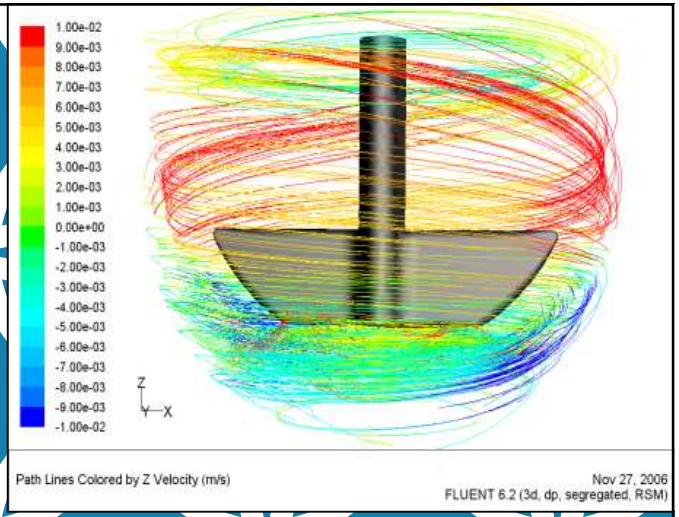


INTRODUCTION TO DISSOLUTION APPARATUS

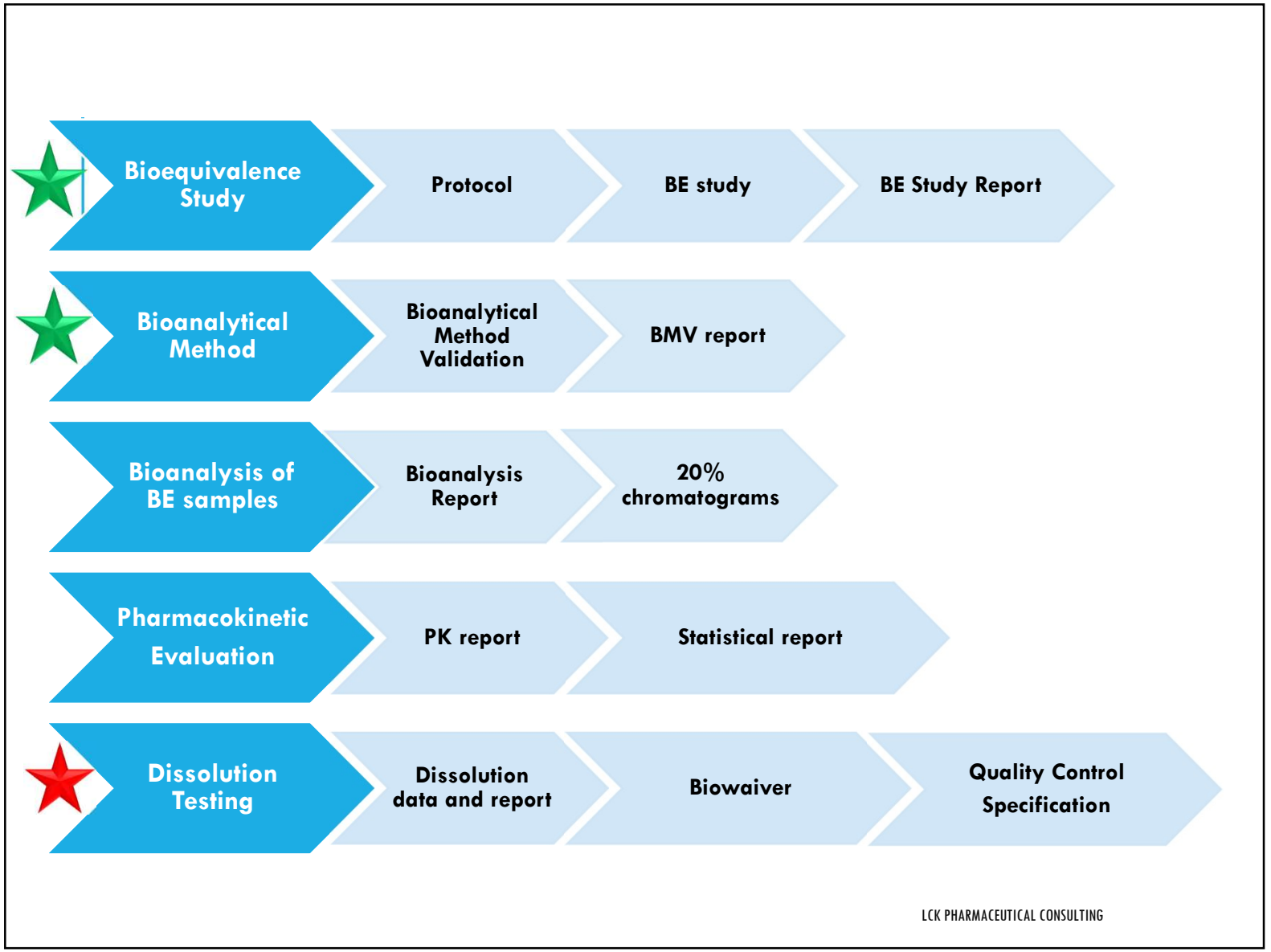
Loice Kikwai, Ph.D.

