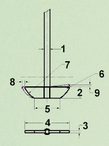
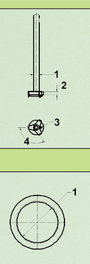
Dissolution Reference Guide

Table 1: Mechanical Qualification of Dissolution Apparatus Comparisons

Parameter	Internationally Harmonized Pharmacopeia	FDA (DPA-LOP.002)	ASTM (E2503-07)	USP Toolkit (2.0 Draft)
Basket/Paddle Depth	25 ± 2 mm	25 ± 2 mm	25 ± 2 mm (or within 8% of desired height)	23-27 mm
Rotational Speed	±4% of specified rate	±2 RPM of target	Within 2% or ±2 RPM of stated rate (use larger)	±1 RPM of set value
Shaft Wobble	No significant wobble	≤1.0 mm total runout	≤1.0 mm total runout	<1.0 mm total wobble
Shaft Verticality	Not measured	≤0.5 ° from vertical	Within bubble	NMT 0.05° from 90.0°
Basket Wobble	±1 mm	≤1.0 mm total runout	≤1.0 mm total runout	<1.0 mm total wobble
Vessel/Shaft Centering	NMT 2 mm from center axis	≤1.0 mm from center line	≤1.0 mm from center line	NMT 2.0 mm for 360° rotation
Vessel Verticality	Not measured	≤1.0 ° from vertical from two positions 90 ° apart	≤1.0 ° from vertical from two positions 90 ° apart	NMT 0.5 ° from 90.0°
Vessel Plate Level	Not measured	Not measured	Not measured	Inclination NMT 0.5° in two orthogonal directions
Performance Verification Test	USP Prednisone Tablets RS	Not measured	Not measured	USP Prednisone Tablets RS

References:
1. Dissolution <711>, USP 32 NF 27, 2009, Vol. 1.
2. Mechanical Qualification of Dissolution Apparatus 1 and 2, FDA DPA-LOP.002, Ver. 2.0, 2006.
3. Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus, ASTM E2503-07, 2007.
4. Dissolution Toolkit Procedures for Mechanical Calibration and Performance Verification Test, Ver. 2.0, USP, March 22, 2010.
5. FIP Position Paper on Qualification of Paddle and Basket Dissolution Apparatus, *AAPS PharmSciTech* 16 July, 2009.

Table 2: Dissolution Apparatus Component Specifications

Component		Dimension Reference	Internationally Harmonized Specification (mm)
Paddle		1	9.4 – 10.1
		2	19.0 ± 0.5
		3	4.0 ± 1.0
		4	74.0 – 75.0
		5	42.0 ± 1.0
		6	1.2 ± 0.2
		7	41.5 ± 1.0
		8	NMT 0.5
		9	NMT 0.5
Basket		1	20.2 ± 1.0
		2	22.2 ± 1.0
		3	37.0 ± 3.0
		4	27.0 ± 1.0
		5	25.0 ± 3.0
		6	20.2 ± 1.0
		7 wire diameter	0.25 – 0.31
		8 opening	0.36 – 0.44
Basket Shaft		1	9.4 – 10.1
		2	5.1 ± 0.5
		3	2.0 ± 0.5
		4	3 clips at 120 °
Vessel		1	98–106
		2	160–210

Reference: Dissolution <711>, USP 32 NF 27, 2009, Vol. 1.

Table 3: Recommended Mechanical Qualification Frequency

Initial Component Verification	• Vessels dimensions • Basket/shaft dimensions • Paddle dimensions	Require documentation of each component's individual dimensions including vessel cylinder and hemisphere. Certificate of Conformance (COC) acceptable if individual measurements are supplied with each component. General certificates stating the product is manufactured according to USP, without individual measurements, does not satisfy this requirement.
Mechanical Parameters to be Verified Before Testing	• Shaft wobble • Paddle shaft verticality • Shaft verticality • Basket wobble • Vessel centering • Vessel verticality • Basket depth • Paddle depth • Rotational speed • Temperature sensor	Verification of proper adjustment must be documented: • Prior to use • As shafts and vessels are exchanged • At a scheduled frequency in accordance with an established written program per 21 CFR Part 211.160 • At least every three months
Required Before Each Test	• Vessel examination • Basket examination • Paddle examination • Vessel temperature • Vibration • Centering • Water bath level	Documentation required that each component is free from defects, residue, scratches, cracks, corrosion and deformity. There can be no significant vibration in the dissolution apparatus or medium.
Scheduled Maintenance	• Belt tension • Inspect for wear • Lubrication • Cleaning	Documentation of routine preventative maintenance is required. Repair and adjustment must be evaluated to determine if such changes have an impact on the integrity of operation of the dissolution apparatus.

