

Dissolution

Background: Dissolution Testing

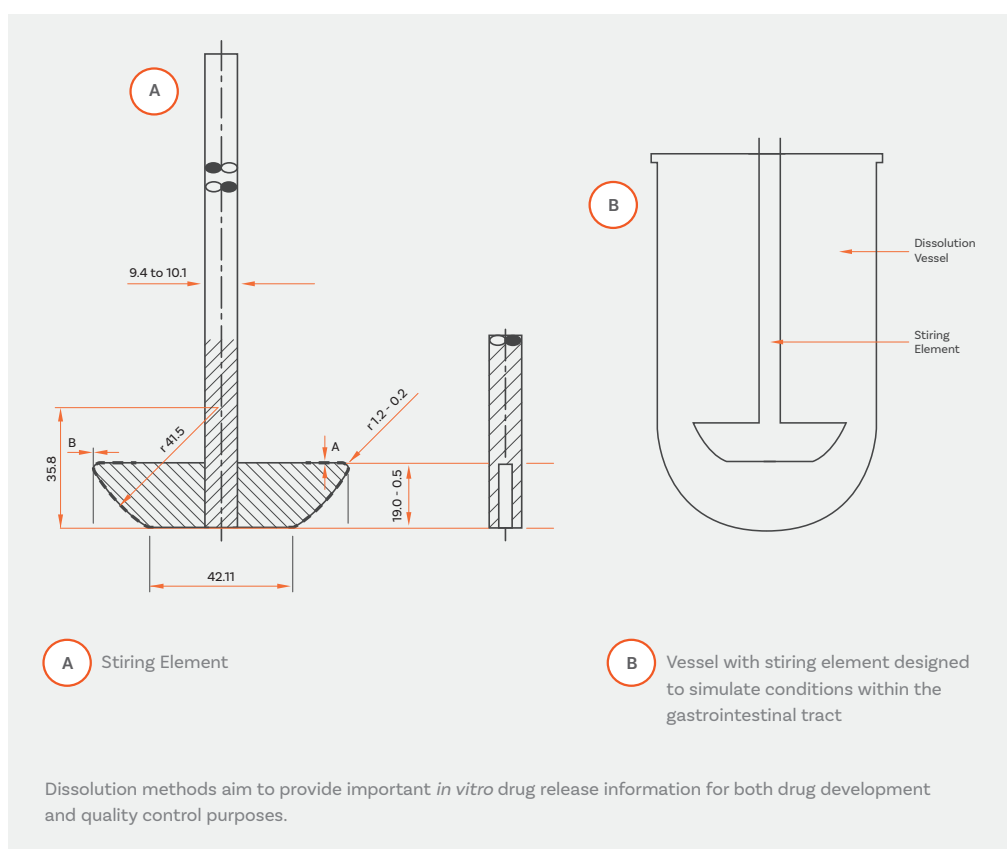
Optimising the amount of a drug available to the body following administration, i.e. its bioavailability, remains one of the greatest challenges the pharmaceutical industry faces. Inadequacies in bioavailability can mean a treatment is ineffective or even potentially dangerous (e.g. overdose).



The effectiveness of tablets or capsules administered orally relies on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation. It is widely acknowledged that the rate at which the drug dissolves is critical to its therapeutic efficacy and as such, is considered a Critical Quality Attribute (CQA) in both the formulation process and final quality control.

Determining bioavailability via *in vivo* drug release analysis studies (e.g. urine or plasma analysis) can be impractical, particularly when such techniques are required on a routine basis. To overcome such issues, official *in vitro* dissolution tests have been rigorously and comprehensively defined in the respective Pharmacopoeias and are essential for:

- Predicting *in vivo* drug bioavailability
- Assessing bioequivalence and its application in scale-up and post-approval changes
- Optimising therapeutic effectiveness during development and stability assessment
- Ensuring uniformity between production lots



Initially developed for oral dosage forms, the role of the 'dissolution test' has now been expanded to the 'drug release' of various other forms such as semisolids topical and transdermal systems (see page 74).

Dissolution

Test Apparatus & Method

The progressive optimisation of dissolution testing for different pharmaceutical forms has led to the introduction of a range of different apparatuses and techniques as detailed in Ph. Eur Chapters 2.9.3, 2.9.4 and USP Chapters <711> and <724>.