Dissolution Webinar Training

LCK PHARMACEUTICAL CONSULTING

DISCLAIMER

- The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration or the Saudi Food and Drug Authority


Bioequivalence Study
Protocol
BE study
BE Study Report
Bioanalytical Method
Bioanalytical Method Validation
BMV report
Bioanalysis of BE samples
Bioanalysis Report
20% chromatograms
Pharmacokinetic Evaluation
PK report
Statistical report
Dissolution Testing
Dissolution data and report
Biowaiver
Quality Control Specification
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PRESENTATION OUTLINE

- General Chapters
  - <711>, <724>, <1092>
- Instrumentation
  - USP Apparatus 1, 2, 5, 6
  - USP Apparatus 3, 7
  - USP Apparatus 4
- Accessories
- Dissolution testing set up
- Summary

USP <711> DISSOLUTION TEST

- Developed in 1950's -1970's
- 1970: Test official in USP XVIII
- Referenced in *General Chapter <711>*
  - Standardized Apparatus #1 in 1970, #2 in 1975,
  - Standardized Apparatus #3 and #4
- Apparatus Suitability Test for Apparatus 1, 2, and 3:
  - Mechanical calibration
  - USP Performance Verification Test Tablets
- Immediate-release dosage forms
- Modified-Release dosage forms
  - Delayed-release (Enteric-coated) dosage forms
  - Extended-release dosage forms
- There are **1102 USP monographs** that call for dissolution testing.
  - **Monograph may have multiple dissolution tests**

USP <724> DRUG RELEASE TEST

- USP Apparatus 5, 6 and 7
  - Transdermal systems
  - There are **21 USP monographs** that call for drug release testing per GC <724>
    - 3 Transdermal patch system
    - 6 ER Tablets
    - Acceptance Tablet 1
      - Progesterone intrauterine Contraceptive system
      - Pilocarpine Ocular system

<1092>THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION

- PRELIMINARY ASSESSMENT
  - 1.1 Performing Filter Compatibility
  - 1.2 Determining Solubility and Stability of Drug Substance in Various Media
  - 1.3 Choosing a Medium and Volume
  - 1.4 Choosing an Apparatus
- METHOD DEVELOPMENT
  - 2.1 Deaeration
  - 2.2 Sinkers
  - 2.3 Agitation
  - 2.4 Study Design 2.4.1 Time Points
  - 2.4.2 Observations
  - 2.4.3 Sampling
  - 2.4.4 Cleaning
  - 2.5 Data Handling
  - 2.6 Dissolution Procedure Assessment
- ANALYTICAL FINISH
  - 3.1 Sample Processing
  - 3.2 Filters
  - 3.3 Centrifugation
  - 3.4 Analytical Procedure
  - 3.5 Spectrophotometric Analysis
  - 3.6 HPLC
- AUTOMATION
  - 4.1 Medium Preparation
  - 4.2 Sample Introduction and Timing
  - 4.3 Sampling and Filtration
  - 4.4 Cleaning
  - 4.5 Operating Software and Computation of Results
  - 4.6 Common Deviations from the Compendia Procedures That May Require Validation

<1092>THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION

- VALIDATION
  - 5.1 Specificity/Placebo Interference
  - 5.2 Linearity and Range
  - 5.3 Accuracy/Recovery
  - 5.4 Precision 5.4.1 Repeatability of Analysis
  - 5.4.2 Intermediate Precision/Ruggedness
  - 5.4.3 Reproducibility
  - 5.5 Robustness
  - 5.6 Stability of Standard and Sample Solutions
  - 5.7 Considerations for Automation
- ACCEPTANCE CRITERIA
  - 6.1 Immediate-Release Dosage Forms
  - 6.2 Delayed-Release Dosage Forms
  - 6.3 Extended-Release Dosage Forms
  - 6.4 Multiple Dissolution Tests
  - 6.5 Interpretation of Dissolution Results 6.5.1 Immediate-Release Dosage Forms
  - 6.5.2 Delayed-Release Dosage Forms
  - 6.5.3 Extended-Release Dosage Forms
- REFERENCES

OTHER PHARMACOPEIAS - EP

- Ph. Eur.: 2.9.3 Dissolution Test for Solid Dosage Forms
- Descriptions of Apparatus 1, 2, 3 and 4
- Acceptance Criteria
- Guidance on dissolution testing and qualification and validation

OTHER PHARMACOPEIAS -EP

- **Ph.Eur. 2.9.4**"Dissolution Test for Transdermal Patches"
- Disk Assembly Method (using stainless steel disk assembly corresponding to App. 5)
- Cell Method (using extraction cells)
- Rotating Cylinder Method (using stainless steel cylinder corresponding to App. 6)

