

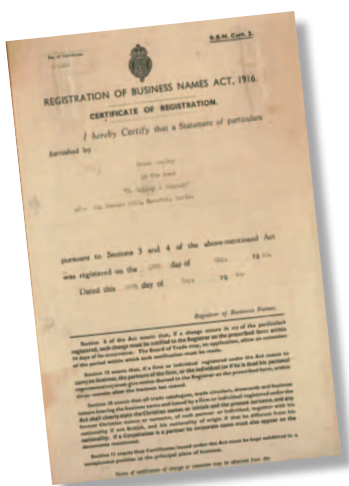


## Quality Solutions for the Testing of Pharmaceuticals

2013 EDITION

TABLETS AND CAPSULES • SUPPOSITORIES • TRANSDERMALS  
DETERGENTS • POWDERS • CREAMS AND OINTMENTS

# Who are Copley



Based in Nottingham, Copley Scientific was founded by Frank Copley in 1946 to manufacture and supply general laboratory equipment and glassware.

In 1957, Copley Scientific began to focus on the supply of pharmaceutical test instrumentation. During the intervening years, we have built up a wealth of experience in supplying and supporting such equipment and systems both in the UK and abroad.

As part of our rapid expansion Copley Scientific is now responsible for the manufacture and supply of its own innovative range of tablet dissolution, disintegration, friability and hardness testers, in addition to test equipment for creams, ointments, powders, semisolids, suppositories, transdermal patches and detergents, throughout the world.

Whilst still operating as a family owned company, Copley Scientific has continued to expand and increase its range of products and services.

During the 1980s Copley Scientific began developing a new range of inhaler test equipment to meet the growing demand for drugs delivered to the respiratory tract. We are now recognised as one of the world's largest manufacturers of inhaler test equipment, with a broad range of equipment, software and services to meet the requirements of inhaled drug development, for both topical and systemic applications.

In 2000, a strategic partnership agreement was signed with MSP Corporation, a US based company that specialises in aerosol particle science, which enabled us to become the first company to offer the full range of United States and European Pharmacopoeia specified cascade impactors for the aerodynamic particle size measurement of inhaled drugs. In 2006, we became MSP's exclusive European distributor for their range of air sampling and aerosol characterisation products, making Copley Scientific a major supplier of research grade aerosol analysis equipment in Europe.

Meanwhile, in 2003 we opened a new sales and service company in Switzerland, to assist in supporting our increasing number of customers in Europe. This was followed in 2005 by the relocation of Copley Scientific's UK based headquarters to a new, larger, purpose-built facility in Nottingham.

Copley Scientific continues to expand its network of specialist distributors in growing markets around the world, to ensure that our broad range of products is supplied and supported to the very highest standards.

The combination of both experience and flexibility within the industries we support, ensures that Copley Scientific will continue to provide innovative, high quality solutions to our customers, well into the future.



Designed, manufactured and tested in the UK



# Scientific?

## Our Philosophy

The pharmaceutical industry of today demands instrumentation that is (a) precise and accurate (b) simple to use and operate and (c) robust and rugged in operation.

The Copley Philosophy is based on the premise that the accuracy and reproducibility of test results, and hence the ability to discern between products, can only be achieved using instrumentation conceived using "quality by design" principles and maintained through the rigorous application of quality control standards within a Quality Management System such as ISO 9001: 2008.

It is the application of this philosophy to the manufacture of all our instruments that guarantees you, the user, an instrument of the highest quality and reliability.

## ISO 9001: 2008 Quality Management System

Copley Scientific is committed to delivering quality products and services to our customers. Continual improvement is an essential part of achieving customer satisfaction and we constantly strive to exceed the expectations of the industries we serve.

In pursuance of these goals, Copley has gained certification for its Quality Management System to the latest ISO 9001: 2008 standard which revised the previous ISO 9001 standard.