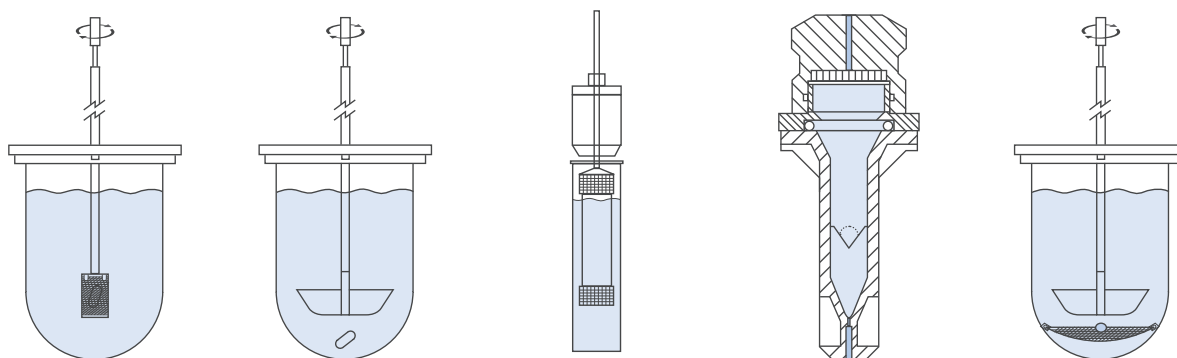
The most commonly used apparatus defined by the Pharmacopoeias to measure the dissolution rate of solid dose forms are the **basket** and **paddle**.

The basic dissolution apparatus consists of a covered cylindrical vessel with a hemispherical bottom, typically holding 1000 mL of simulated gastric juice.

The vessel is immersed in a water bath capable of maintaining the temperature of the vessel contents at 37°C. For the basket method, the tablet or capsule is constrained in a cylindrical basket, constructed of sieve mesh, of defined proportions. The basket is attached to a metal drive shaft, positioned so that the bottom of the basket is 25 mm from the bottom of the vessel.

With the **paddle** method, the basket is replaced by a paddle and the sample to be tested is allowed to sink to the bottom of the vessel. During a test run, a motor is used to rotate the shaft at a speed specified by the appropriate Pharmacopoeias.

The **paddle over disk** technique is used for the determination of the drug release rate from transdermal patches. It is described in the Ph. Eur. under Chapter 2.9.4 and under Chapter <724> as Method 5 in the USP. Using a suitable adhesive, the transdermal patch is simply mounted on a disk designed to hold it at the bottom of the vessel. The **rotating cylinder** (Ph. Eur. Chapter 2.9.4, USP Method 6) is an alternative to the paddle over disk method.

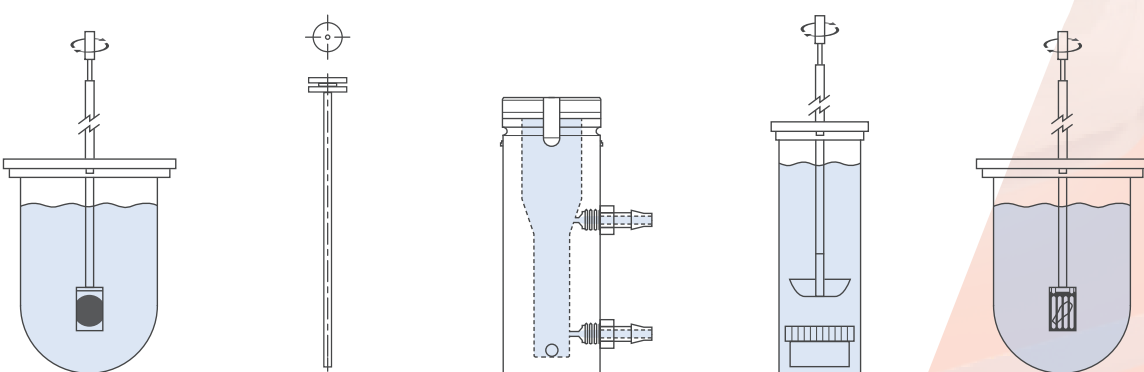


Basket	Paddle	Reciprocating Cylinder	Flow-Through Cell	Paddle Over Disk
Ph. Eur. 2.9.3	Ph. Eur. 2.9.3	Ph. Eur. 2.9.3	Ph. Eur. 2.9.3	Ph. Eur. 2.9.4
USP App 1 <711>	USP App 2 <711>	USP App 3 <711>	USP App 4 <711>	USP App 5 <724>



Samples of the dissolution medium are taken at predefined time intervals to determine the percentage of dissolved drug present – typically using a UV/Vis Spectrophotometer or high-pressure liquid chromatography (HPLC). Dissolution of all but the most specialised oral pharmaceutical dosage forms can be tested with either the basket or paddle methods.

Other techniques specified in the USP for dissolution testing include: Reciprocating Cylinder (Apparatus 3), Flow-Through Cell (Apparatus 4) and Reciprocating Holder (Apparatus 7). These are not routinely required except for highly specialised dosage forms.