OTHER PHARMACOPEIAS - JP

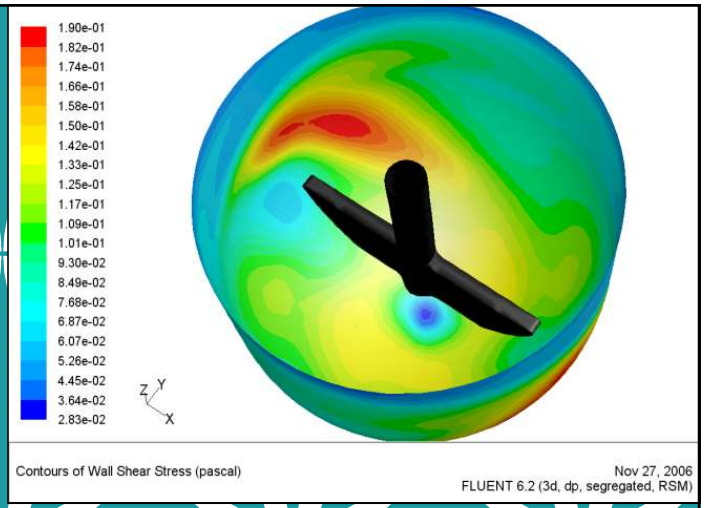
- JP: General Tests Processes and Apparatus 6.10 Dissolution Test
- Descriptions of Apparatus for solid preparations for internal use
  - Basket Method (Apparatus 1),
  - Apparatus for Paddle Method (Apparatus 2), and
  - Apparatus for Flow-Through Cell Method (Apparatus 3)
- Procedure and Interpretation including acceptance criteria
- **JP:** no methods described for transdermal delivery systems

MONOGRAPHS FOR DRUG PRODUCTS

- The USP monograph provides information about the test procedure for a specific drug product
- The USP monograph provides the acceptance criteria which the drug product must meet
  - Q values for Immediate Release products (single time-point)
  - Tolerances are given in acceptance tables for multiple time-points
- Dissolution tests in USP reflect the dissolution conditions approved by FDA for products sold in the USA
- Results of a compendial dissolution test do not prove bioavailability or bioequivalence

MONOGRAPHS FOR DRUG PRODUCTS

- Multiple dissolution tests are allowed in a USP drug product monograph
  - The test to which the drug product complies must be stated on the label
- The sponsor of the original monograph will submit a dissolution test along with other tests, procedures and acceptance criteria
- Another manufacturer of the same drug product may submit an alternate dissolution test
  - Usually for extended release drug products



INSTRUMENTATION

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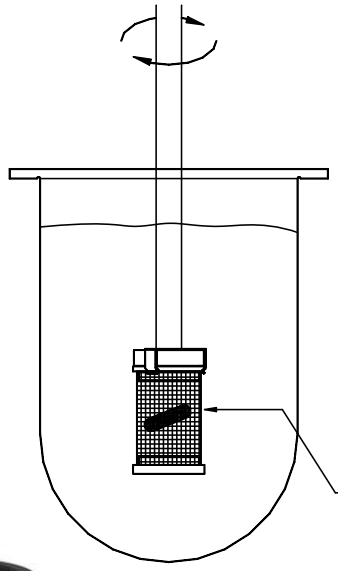
USP APPARATUS 1

ROTATING BASKET



STANDARD

- **40 Mesh Stainless Basket**
- 1 L Vessel
- 100 RPM (50-120 RPM)

MODIFICATIONS

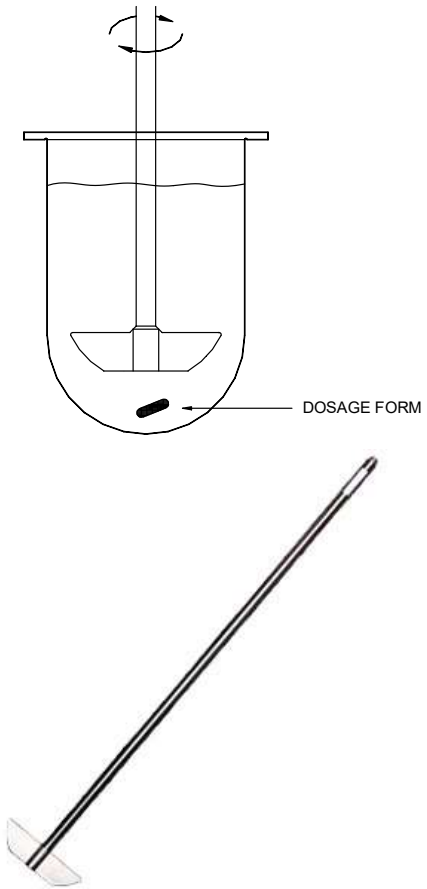
- 10 or 20 Mesh Baskets
- 2 L, 4 L Vessels
- Gold-coated Basket
- pH Change During Test

USEFUL FOR

- Solid Oral Dosage Forms
- Floaters
- Beads
- IR, ER, DR Dosage Forms
- Surfactants in Media
- Suppository (3.2mm slits)

USP APPARATUS 2

PADDLE



STANDARD

- Teflon or Stainless Paddle
- 50 RPM (25-100 RPM)
- 1 L Vessel
- Wire sinker for Floaters

MODIFICATIONS

- 2 L, 4 L Vessels
- Surfactants in Media
- Media pH Change
- Apparatus 5

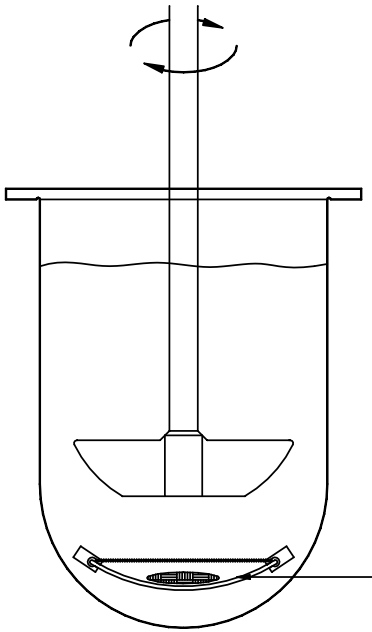
USEFUL FOR

- Solids
- IR, ER, DR Dosage Forms
- Transdermal Patch

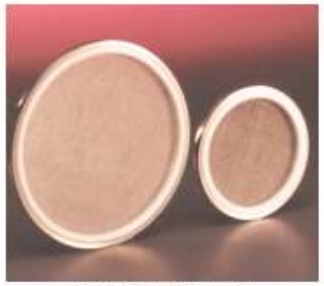
http://www.chem.agilent.com/Library/brochures/Varian705DS11.pdf