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## EQUIPMENT SELECTION GUIDE

Dosage Form	European Pharmacopoeia	United States Pharmacopoeia	Page No. (in this brochure)
GASTROINTESTINAL - Tablets & Capsules - Disintegration	Chapter 2.9.1	Chapter 701	Pages 7-11
GASTROINTESTINAL - Tablets & Capsules - Dissolution	Chapter 2.9.3	Chapter 711	Pages 12-41
GASTROINTESTINAL - Tablets & Capsules - Friability	Chapter 2.9.7	Chapter 1216	Pages 42-44
GASTROINTESTINAL - Tablets & Capsules - Breaking Force	Chapter 2.9.8	Chapter 1217	Pages 47-52
GASTROINTESTINAL - Tablets & Capsules - Weight & Thickness	Chapter 2.9.5	Chapter 905	Page 52
GASTROINTESTINAL - Powders - Bulk & Tapped Density	Chapter 2.9.34	Chapter 616	Pages 58-59
GASTROINTESTINAL - Powders - Flowability	Chapter 2.9.16 & 2.9.36	Chapter 1174	Pages 53-57
GASTROINTESTINAL - Granules & Pellets - Friability	Chapter 2.9.41	----	Pages 45-46
MUCOSAL MEMBRANE - Rectal & Vaginal - Drug Release	Chapter 2.9.2 & 2.9.4	----	Pages 64-65
MUCOSAL MEMBRANE - Oropharyngeal, Ophthalmic, Otic & Urethral	Outside the scope of this brochure		
SKIN SURFACE - Semisolids - Drug Release - Permeation	----	----	Pages 60-63
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INJECTION - Injections & Infusions	Outside the scope of this brochure		
LUNGS - Inhalers & Nebulisers	Chapter 2.9.18, 2.9.44 & 0671	Chapter 601 & 1601	Pages 30-31
NASAL - Inhalers & Sprays	Chapter 2.9.18 & 0676	Chapter 601	See separate brochure
ANALYTICAL INSTRUMENT QUALIFICATION - Guidelines	----	Chapter 1058	Page 70

## THE CLASSIFICATION OF MEDICINES

One of the clearest taxonomic guides for the categorisation of pharmaceutical dosage forms is to be found in Pharmaceutical Forum. 2003; 29: Pages 1742-44 under the title "Development of a compendial taxonomy and glossary for pharmaceutical dosage forms".

This proposes a three tier system with the first tier being based on the region

of the body to which the drug is to be administered, i.e., gastrointestinal (oral), mucosal membrane (rectal, vaginal, oropharyngeal, ophthalmic, otic and urethral), skin surface (topical, transdermal), injections including infusions or lungs (pulmonary).

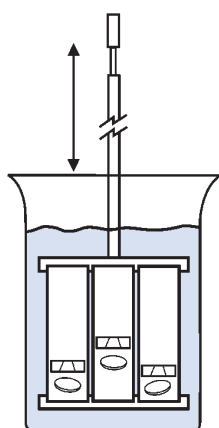
It is this first tier classification which has been used as the basis for the

Equipment Selection Guide to be found above. This lists the dosage form and test parameter concerned, the chapter relating to that test parameter in both European and US Pharmacopoeia (where applicable) and, in the final column, the page number in this catalogue where a description of the test instrumentation concerned can be found.



# Disintegration

## INTRODUCTION ▶▶▶



### Copley Philosophy

Robust	✓	Reliable	✓
Easy to use	✓	Compliant	✓

Approximately two-thirds of all medicines prescribed today take the form of solid dosage forms and half of these are tablets. These tablets comprise a mixture of active drug and other excipients, usually in powder form, pressed or compacted into a solid.

It has long been recognised that before a tablet/hard gelatin capsule can dissolve and hence allow the active drug to be absorbed into the body, it must first disintegrate into smaller particles.

The current apparatus described in the pharmacopoeia was designed to provide a reproducible and standardised method of ensuring that disintegration had taken place. Each of the tablets to be tested is placed in one of six vertical tubes each measuring approx. 77.5 mm long x 21 mm inside diameter arranged in a circular basket arrangement. The lower end of the tubes is covered by a 2 mm sieve mesh.

A larger basket is available for large tablets, capsules and boluses according to Ph.Eur. Chapter 2.9.1 Test B and for dietary supplements according to USP Chapter <2040>.