Cylinder	Reciprocating Holder	Vertical Diffusion Cell	Special Immersion Cell	Special Suppository Basket
Ph. Eur. 2.9.4	-	-	-	-
USP App 6 <724>	USP App 7 <724>	USP <1724>	USP <1724>	-

Dissolution: DISi Series

Expertly engineered systems for everyday dissolution testing

Meeting the latest specifications as laid down in the European, United States and associated Pharmacopoeias, the DISi Series from Copley is a range of reliable and cost-efficient dissolution tester systems designed with the highest standards of solid dosage testing performance in mind.

Ideal for use in both R&D and QC environments, the DISi Series is equipped with precision ground shafts that will accept any of the baskets, paddles or rotating cylinders described in the Ph. Eur., USP and associated Pharmacopoeias.

Designed to minimise user training and reduce the burden of routine equipment maintenance, the DISi Series simplifies the dissolution testing process, without compromising on data quality.



Ph. Eur. and USP compliant



Integrated, precision temperature control and measurement



Intuitive touchscreen control to simplify operation



Single-point electronic temperature calibration



Six and eight test station unit configurations available



Extensive data output options



Wide speed range to accommodate broad scope of methods



Option to automate and remotely control DISi Systems



DISi Series: Key Features

Easy-clean Viton® membrane-sealed zero-evaporation lids included as standard

Intuitive touchscreen control with icon-based menu structure simplifies operation

Robust metal case with advanced corrosion protective coating

PT100 temperature probe monitors bath and vessel temperature with electronic calibration feature

Independent digital heater/circulator maintains a constant temperature and minimises vibration

Easily removable leak-proof water bath with convenient drain tap eases bath water emptying

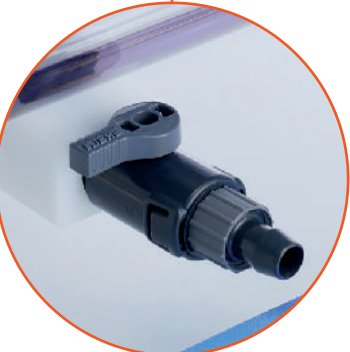
All vessels are serial-numbered as standard

Maximum fill line indicator

Convenient screw-in basket/paddles enable easy method change in seconds

'Easy-Centre' centring system for precise vessel positioning

Note:
Full automation-compatible to support high-throughput workflows

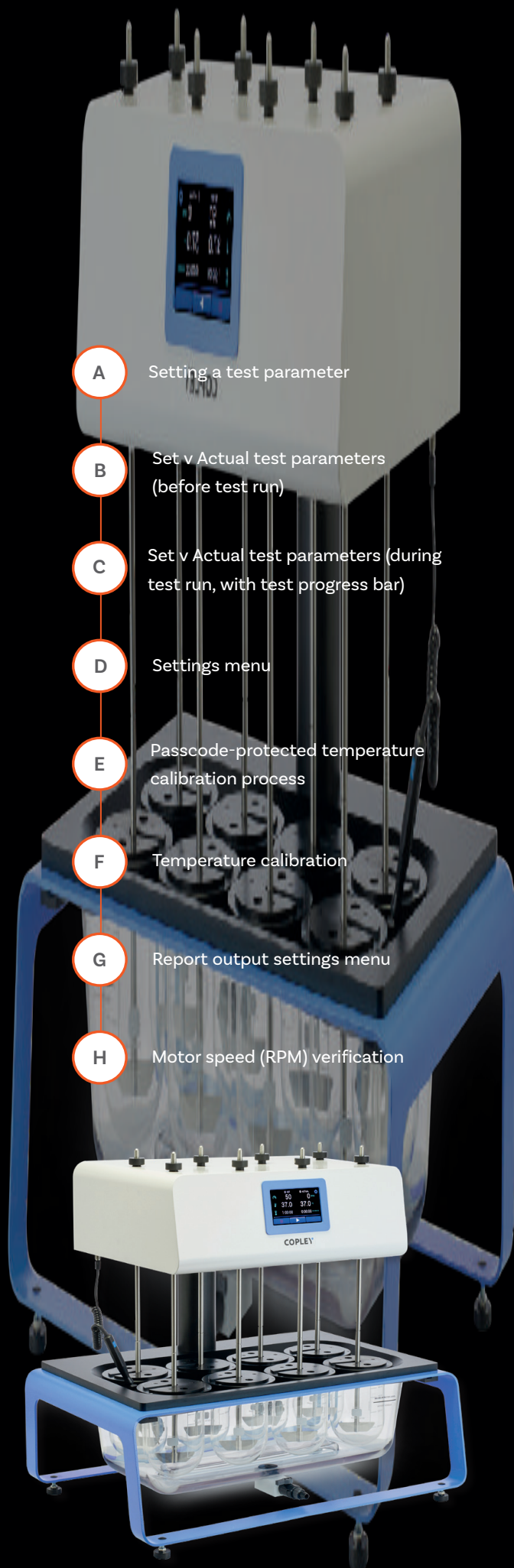


DISi Series: Touchscreen User Interface



Key Features:

- **Intuitive menu structure** enables users to locate features quickly and easily
- **Easy-set** user-configurable **test parameters**:
 - Speed (revolutions per minute)
 - Temperature (°C)
 - Test duration (HH:MM:SS)
- Status of **'Actual' v 'Set'** test parameters clearly **displayed** throughout testing
- **Test progress bar** provides clear and constant indication of run status
- Resistive touchscreen interface can be **operated with gloves on**
- Hygienic **wipe-clean** screen
- **Passcode-protected** temperature calibration
- High productivity - **easy system set-up** and **operation** minimises training burden



A Setting a test parameter

B Set v Actual test parameters (before test run)

C Set v Actual test parameters (during test run, with test progress bar)

D Settings menu

E Passcode-protected temperature calibration process

F Temperature calibration

G Report output settings menu

H Motor speed (RPM) verification

Reporting

Extensive data output options are available as standard, including direct reporting to a printer or PC.

Reported parameters

- **Speed (revolutions per minute)**

Set
Average
Maximum
Minimum



RS 232

- **Temperature (°C)**

Set
Average
Maximum
Minimum



USB A



USB B

- **Test Duration (HH:MM:SS)**

Set
Actual

- **Calibration Data**

Calibration date
Temperature calibrated at (°C)

Compliance & Maintenance



- ✓ Certificate of compliance to Ph. Eur./USP provided as standard
- ✓ Comprehensive IQ/OQ/PQ documentation packages and toolkits available
- ✓ Passcode-protected single-point electronic temperature calibration
- ✓ Latest temperature calibration information stored and available to export/print

Choose your DISi Dissolution System



DIS 600i

With bench space a premium in many laboratories, the DIS 600i is one of the most compact dissolution testers available on the market today.

Cat. Number

1336

No. Stirred Vessels

6

Ph. Eur. and USP Test Methods Supported

1, 2, 5, 6

Heater

Low vibration integrated digital heater/circulator

Unit Dimensions (w x d x h)

728 x 495 x 689 mm



DIS 800i

Maximising visibility and access to the critical sampling area above the bath, the DIS 800i represents the very latest in tablet dissolution testing technology.

Cat. Number

1338

No. Stirred Vessels

8

Ph. Eur. and USP Test Methods Supported

1, 2, 5, 6

Heater

Low vibration independent external digital heater/circulator

Unit Dimensions (w x d x h)

728 x 495 x 689 mm (unit)
260 x 330 x 150 mm (heater)

DISi Series: Technical Specifications

Pharmacopoeial Compliance	Ph. Eur. Chapters: 2.9.3, 2.9.4 USP Chapters: <711> <724>
User Interface	Resistive touchscreen
Speed Range	20 - 220 rpm +/- 2%
Heater Accuracy	± 0.1°C
Heater Temperature Range	Ambient - 50 °C
Vibration Elimination	Low vibration heaters
Test Run Time	Up to 99 hours, 59 minutes, 59 seconds
Alarm(s)	1. End of testing (audible) 2. Low bath water level warning on-screen indicator
Data Output	RS 232 USB A (for connection with a USB printer) USB B (for connection with a PC)

Temperature Calibration



Single-point electronic temperature calibration.

Calibration of the DISi Series temperature probe is simple, through the use of an electronic calibration key and passcode-protected calibration menu

designed to guide users through the process without fuss. The latest temperature probe calibration information is stored and available to print/export when convenient to the user.

DISi Series

Cat. No.	Description
1336	Dissolution Tester DIS 600i (incl. 6 Drive Shafts)
1338	Dissolution Tester DIS 800i (incl. 8 Drive Shafts)
1209	Electronic Temperature Calibration Key
1309	IQ/OQ/PQ Documentation Pack
1307	Printer (including USB cable)



Electronic Temperature Calibration Key

Choose your DISi System Accessories

All DISi Series are equipped with precision-ground shafts that will accept any of the baskets, paddles or rotating cylinders described in the Pharmacopoeias. Each clutch can be raised, lowered or engaged independently of the drive head, ensuring users have maximum accessibility to the vessels, whilst also making the systems suitable for staggered starts.

Each element can be supplied with a Teflon coating for additional protection against aggressive media, if required and can be laser numbered and certified upon request.