USP APPARATUS 5

PADDLE OVER DISK



(SANDWICH)
DOSAGE FORM
COVERED BY SCREEN



Paddle Over Disk Assembly

STANDARD PADDLE USED

- Standard 1 L Vessel

MODIFICATIONS

- Disk Design
- Vessel Size

USEFUL FOR:

- Transdermal Patches

USP APPARATUS 6

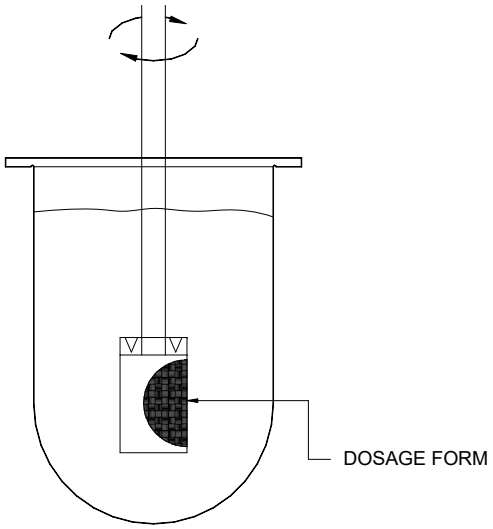
ROTATING CYLINDER

Modification of Apparatus 1

- Special Cylinder Used

USEFUL FOR:

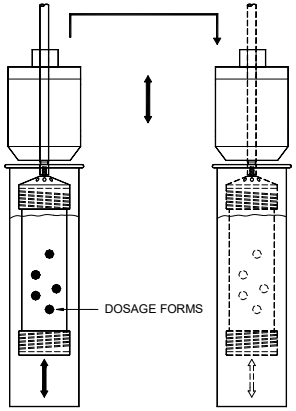
- Transdermal Patches



http://www.mckscientific.com/program/fixedPriceMod.cfm?do=detail&productID=157&categoryID=32