The basket assembly is raised and lowered in simulated gastric fluid at body temperature (37 degrees Celsius) through a distance of 55 mm at a constant frequency of 30 cycles per minute. A plastic disc of defined proportions "hammers" the tablet during the operation thus assisting in the disintegration process.

The tablet is said to pass the test providing that no tablet residue remains on the sieve mesh after the designated time, typically 30 minutes for ordinary tablets and 60 minutes for enteric coated tablets.

All Copley Tablet Disintegration Testers feature:

- Sturdy, robust design including novel "quick release" basket, one-piece water bath and independent heater/circulator
- Simple, easy-to-use operation ensures that the number of operations required to perform a test are kept to a minimum
- Full supporting documentation (including full IQ/OQ/PQ qualification documentation if required)
- Special accessories available for hard/soft gelatin capsules and large tablets, capsules and boluses





◀ Disintegration Tester DTG 1000

Disintegration Tester DTG 2000 ▶



## DISINTEGRATION TESTERS SERIES DTG

The Disintegration Tester Series DTG is the result of over 50 years experience in the field of pharmaceutical testing.

The Testers have been specifically designed for use in the quality and production control of normal, plain coated and delayed release coated tablets and gelatin capsules in accordance with the specifications as laid down in European, United States and associated Pharmacopoeias.

The series is available with one (DTG 1000), two (DTG 2000), three (DTG 3000) or four (DTG 4000) test stations. Each individual test station is capable of accepting one batch of six tablets or capsules.

Foremost in the design specification were those features that you, the user, identified as being essential to the "ideal" disintegration tester.

### PHARMACOPEIAL COMPLIANCE AND QUALIFICATION

The most critical factors in the design of any disintegration tester are (a) that it complies with the respective Pharmacopoeia, (b) that this compliance can be proved or qualified and (c) that both compliance and qualification are documented.

Copley offer a three tier approach to address these points:

- **Certificate of Compliance to USP/ Ph.Eur.:** Provided free of charge with each unit. This is a written statement that the product, by design, complies with the current pharmacopoeial specifications.
- **Laser Numbering and Certification:** Identification and measurement of critical components to provide documented verification of compliance with current pharmacopoeial specifications. Available as an optional service.
- **IQ/OQ/PQ Qualification Documentation:** Comprehensive documentation to guide the user through the installation, operating and performance checks of the equipment in its operating environment, using specified test protocols. This optional service provides a comprehensive record of the suitability of the equipment to perform its specified task, to be created and archived.

Please see the ordering information for further details on our verification and qualification services.

### DESIGN AND CONSTRUCTION

All of the DTG series feature a motor drive operating at a fixed speed of 30 rpm (+/- 1) and a stroke of 55 mm (+/- 1).

Depending on the model, the DTG has the capacity of testing one, two, three or four different tablet batches of six tablets/capsules simultaneously, under identical test conditions.

The control of all models is provided by a membrane keypad linked to a 4-line 20 character back-lit LCD screen, which together with the electronics is mounted in the head of the instrument so as to avoid any accidental spillages in the test area.

Particular attention has been given to the design of the basket rack assembly in respect of its removal and cleaning.

The novel "quick-release" basket design not only provides a firm and rigid location for the basket during operation but also allows the basket to be removed from the instrument for rapid cleaning.

Another unique feature of the basket design is the use of thumb screws to hold the various components together.





Disintegration  
Tester DTG 3000



Disintegration Tester DTG 4000 ▲

## DISINTEGRATION TESTERS SERIES DTG

This means that if it is necessary to disassemble the basket before cleaning, this can be done very quickly and without the use of any specialised tools.

A common problem associated with fabricated water baths, used for warming the media, is that of leaks.

This problem has now been eliminated through the use of a **one-piece water bath** vacuum formed in rigid PETG. This construction not only eliminates any possibility of leaks but also makes it far easier to clean because of its rounded corners. The bath is fitted with a sturdy 8 mm clear view lid and secured to the base by four easily removed thumb screws.