Baskets, Paddles & Rotating Cylinders



Basket Stirring Elements (Ph. Eur. /USP Method 1)

Cat. No.	Description
1302B	Set of 6 Baskets (Ph.Eur./USP Method 1)
1302A	Set of 8 Baskets (Ph.Eur./USP Method 1)
1302	Basket only in 316 Stainless Steel (40 mesh)
1317	Basket Holder in 316 Stainless Steel
1331	3-Prong Retention Spring in Hardened 17-7 Steel
1333	Basket Stirring Element complete with Drive Shaft

Paddle Stirring Elements (Ph. Eur. /USP Method 2)

Cat. No.	Description
1304B	Set of 6 Paddles (Ph.Eur./USP Method 2)
1304A	Set of 8 Paddles (Ph.Eur./USP Method 2)
1304	Paddle only in 316 Stainless Steel
1341	Paddle Stirring Element complete with Drive Shaft
1343	Paddle Stirring Element complete - Teflon Coated

Dissolution Drive Shaft

Cat. No.	Description
1329	316 Stainless Steel Drive Shaft only

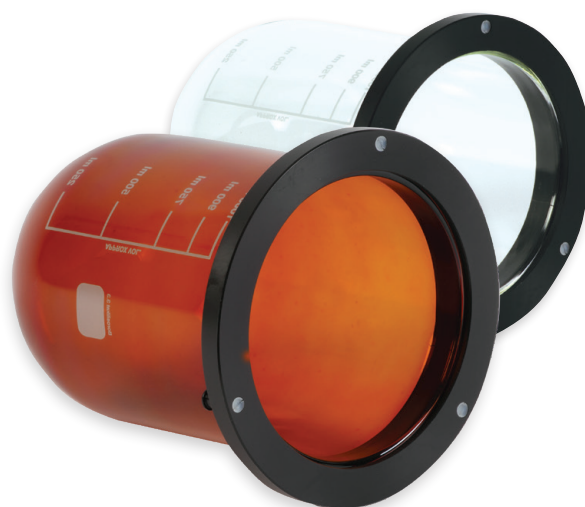
Capsule Sinkers & Weights

Cat. No.	Description
1356	Set of 6 316 Stainless Steel Sinkers
1356A	Set of 8 316 Stainless Steel Sinkers
1345	Set of 6 USP/Ph.Eur. Alternative Sinkers
1345A	Set of 8 USP/Ph.Eur. Alternative Sinkers
1348	Wire, 316 Stainless Steel (50 ft length)
1357	Set of 6 3-Prong Plastic Sinkers

Vessels

Compliant with Ph. Eur. and USP specifications, all DISi Series vessels feature unique Easy-Centre systems ensuring perfect positioning every time. Locking the vessel into the correct position relative to the drive shaft, the fixture ensures that the vessels will not become loose or float, even when empty. UV-resistant vessels are also available for products sensitive to UV.

Easy-clean Viton® membrane-sealed low evaporation lids are included as standard with each vessel.



Vessels

Cat. No.	Description
1344	Vessel, 1000 mL
1346	Vessel, 1000 mL, with “Easy-Centre”
1352	Amber Vessel, 1000 mL
1349	Amber Vessel, 1000 mL, with “Easy-Centre”
1366	“Easy-Centre” Vessel Ring

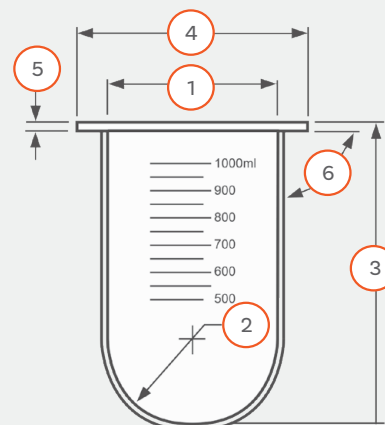
EMC Ultra-Precision Dissolution Vessels

With dimensional tolerances a factor of 2 higher than those specified in the FDA Enhanced Mechanical Calibration, the EMC Ultra-Precision Dissolution Vessel brings even higher levels of accuracy to dissolution testing.

All relevant parts are individually serialised as standard.



1. Inside Diameter	101.19 +/- 0.13 mm
2. Inside Spherical Radius	50.59 +/- 0.13 mm Radius
3. Height (Inside Spherical Radius to top)	154.75 +/- 0.50 mm
4. Flange OD	120.00 +/- 0.50 mm
5. Flange Thickness	3.50 +/- 0.50 mm
6. Perpendicularity (Inside Vessel Dia. to Flange Underside)	0.50° Max



Cat. No.	Description
1398	EMC Dissolution Vessel, 1000 mL, with “Easy-Centre”



Vessel Cover for DIS 600i/800i



Automatic Tablet Drop Vessel Cover for DIS 600i/800i

Vessel Covers

Cat. No.	Description
1354	Vessel Cover for DIS 600i/800i
1393	Automatic Tablet Drop Vessel Cover (Set of 6 for DIS 600i)
1394	Automatic Tablet Drop Vessel Cover (Set of 8 for DIS 800i)
1355	Plug for Vessel Cover