USP APPARATUS 3

RECIPROCATING CYLINDER



RECIPROCATING CYLINDER

With Mesh Screen at

Top and Bottom

SEQUENTIAL MEDIA TUBES

Typical Volume 200mL

USEFUL FOR

- pH Profile
- Beads
- IR, MR Dosage Forms

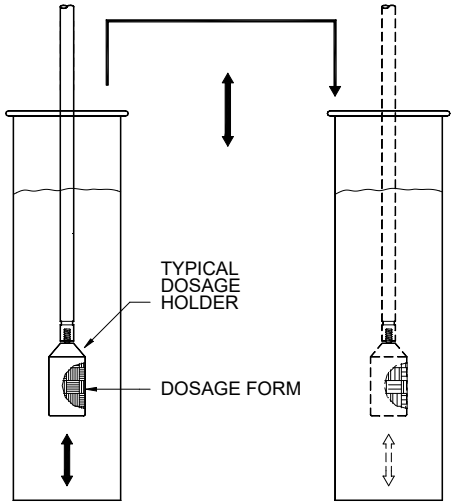
MODIFICATIONS

- Size
- Volume
- Number of Rows
- *** not accepted by JP**

http://www.chem.agilent.com/Library/datasheets/Public/SI-0917_BIO-DIS_DS_v06.pdf

USP APPARATUS 7

RECIPROCATING DISK



RECIPROCATING DISK

•Sample Holder

SEQUENTIAL MEDIA TUBES

•Typical Volumes 50-400mL

USEFUL FOR

•Solid Oral Dosage Forms

•Transdermal Patches

•pH Profile

•Small Volume

MODIFICATIONS

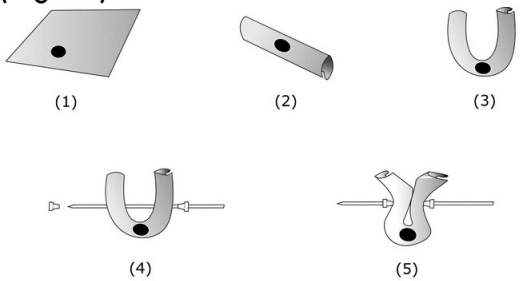
•Volume 20 To 200mL

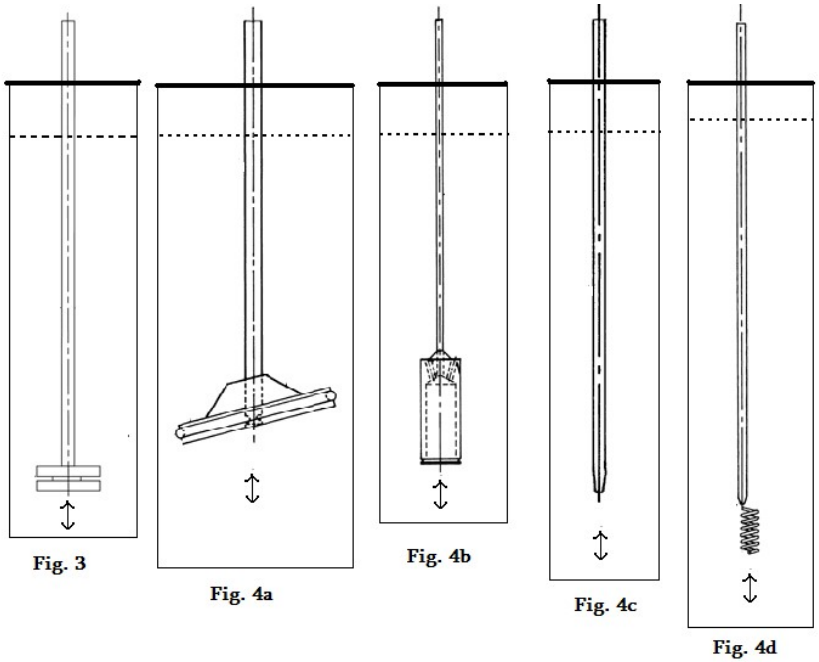
•Dosage form holder

http://www.chem.agilent.com/Library/datasheets/Public/SI-0917_BIO-DIS_DS_v06.pdf

USP APPARATUS 7
RECIPROCATING HOLDER ACCESSORIES

- Reciprocating Disk (Fig. 3)
- Transdermal system holder – angled disk (Fig 4a)
- Transdermal system holder – cylinder (Fig 4b)
- Oral ER Tablet holder – Rod, pointed for gluing (Fig 4c)
  - Example - Pseudoephedrine Hydrochloride Extended-Release Tablets
- Oral ER Tablet holder - Spring Holder (Fig 4d)





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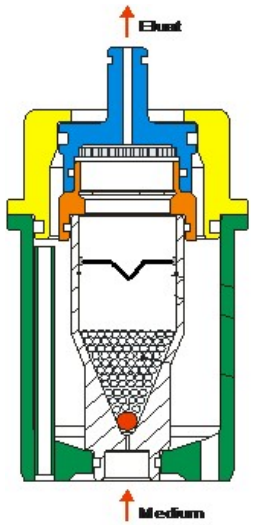
USP APPARATUS 4

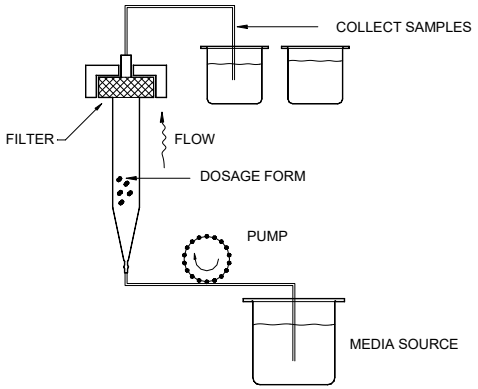
FLOW-THROUGH CELL



http://www.sotax.com/USP-4-Semi-automated-systems.127.0.html

USP APPARATUS 4

FLOW-THROUGH CELLS



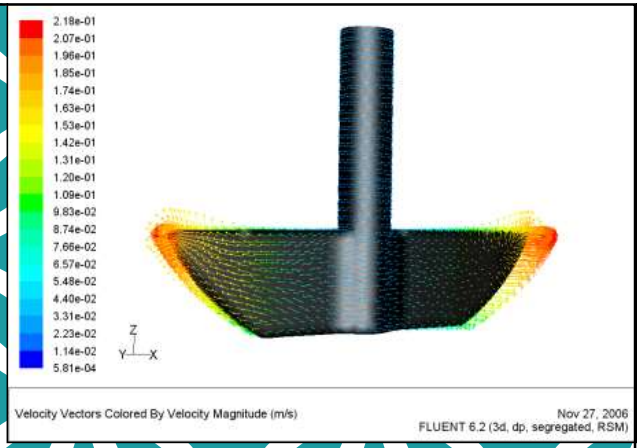
USEFUL FOR

- Low-Solubility Drugs
- Rapid Degradation
- Media pH Changes
- **Not yet specified in any USP drug product monograph**

VARIATIONS

- Large, Small Cell Sizes
- Flow Rate
- Filter

http://www.cspl.in/images/products/Dissolution/CE7smart%20USP4_euro.pdf



ACCESSORIES

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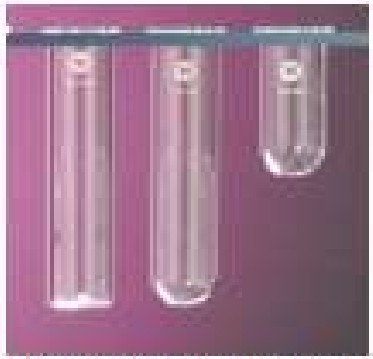
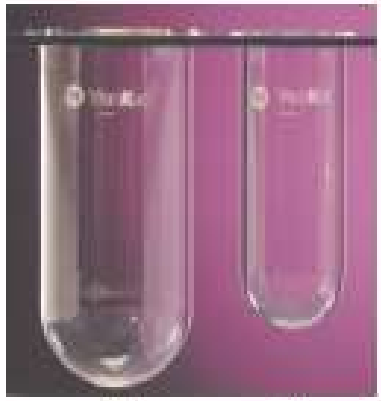
DISSOLUTION VESSELS