The temperature of the warming solution is controlled by means of an **independent digital heater/circulator** to an accuracy of **+/- 0.25 degrees C**. This has two advantages: firstly, it removes the necessity for priming and secondly, it can be removed for cleaning without dismantling the whole disintegration tester. A **low water-level alarm** indicator is built into the unit as standard.

### OPERATION

Considerable attention was paid to the design of the DTG series to ensure that the number of actions necessary to perform a test are kept to a minimum.

The membrane keypad allows for the selection of test run times up to **99 hours 59 minutes 59 seconds**. Thereafter, it is only necessary to press the START key to automatically lower the basket rack assemblies into the test media and begin or repeat a test.

During the test, the time elapsed from the start of the test (or if you prefer, time remaining to the end of the test) is displayed on the LCD screen.

At the end of the test, the **basket rack assemblies are automatically removed from the test media** and an audible alarm alerts the user that the run is completed.

Bath and beaker temperatures can be constantly monitored using the **PT100 temperature probe** provided for this purpose. Temperature is critical to the test and is displayed permanently on the LCD screen as soon as the unit is switched on.

Ordinarily, temperature calibration can prove to be a time-consuming and inaccurate process involving the use of iced water. This is not the case with the DTG series. Available as an option, the **electronic temperature calibration kit** comprises two UKAS certified test keys (0 and 37 degrees C) which you simply plug into the PT100 socket to perform the calibration.

Dimensions (mm):  
DTG 1000/2000 = 450 x 450 x 720 mm (w x d x h)

DTG 3000/4000 = 700 x 450 x 720 mm (w x d x h)

### Cat. No. Description

1201	Disintegration Tester Model DTG 1000 (1 Station)
1202	Disintegration Tester Model DTG 2000 (2 Station)
1203	Disintegration Tester Model DTG 3000 (3 Station)
1204	Disintegration Tester Model DTG 4000 (4 Station)
1205	Extra for Numbering and Certification (per basket)
1206	IQ/OQ/PQ Documentation Pack
1207	Electronic Temperature Calibration Kit
1228	Qualification Tools (Certified Stopwatch, Thermometer & Rule)



"Quick-Release" Basket Assembly ▲

## DISINTEGRATION TESTERS SERIES DTG

The Disintegration Tester Series DTG described on the preceding two pages is ideal for quality control and R&D where it is important that the testing is carried out under identical test conditions.

As previously stated, the series offers the user an unparalleled number of standard features including:

- Conforms to all current Ph.Eur. and USP specifications
- Choice of 1, 2, 3 or 4 test baskets



Drain tap used on rear of DTG 3000 and DTG 4000 water bath

- "Quick-Release" basket design combines stability with easy removal
- Automatically lowers and raises the baskets out of the test media at the start and finish of the test
- Easy to clean vacuum-formed water bath eradicates leaks
- Independent digital heater/circulator: no priming and easy to remove
- Low liquid level sensor
- Easy to use membrane control panel
- 99 hour test programme permits delayed release as well as normal testing
- Acoustic signal at the end of the test
- PT100 temperature sensor as standard
- Constant monitoring of time and temperature via LCD screen
- Electronic temperature calibration kit (option)
- Certification and IQ/OQ/PQ documentation packs available (option)



▲ Disintegration Tester DTG 2000 IS

### DISINTEGRATION TESTER DTG 2000 IS

There are however certain occasions when it is useful to have **independent control over each of the test stations**.

This is particularly helpful in research and development when the user is comparing one formulation directly against another, or one formulation under varying conditions, or in the case of delayed release or enteric coated tablets where it is necessary to immerse the sample for specified periods of time in different media.

Alternatively, there are times in QC operations when it is more convenient to carry out tests at different times, e.g. when one disintegration tester serves to support two tablet presses.

The **DTG 2000 IS** is a two-station unit which has been specifically designed for these types of tests. It has all of the features of the standard DTG series mentioned above.

However, on this unit, **each basket rack assembly** can be controlled, started and stopped **individually** using separate membrane keypads.