Automatic Tablet Drop

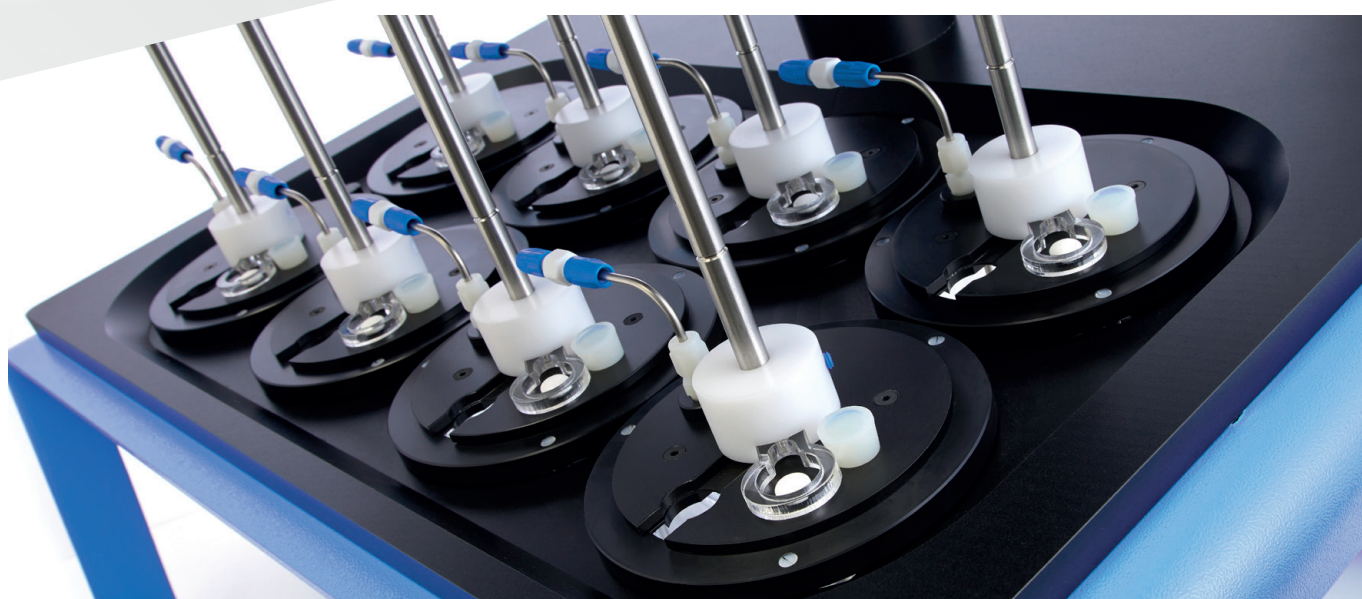
Eliminate the need for time-lag correction factor calculations with the Automatic Tablet Drop system. Guaranteeing simultaneous tablet ejection at the start of the test run, synchronised sampling is simplified.

Automatic Tablet Drop

Cat. No. Description

1393 Automatic Tablet Drop Vessel Cover (set of 6 for DIS 600i)

1394 Automatic Tablet Drop Vessel Cover (Set of 8 for DIS 800i)



Sampling Probes

Choose from a range of dissolution sampling probe systems, optimised for different user requirements:

1. Manual sampling cannula: with a Luer fitting to accept a 20 mL syringe, bent at the top to enable easy positioning within the dissolution vessel.

2. Resident probe: designed to be left *in-situ* in the dissolution vessel for the duration of the test and is height adjustable, in accordance with differing methods described in the pharmacopoeias. 3 different types are available:

- a. For automated systems: fitted with Omnifit fittings used in conjunction with the return line inserts
- b. For automated systems: fitted with Omnifit fittings
- c. For manual sampling (with Luer fittings)





Sampling Probes

Cat. No. Description

- 1313** Manual Sampling Cannula Assembly complete (each)
1314 Resident Probe with Luer Fitting (each)
1315 Resident Probe with Omnifit Fitting (each)
1316 Return Line Insert (each)



Filters (Polyethylene)

Cat. No. Description

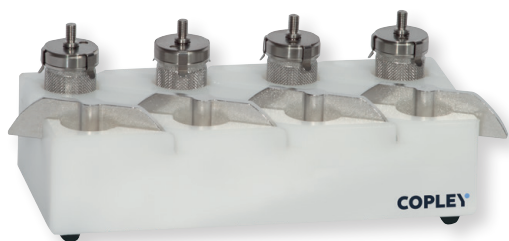
- 1358** Pack of 50 Filters (20 micron)
1359 Pack of 50 Filters (10 micron)
1360 Pack of 50 Filters (4 micron)