1000 mL


200 mL 200 mL 100 mL
PN 12-5055


4L 2L


Amber-tinted


500 mL


Pear

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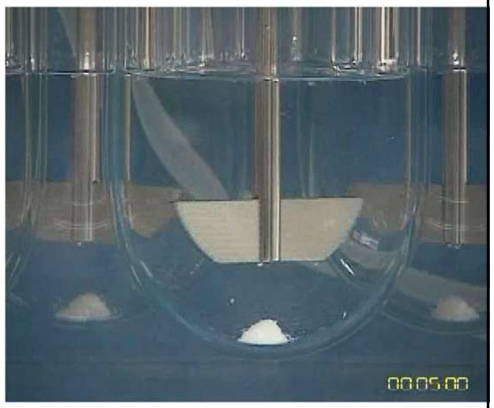
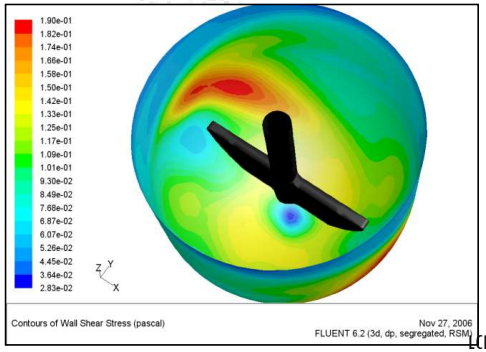
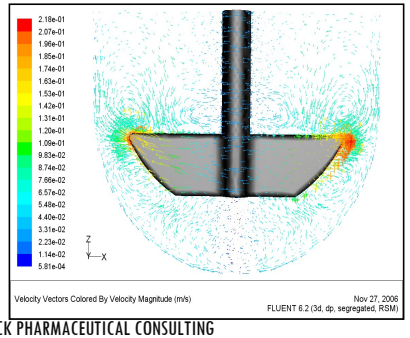
PEAK VESSELS

- Developed to eliminate the coning effect of disintegrated tablets and reduce variability
- DBE Policy –
  - Use not encouraged
  - Not compendial
  - Not standardized
  - Can use peak vessel to justify the change in rpm







VESSEL COVERS

- Minimize evaporative loss of medium
- Sample delivery port
- Sampling port
  - Manual
  - automated

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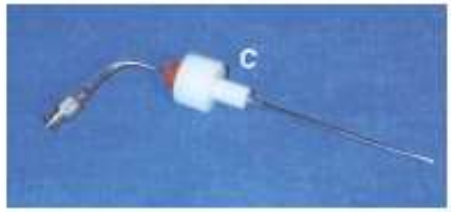
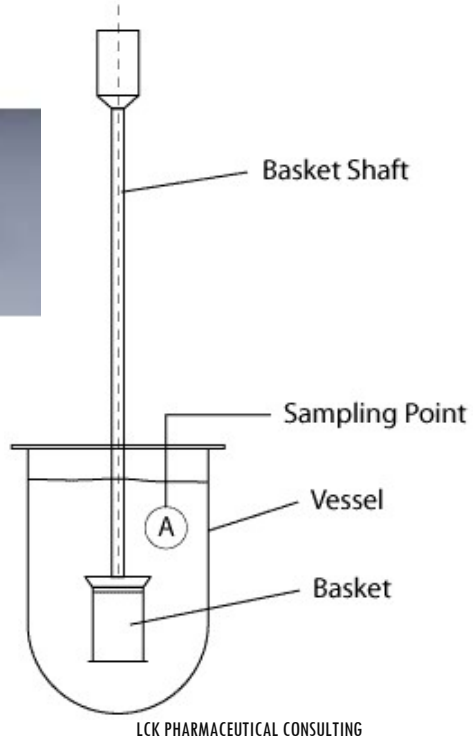
MANUAL SAMPLING





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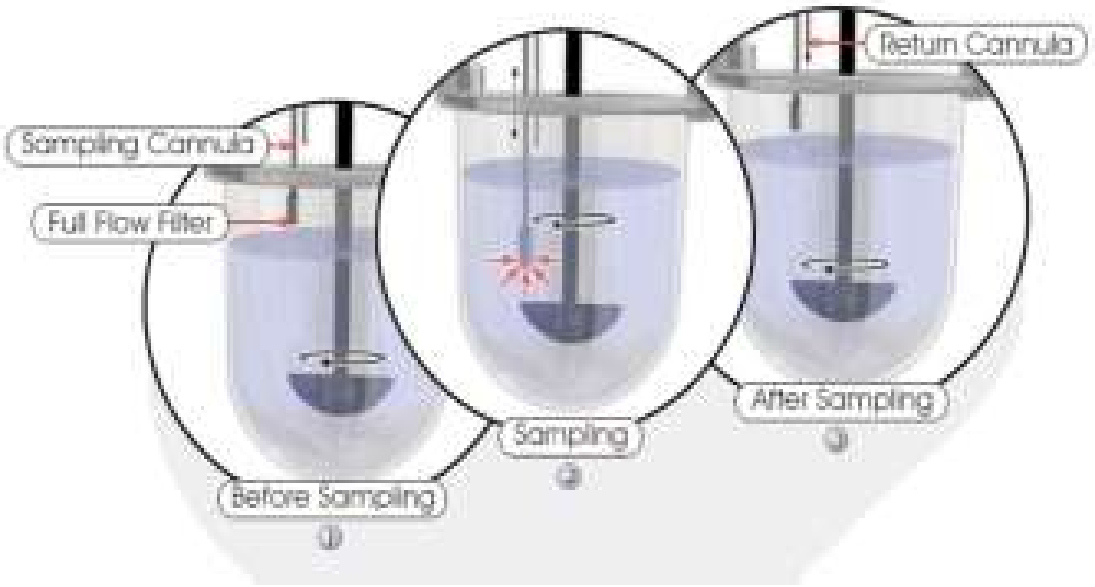
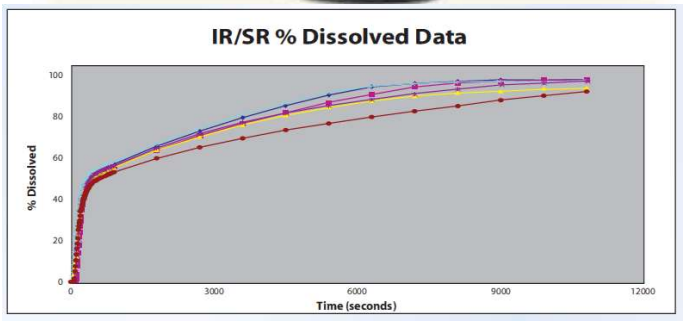
AUTOMATED SAMPLING



