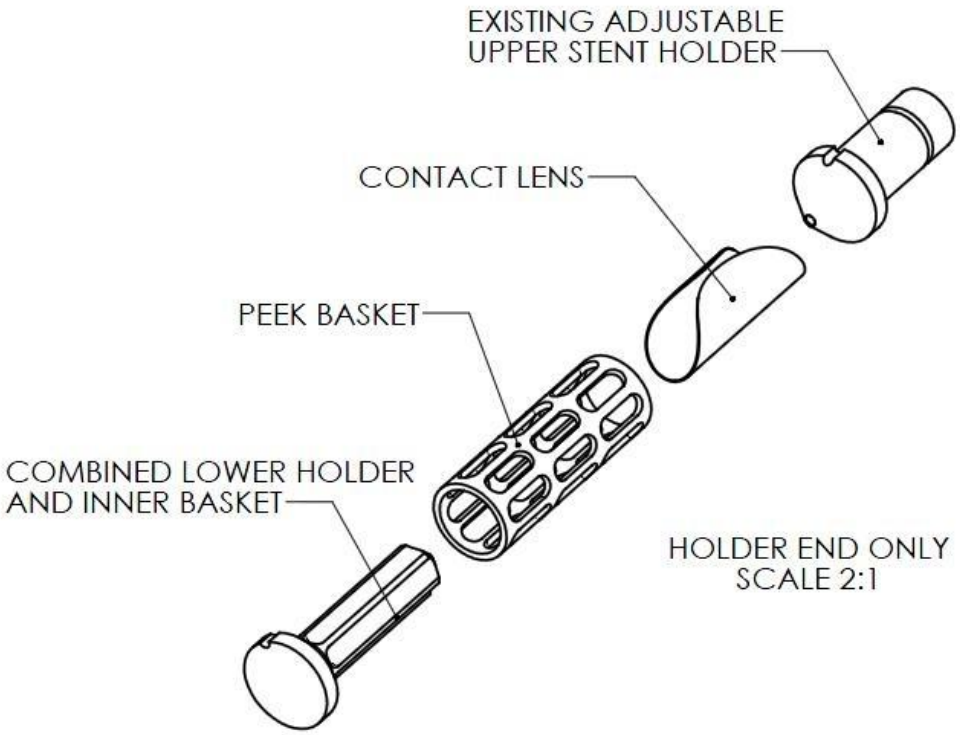
- Drug Coated Stents
- Pacemaker leads
- Catheters
- Transdermals
- Extractables/Leachables
- Other Medical Devices
- Novel Dosage Forms
- Micronized powders



Variety of Holders Available



Contact Lens/Woven Material Holder



Agilent 400-DS: Key Features and Benefits

- **Small volumes:** 5 mL or 10 mL dissolution cells can use from 3 mL to 12 mL media for testing
- **Bathless:** heater jackets provide stable temperature control for extended run times
- **Automated media replacement:** Integrated fluidics module provides total media replacement with up to four different types of media
- **Negligible evaporation:** <0.2% volume per 24 hrs ensures reliable results even for long test runs
- **Integrated autosampler:** samples 1 mL – 4 mL from dissolution cells into sealed vials for analyses
- **Smaller size:** Occupies about 35% less space on a lab bench compared to traditional Apparatus 7
- **Automation of convenience and throughput:** One instrument can run 13 test samples (two sets of six, plus a standard or control) and 400-DS software running on a single PC can control up to four instruments (up to 52 test samples)
- **Regulatory Compliance:** 400-DS is a compendial Apparatus VII and the software is compliant with 21 CFR Part 11 guidelines for electronic records

Upcoming Webinars

http://dissolution.chem.agilent.com/

Small Volume Dissolution Methodology – August 22nd

Online UV Dissolution Method Development – October 3rd

Fiberoptic UV Dissolution Method Development – December 5th

Thank You!

Questions?

You can also reach me at:

Ken.Boda@agilent.com

Dissolution.Hotline@agilent.com

www.dissolution.com