References:
1. Mechanical Qualification of Dissolution Apparatus 1 and 2, FDA DPA-LOP.002, Ver. 2.0, 2006.
2. Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus, ASTM E2503-07, 2007.

Table 4: Sources of Vibration Affecting Dissolution Apparatus

Benchtop (items to be eliminated from the dissolution environment)	• Unstable bench top composition or construction • Fume hood • Shakers and mixers • Ultrasonic baths • Centrifuges • Tapped density equipment • Sieve testing equipment • Loud radios • Vacuum pumps • Printers and copiers
Environmental (factors which contribute to vibration)	• Media prep areas • Slamming doors • Stairways • Production equipment • Construction • Traffic from pallet jacks and lift trucks • Close proximity to railroad
Internal	• Drive belt tension or drive mechanism failure • Worn or loose parts, pulleys or bearings • Lack of lubrication of internal components • Circulator touching the apparatus • Water bath turbulence, missing deflector • Loose paddles or baskets

Table 5: Mathematical Models Used To Describe Drug Dissolution Curves

Zero Order	$Q_t = Q_0 + K_0 t$
First Order	$\ln Q_t = \ln Q_0 + K_1 t$
Second Order	$Q_t/Q_\infty = (Q_\infty = Q_t)K_2 t$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_x t$
Weibull	$\log [-\ln(1 - (Q_t/Q_\infty))] = b \bullet \log t - \log a$
Higuchi	$Q_t = K_H \sqrt{t}$
Baker-Lonsdale	$(3/2)[1 - (-1(Q_t/Q_\infty)]^{2/3}] - (Q_t/Q_\infty) = Kt$
Korsmeyer-Peppas	$Q_t/Q_\infty = K_t t^n$
Quadratic	$Q_t = 100(K_1 t^2 + K_2 t)$
Logistic	$Q_t = A/[1 + e^{K(t-y)}]$
Gompertz	$Q_t = A\, e^{-e \cdot K(t-y)}$
Hopfenberg	$Q_t/Q_\infty = 1 - [1 - k_0 t/C_0 a_0]^n$

Reference: Costa, P.; Lobo, J. Modeling and Comparison of Dissolution Profiles. *Eur. J. Pharm. Sci.* 2001, 13, 123-133.

Table 6: Summary of Fundamental Dissolution Theories

Theory	Equations	Associated Characteristics
Diffusion Layer		
Fick's First Law	$J_x = Di(\delta c/\delta x)$	Eq. 1. Considers diffusion only under steady-state conditions.
Fick's Second Law	$\delta c/\delta t = D(\delta^2 c/\delta x^2)$	Eq. 2. Used when drug concentration decreases with time; hence, considers non-steady state conditions.
Noyes and Whitney	$dc/dt = K\,(c_s - c_t)$	Eq. 3. Description of drug dissolution based on constant surface area.
Brunner and Tolloczko	$dc/dt = KS\,(c_s - c_t)$	Eq. 4. Manipulation of Noyes-Whitney's Eq. 3 by incorporation of surface area term *S*. Proposed the formation of a stagnant layer around the dissolving particle, a layer through which solute diffuses through into the bulk.
Nemst-Brunner	$dc/dt = kDS/vh\,(c_s - c_t)$ *If* $c_t << c_s$ (i.e. <10%) $\rightarrow$ $dc/dt = kDS/vhc_s$ *If* v and S are constant $\rightarrow$ $dc/dt = K$	Eq. 5-7. Manipulation of Fick's First Law and expansion of Eq. 4 by incorporation of a diffusion coefficient *D*, stagnant layer thickness *h*, and volume of dissolution medium *v*.
Hixson-Crowell Cube Root	$w_0^{1/3} - w^{1/3} = (4\pi\rho\eta/3)^{1/3}(Dc_s/h\rho)t$ or $w_0^{1/3} - w^{1/3} = Kt$	Eq. 8-9. Originally developed for single particles but has been extended to use in multiparticulate systems.
Surface Renewal	$Vdc/dt = dW/dt = S(\gamma D)^{1/2}\,(c_s - c_t)$	Eq. 10. Assumes solid-solution equilibrium is achieved at the interface and that mass transport is the rate-limiting step in the dissolution process.
Limited Solvation	$G = k_l(c_s - c_t)$	Eq. 11. An intermediate drug concentration less than saturation may exist at the interfacial barrier between the solid surface and solvent. Different faces of a crystal may have different interfacial barriers and, therefore, make different contributions to the dissolution process.