FIBER OPTIC SAMPLING

G2 ARCH™ Probes. Shown in 1 mm and 10 mm Pathlengths.



Time (minutes)	Max Result	Min Result	USP Spec	%RSD
15	61.4%	53%	45-65%	4.1
60	84.0%	69.5%	60-85%	5.7
180	103	92.1	>85%	2.7

http://www.distekinc.com/WhatsNew/EAS%2006%20Poster.pdf

WATER BATH / BATHLESS SET UP

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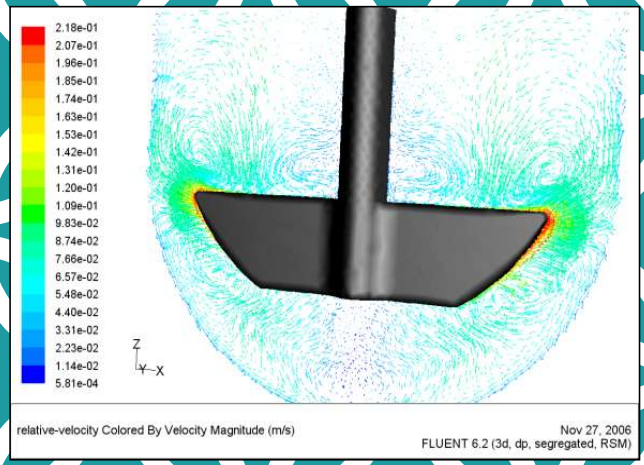
SINKERS

- GC <711> Sinker similar to the Japanese sinker
- GC <1092> Additional information on sinker
  - Stainless steel wire
  - Capsule weights
  - Sinker baskets
  - Japanese sinker baskets
  - Spiral Capsule Sinker

Stainless Steel Wire

VanKel Type Capsule Weights

Japanese Sinker Baskets



SETTING UP AND RUNNING A DISSOLUTION TEST?

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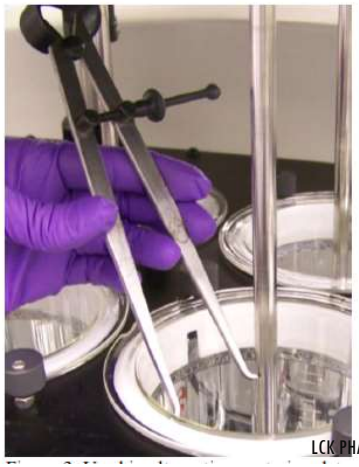
APPARATUS SUITABILITY

- Mechanical Calibration Tools
- Calibration documentation (USP)
- Environment
  - Vibration
  - Level bench top
- Assembly
  - Serialized compendial parts of assembly
  - Alignment
    - Wobble (paddle and basket)
    - Verticality (shaft and vessel)
    - Centering
    - Height (paddle or basket)
  - Motor and transmission (rpm)
  - Temperature Control
- Performance Verification test using USP Reference Standards
- **YouTube videos – QLA – Mechanical calibration**

MECHANICAL CALIBRATION

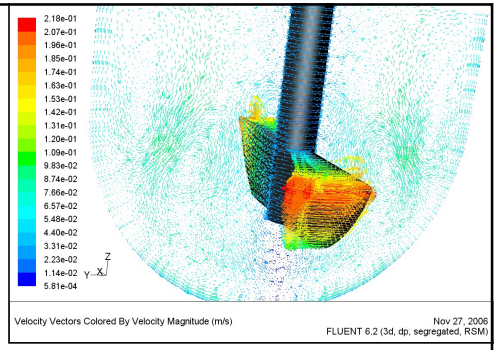
Figure 1. Electronic level giving 0.0° reading on the base plate of a test assembly.