Sundries

Cat. No. Description

- 1365** Carrying Case for 8 Baskets/Paddles and Shafts
1339 Carrying Rack for 4 Vessels
1367 Pack of 8 Peristaltic Pump Tubes (Green/Green)
1368 Pack of 8 Peristaltic Pump Tubes (Purple/White)
1369 8-Channel Colour Coded Ribbon Tubing (per metre)
1370 Pack of 10 Connectors
1321 Storage Rack for 8 Baskets or Paddles



Laser Numbering and Certification (each)

Cat. No. Description

- 1332** Certification of 316 Stainless Steel Drive Shaft
1310 Certification of Basket in 316 Stainless Steel (40 Mesh)
1335 Certification of Basket Stirring Element complete
1318 Certification of Paddle only in 316 Stainless Steel
1342 Certification of Paddle Stirring Element complete
1350 Certification of Vessel, 1000 mL

Performance Verification Testing (PVT)

Formulated to produce reproducible results under standard dissolution test conditions, these standard drug references supplied by USP (Rockville, Maryland, USA) can be used to help verify the source of anomalies.

Cat. No. Description

- 1373** Pack of 30 Prednisone Tablets - USP Disintegrating
1375 Prednisone Reference Standard (250 mg pack)



DISi Series: Qualification & Maintenance

DISi Series: Qualification Tools

To calibrate all other aspects of the DISi Series, our complete range of calibration and qualification tools can be used to safeguard compliance with the appropriate pharmacopoeial, regulatory guidance and Enhanced Mechanical Calibration (EMC) requirements.



For further information about the full range of Copley Qualification Services available see Page 96



Hygiene: Anti-Bacterial/Algae Treatment

The addition of 1 mL of Aqua Stabil per month will prevent the build-up of bacteria and algae in the water bath, keeping the water clear, safe and odour-free.



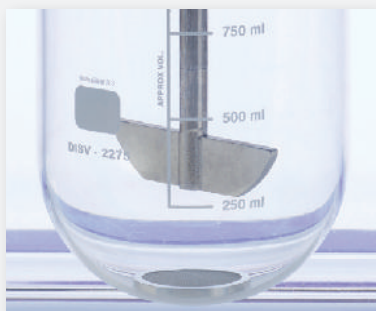
Cat. No.	Description
1372	100 mL Bottle of Aqua Stabil
1508	Calibration Tool Kit complete
1516	Re-calibration of Calibration Took Kit complete

Special Applications

Transdermal Patch Testing

Copley offers equipment for three different methods for the determination of the rate of drug release from transdermal patches.

1. Paddle Over Disk



A modification of Method 2 (Paddle), the *Paddle Over Disk* technique is suitable for patches up to a maximum of 16 mm outside diameter. Using a suitable adhesive, the transdermal patch is simply mounted on the disk, release side up.

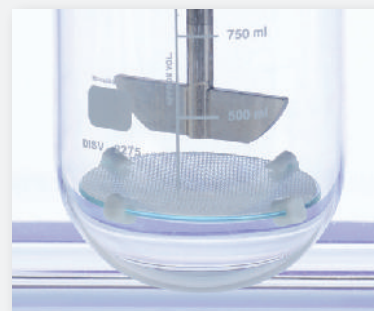
2. Rotating Cylinder



An alternative approach employs the same dissolution equipment as USP Method 1 (Ph. Eur 2.9.4 Method 3) with the basket replaced by a cylinder stirring element. In this method, the adhesive side of the transdermal patch is placed on an inert, porous cellulosic material. This is then attached to the exterior of the cylinder using a suitable adhesive.

An extension piece is included in the kit for larger patches.

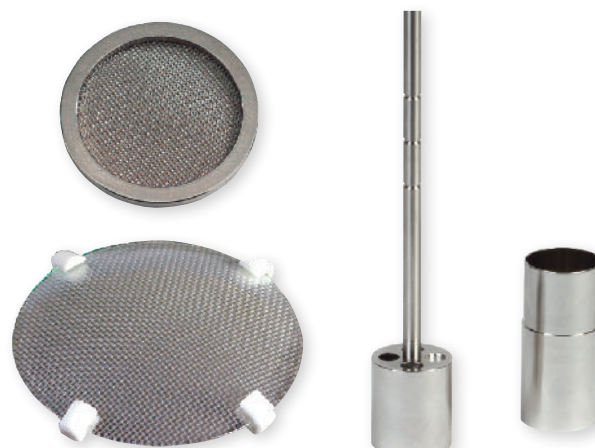
3. Watch Glass / Patch



A second larger version of the disk comprising a 90 mm diameter watch glass-patch-PTFE assembly is available for larger patches.