Key to symbols and abbreviations: J_x : (mg/cm^2 s^{-1}); D_i: diffusion coefficient; $\delta c/\delta x$: concentration gradient; $\delta c/\delta t$ or dc/dt: drug dissolution rate; K: first-order dissolution constant; c_s: equilibrium drug concentration; c_t: drug concentration at time t; k: dissolution constant; S: surface area; v: volume of dissolution medium; h: thickness of stagnant layer; w_0: initial powder weight; w: powder weight at time t; ρ: particle density; η: viscosity; h: thickness of diffusion layer; γ, interfacial tension; G: dissolution rate per unit area; k_l: effective interfacial transport constant.

Reference: Pillay, V.; Fassihi, V. Unconventional Dissolution Methodologies, *J. Pharm. Sci.* 1999, 88, No. 9, 843-851.

Table 7: Summary of Basic Theories of Dissolution Profile Analysis

Theory	Equations	Associated Characteristics
Wagner	$\log (w^\infty - w) = \log M - k_y/2.303\,(t - t^0)$ where $M = K/k_x C_s S^0$	Eq. 12-13. Relates apparent first-order kinetics under sink conditions to the distribution of available surface area and not dissolution per se. In case of exponential decrease in surface area with time, then first-order kinetics could be related to dissolution data.
Kitazawa	$\ln w^\infty/(w^\infty - w) = K't$	Eq. 14. Assumes constant surface as long as sink is maintained. Under these conditions C^∞ is not always equal to C_s. A plot of $\ln w^\infty/(w^\infty - w)$ vs. t yields a straight line with slope as the dissolution rate constant K'.
El-Yazigi	$(100 - f_2) = 100k_d/(k_d - k_s)e^{-kst} - 100k_r/(k_d - k_s)e^{-kdt}$	Eq. 15. Disintegration and dissolution are consecutive first-order processes. Because disintegration is usually much faster than dissolution, the semi log plot of $(100 - f_2)$ vs. t yields a biexponential curve.
Carstensen	If q is small and Flq <<1 $\rightarrow$ $\ln m = -q\theta + \ln m_0$ If q is large $\rightarrow$ $\ln m = -q\theta + q\theta_2 + \ln m_0\, 6(Flq)3$	Eq. 16-17. Considered that the dissolution process in the USP basket proceeds in three steps: • Some disintegration but particles not dislodged from basket • More disintegration and particles move out of basket • More disintegration and first particles have completely dissolved. These three phases have to be mathematically explained to calculate the mass of solute undissolved at time $t = 0$.

Key to symbols and abbreviations: w^∞: amount of drug in solution at infinite time; $(w^\infty - w)$: amount of undissolved drug; K: dissolution constant; k_s: dissolution rate constant; t: time in question; t^0: time $t = 0$; C_s: aqueous solubility of drug; S^0: surface area at time t^0; K': dissolution constant; f_2: cumulative percentage of drug dissolved at time t; k_d: disintegration rate constant; k_s: dissolution rate constant; q: erosion constant; m: mass of undissolved solute; θ: experimentally observed time; F: factor as a function of the intrinsic dissolution rate (either in basket or vessel), drug solubility, and particle density.

Reference: Pillay, V.; Fassihi, V. Unconventional Dissolution Methodologies, J. Pharm. Sci. 1999, 88, No. 9, 843-851.

Table 8: Dissolution Profile Comparison f_2

When the two profiles are identical, f_2=100. An average difference of 10% at all measured timepoints results in an f_2 value of 50. The FDA set a public standard of f_2 value between 50-100 to indicate similarity between two dissolution profiles.

$$f_2 = 50 \bullet \log \{[1+(1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

For a dissolution profile comparison:
At least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data, the % coefficient of variation at the earlier point should not be more than 20%; should not be more than 10% at other timepoints.
For circumstances where wide variability is observed, or a statistical evaluation of f_2 metric is desired, a bootstrap approach to calculate a confidence interval can be performed.
The dissolution measurements of the two products (test and reference, pre- and post-change, two strengths) should be made under the same test conditions. The dissolution timepoints for both profiles should be the same, e.g., for immediate release products 15, 30, 45 and 60 minutes, for extended release products 1, 2, 3, 5 and 8 hours.
Because f_2 values are sensitive to the number of dissolution timepoints, only one measurement should be considered after 85% dissolution of the product.
For rapidly dissolving products, i.e., more than 85% in 15 minutes or less, a profile comparison is not necessary.
An f_2 value of 50 or greater (50-100) ensures sameness or equivalence of the two curves and, thus, the performance of the two products.