<1092>THE DISSOLUTION METHOD VALIDATION

- VALIDATION
  - 5.1 Specificity/Placebo Interference
  - 5.2 Linearity and Range
  - 5.3 Accuracy/Recovery
  - 5.4 Precision 5.4.1 Repeatability of Analysis
  - 5.4.2 Intermediate Precision/Ruggedness
  - 5.4.3 Reproducibility
  - 5.5 Robustness
  - 5.6 Stability of Standard and Sample Solutions
  - 5.7 Considerations for Automation

DISSOLUTION TESTING



- Use an instrument that
  - Mechanically calibrated
  - Valid PVT
- Use an method that
  - Validated
- Turn on the water bath (optional)
- Prepare Medium
  - Heat
  - Deaerate
- Place medium in vessel (±1% of specified volume)
- Place vessel in to the assembly and cover
- Equilibrate medium to 37 ± 0.5°C
- Lower the stirring element
  - Verify height (±2 mm)
  - Paddle and Basket
- Timing
  - Staggered or simultaneous (±2%)
- Place dosage for in to the vessel
- Start the stirrer/test
- Observation
- Sample at desired time intervals
  - Automated or manual
  - Filter each sample
- Analytical procedure
  - HPLC
  - UV
- Data interpretation

http://www.youtube.com/watch?v=Eqz0X3y3vjs&feature=player_detailpage

Figure 1

Table 1

TYPICAL DISSOLUTION PARAMETER OVERVIEW USP APPARATUS 1 AND 2	
Media	• Evaluate Degassed vs. Non-Degassed • Acid (HCl 0.1 – 0.001 N) • Buffers: Acetate (pH 4.1 – 5.5, 0.05 M), Phosphate (pH 5.8 – 8.0, 0.05 M) • Simulated Fluid: Gastric Fed and Fasted, Intestinal Fed and Fasted
Media Volume	• 900 mL, 500 mL (for low dosage strengths) • 1000 mL, 2 L or 4 L (for increased sink) • 200 mL or smaller volumes (as justified)
Surfactants (anionic, cationic, neutral)	• Cetyl trimethylammonium bromide Cetrimide (CTAB) • Polysorbate (Tween™) 20 - 80 • Polyethoxylated alcohols • Polyoxyethylene sorbitan • N,N-dimethyldodecylamine-N-oxide • Hexadecyltrimethylammonium bromide • Polyoxyl 10 lauryl ether • Nonylphenol ethoxylate (Tergitol™) • Cyclodextrins • Lecithin • Methylbenzethonium chloride (Hyamine®) • Sodium dodecyl sulfate (SDS) • Lauryldimethylamineoxide (LDAO) • Brij® • Triton™ X • Cremophor® • Solutol®
Speeds	**Paddle** • 50 rpm (preferred for BCS) • 75 rpm (to eliminate coning/variability) • 25 rpm (for suspensions) • 100 rpm (needs justification for IR, common for ER) **Basket** • 50 - 100 rpm
Temperature	• 37 °C ± 0.5 °C
Sampling Aliquot	• Into centrifuge tubes (3 - 5 mL) or HPLC vials (1.5 mL)
Sampling Time Points	• 5 min (disintegration occurring, may give profile information for very fast releasing formulations) • 10, 15, 20, 30, 45, 60 min • Infinity time (after running at fast stir 150 - 200 rpm for 15 - 30 min)
Observations or Dissolution Characteristics	• Observe all vessels • Particle disintegration pattern/freely dispersing • Floating material or chunks and particle size • Coning/mounding • Gumming/swelling • Capping or odd erosion pattern • Center/off-center, sticking • Particles adhering to vessel or apparatus shaft • Air bubbles

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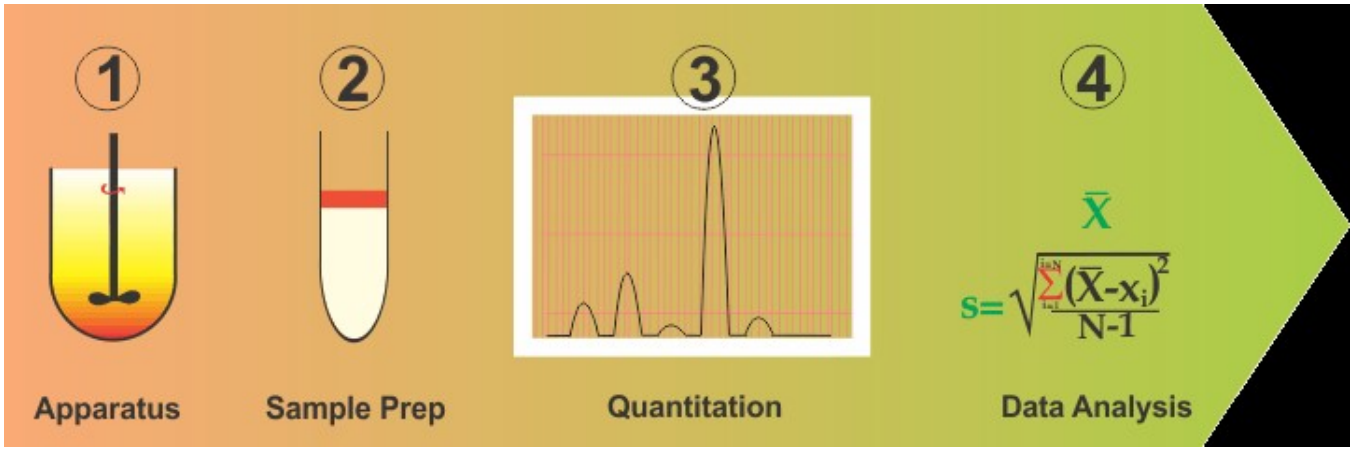

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QUESTIONS