Transdermal Patch Testing

Cat. No.	Description
1384	Standard disk according to USP Method 5
1384A	Watch Glass/patch/PTFE Assembly to USP Method 5
1385	Hollister Medical Grade Adhesive (90 gm spray)
1386	Cylinder Stirring Element including Extension (USP Method 6)
1386B	Height Gauge for Cylinder Stirring Element
1387	Cuprophane Flat Sheets, 128 x 345mm, Pack of 10

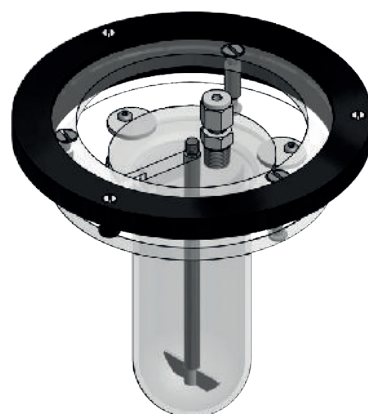
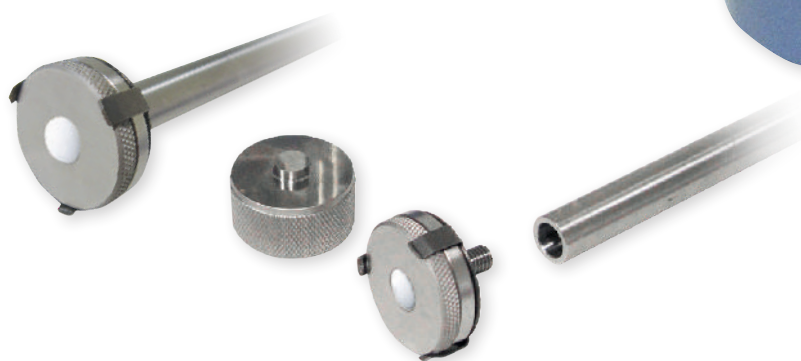


Intrinsic Dissolution

Based on the same principles as the Rotating Disk apparatus as described in USP Chapter <1087>, Copley offers punch and die kits, together with a hand operated press for intrinsic dissolution methods.

Intrinsic Dissolution

Cat. No.	Description
1364	Punch and Die Set Kit (each)
1364A	Hand Operated Press



Small Volumes

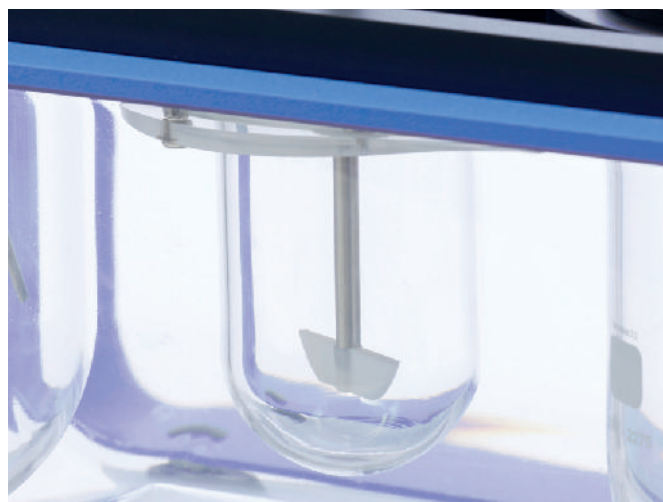
For dosage forms with small quantities of drug, or extended release where much lower concentrations are required than that provided by the standard 1000 mL vessel, 100 mL and 200 mL conversion kits are available.

Each conversion kit comprises:

- ✓ Mini Vessel (100 mL or 200 mL)
- ✓ Mini Paddle
- ✓ Vessel Cover
- ✓ Centring Ring Assembly

Small Volume Conversion Kits

Cat. No.	Description
1371-100	Conversion Kit for Small Volumes - 100 mL
1371-200	Conversion Kit for Small Volumes - 200 mL



Special Baskets

For solid dosage forms that have a tendency to block the standard 40 mesh basket, a basket with a coarser mesh is available to retain the dosage form in the basket, whilst allowing media penetration without clogging.

Special Baskets

Cat. No.	Description
1361	Basket only in 316 Stainless Steel (20 Mesh)
1362	Basket only in 316 Stainless Steel (10 Mesh)



Basket for Suppository Dissolution

Oil-based suppositories give unacceptable and unreproducible results, since the suppository base tends to block the filter mesh.

With the same basic basket specification as the USP standard, the special suppository basket provides the equivalent porosity to a basket of 10 mesh, allowing suppository dissolution testing to take place unimpeded.

Basket for Suppository Dissolution

Cat. No.	Description
1363	Special Suppository Basket