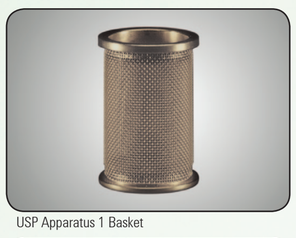
Reference: Shah, V.; Tsong, Y.; Sathe, P.; Williams, R. Dissolution Profile Comparison Using Similarity Factor f_2. *Dissolution Technologies* 1999, 6, Issue 3.

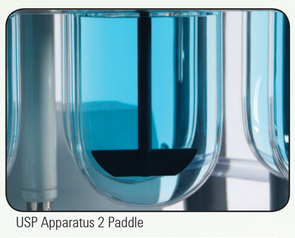
Table 9: Agilent Dissolution Seminar Series

Fundamentals of Dissolution	Designed for new or experienced dissolution analysts, the course emphasizes basic dissolution fundamentals and theory. Includes focused discussions on dissolution apparatus, mechanical and performance verification, dissolution technique and regulatory issues.
Advanced Dissolution: Principles and Theory	Intended for the advanced dissolution analyst as well as those involved in drug metabolism and disposition, pharmacokinetics and analytical methods development. Specific focus on *in vitro*/*in vivo* correlation and the use of dissolution data relating to bioequivalence.
Dissolution Method Development and Validation	Lectures provide regulatory guidance and practical knowledge required for rugged, biorelevant dissolution methods. Developed for experienced R&D, method development or QC chemists interested in developing discriminating *in vitro* dissolution methods.

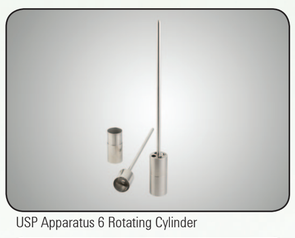
These two-day courses may be held at either a Agilent facility or on-site at a customer facility. For detailed Seminar Series information, visit www.agilent.com

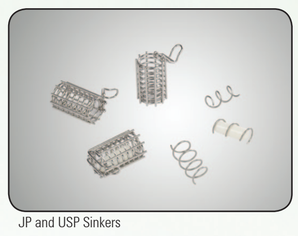
Photo References

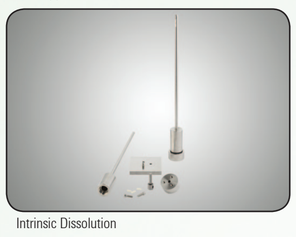

USP Apparatus 1 Basket

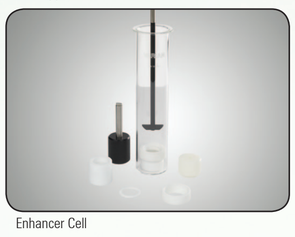

USP Apparatus 2 Paddle


USP Apparatus 5 Paddle Over Disk

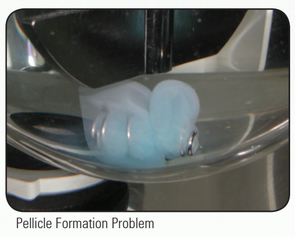

USP Apparatus 6 Rotating Cylinder

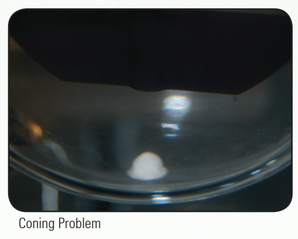

JP and USP Sinkers


Intrinsic Dissolution


Enhancer Cell


Small-Volume Paddle


Pellicle Formation Problem


Coning Problem

708-DS Dissolution Apparatus

Table 10: Dissolution Resources

Dissolution Discussion Group (DDG)	www.dissolution.com
Dissolution Technologies Publication	www.dissotech.com
American Association of Pharmaceutical Scientists (AAPS) *In Vitro* Release Dissolution Testing (IVRDT) Focus Group	www.aapspharmaceutica.com/inside/focus_groups/InVitro/index.asp
US Federal Drug Administration (FDA) Biopharmaceutics Guidance Page	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm
FDA Recommended Dissolution Methods Database	www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm
United States Pharmacopeia (USP)	www.usp.org
European Pharmacopeia (EP) / European Directorate for the Quality of Medicines and Health Care (EDQM)	www.edqm.eu
Japanese Pharmacopeia (JP) / National Institute of Health Science (NIHS)	www.nihs.go.jp/english/index.html
Controlled Release Society (CRS)	www.controlledrelease.org

Table 11: Common Dosage Forms and Typical Test Conditions with Basket and Paddle Dissolution Apparatus

Dosage Forms	Test Conditions
Capsules and Tablets	
Immediate and Modified Release	Basket (USP Apparatus 1), typical speeds 50, 75 or 100 RPM; Paddle (USP Apparatus 2), typical speed 50 or 75, with sinker option for floating forms
Enteric-Coated	Basket or paddle: acid stage typically 0.1N HCl followed by buffer stage typically pH 6.8 phosphate buffer • Method A: media addition method • Method B: media exchange method
Chewables	Paddle with agitation ≥ 100 RPM
Osmotics	Basket, paddle with stationary basket method
Swelling Dosage Forms	Basket, paddle, paddle over disk or sinker basket
Suppositories	Basket, slotted basket
Beads	Basket, paddle, sinker basket, fine-mesh basket
Suspensions	Paddle with syringe introduction, suspension cup, basket with fine-mesh, speed 25-50 RPM
Transdermal Systems	Paddle over disk or rotating cylinder
Semisolid	Paddle with suspension cup or mini paddle, 200 mL small-volume vessel and enhancer cell
Powders	Intrinsic dissolution holder, paddle with powder in capsule and sinker, or fine-mesh basket

Table 12: Aberrant Dissolution Data Checklist

Laboratory Investigation Triggers
• Out of specification results (OOS) • Possible sample mix-up or dilution error • Multi-timepoint results decrease more than 5% • Results > upper content uniformity limit • Results > 125% • Stability results > 10% of the previous timepoint • Stability packaging configurations > 15% agreement (same timepoint)
Requirements of the Investigation
• Use cause and effect relationships as a tool for investigation • Look for key factors that cause high or low dissolution results (temperature, speed, etc.) • Ensure samples have been retained

Dissolution Apparatus	
Baskets	• Conform to USP or compendial specifications? • Corrosion present? • Straight with parallel and smooth surface? • Frayed appearance? • Clips hold basket tightly?
Paddles	• Conform to USP or compendial specifications? • Surface irregularity with peeling Teflon coating or pitted surface? • Straight with perpendicular blade attached? • Has the validated sinker been used (tremendous variation)?
Sampling and Filtering — dissolution does not stop until filtration is performed	• Correct sampling position? • Separate, clean, dry equipment used? • Sampling materials validated? • Samples filtered immediately? • Proper filters used? • Filters validated for drug adsorptivity at the lowest concentration? • Proper amount of sample discarded? • Centrifuge is not an option to clarify dissolution samples.
Vessels	• Scrupulously clean, no residue, film or buildup? • Surface irregularities; cracks, scratches, chips? • Vessels should be numbered and in dedicated positions.
Vibration	• See Table 4: Sources of Vibration Affecting Dissolution Apparatus. • Sources of vibration must be removed from the dissolution laboratory.
Media, Volumetric Measurement and Deaeration	• Proper and validated deaeration technique used? • Media gently transferred to the vessel? • Media equilibrated to 37.0 ± 0.5 °C prior to test? • Were bubbles or air films present during testing? • Was the proper volumetric glassware used to deliver the media? • Has the volume been kept to 1% accuracy during the test? • Have proper covers been used to minimize evaporative loss? • Preheated media may be weighed with great accuracy.
Mechanical and Performance Qualification	• See Table 3: Recommended Mechanical Qualification Frequency. • Apparatus must be maintained in a qualification schedule.
Dissolution Procedure	• Correct test method used? • Raw data properly documented and scientifically correct? • Temperature, pH, media preparation correct? • Correct reference standard(s) used, prepared and within expiration? • Analytical solution properly stored?
Dissolution Analyst	• Analyst been properly trained in dissolution? • Analyst been properly trained in the analytical methodology? • Test method followed as written?

All specifications are current as of August 2010. Specifications are constantly subject to change. Reference your local pharmacopeia or applicable standard for the most current specifications.

This information is subject to change without notice.

© Agilent Technologies, Inc. 2010

Published in USA, September 29, 2010
5990-6492EN

The Measure of Confidence

Agilent Technologies