### Cat. No. Description

1208	Disintegration Tester Model DTG 2000 IS
1205	Extra for Numbering and Certification (per basket)
1206	IQ/OQ/PQ Documentation Pack
1207	Electronic Temperature Calibration Kit
1228	Qualification Tools (Certified Stopwatch, Thermometer and Rule)





▲ Left: Basket fitted with Special Cover Right: Special Basket for Large Tablets Glass Tubes, Fluted Discs and Sieve Meshes ▲

## DISINTEGRATION ACCESSORIES

### STANDARD ACCESSORIES

Copley Scientific offers a complete range of accessories for use with the DTG series, from complete basket rack assemblies to individual tubes, discs and sieve meshes.

All parts are manufactured to tolerances that are equal to or better than those quoted in the respective Pharmacopoeias and carefully checked prior to despatch.

### BASKET RACK ASSEMBLY COVER FOR HARD & SOFT GELATINE CAPSULES (as per USP Chapter <701>)

Converts standard basket to special cover version for testing hard or soft gelatine capsules according to USP Chapter <701>.

USP specifies that, when testing hard or soft gelatine capsules, the top of the basket rack assembly should be covered by a further sieve mesh (2 mm x 0.63 mm).

Comprises basket cover with integral sieve meshes, plus central locking device for easy assembly.

### SPECIAL BASKET RACK ASSEMBLY FOR LARGE TABLETS & CAPSULES (as per Ph.Eur. Chapter 2.9.1 Test B and USP Chapter <2040>)

Special basket rack assembly for large tablets, capsules and boluses according to Ph.Eur. Chapter 2.9.1 Test B and for dietary supplements according to USP Chapter <2040>.

In this version, the six standard tubes are replaced with three tubes having an inside diameter of 33 mm.

Supplied complete with the special cylindrical discs specified in the Pharmacopoeia.

Can be supplied with Certificate of Compliance on request.

### HYGIENE: ANTI-BACTERIA/ALGAE SOLUTION

Keep your water bath free of bacterial, algal or slime growth.

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

Available in 100 mL bottles.

### Cat. No. Description

1210	Standard Basket Rack Assembly
1205	Extra for Numbering and Certification (per basket)
1211	Set of 6 Glass Tubes for Standard Basket
1212	Set of 6 Fluted Discs for Standard Basket
1213	Set of 6 Sieve Meshes for Standard Basket
1214	1000 mL Beaker
1215	Basket Rack Cover for Hard & Soft Gelatine Capsules
1216	Extra for Numbering and Certification (per cover)
1217	Special Basket Rack Assembly for Large Tablets & Capsules
1218	Extra for Numbering and Certification (per basket)
1219	Set of 3 Glass Tubes for Special Basket
1220	Set of 3 Cylindrical Discs for Special Basket
1221	Sieve Mesh for Special Basket
1372	100 mL Bottle of Aqua-Stabil

# Dissolution

## INTRODUCTION ▶▶▶

### Copley Philosophy

Robust	✓	Reliable	✓
Easy to use	✓	Compliant	✓

The ultimate responsibility for the safety, quality and efficacy of medicines lies with the various national regulatory bodies designated to safeguard public health.

In Europe and in the USA, this function is provided by the **European Medicines Agency (EMA)** and by the **Food and Drug Administration (FDA)** respectively.

The regulators are supported in this role by the **Pharmacopoeias** who define the standards with which the drug formulation shall comply and the methods by which compliance will be adjudged.

In 2002, the FDA launched a new initiative "Pharmaceutical cGMPs for the 21st Century" in which it proposed a new approach to pharmaceutical manufacturing.

This initiative gave birth to **Process Analytical Technology (PAT)**, a framework for understanding and improving the processes involved in pharmaceutical development, manufacturing and quality control described in the FDA's guidance in 2004.

PAT's goal is to ensure final product quality by understanding and controlling the processes involved in the manufacturing operation.

The **Quality by Design (QbD)** approach recently recommended for adoption by the EMA, FDA and the Japanese MHL in the form of the four quality related guidelines, ICH Q8, Q9, Q10 and Q11 published by the **International Conference on Harmonisation (ICH)** extends the PAT philosophy to all parts of the product cycle from product development, transfer to manufacturing, manufacturing, and finally product end.

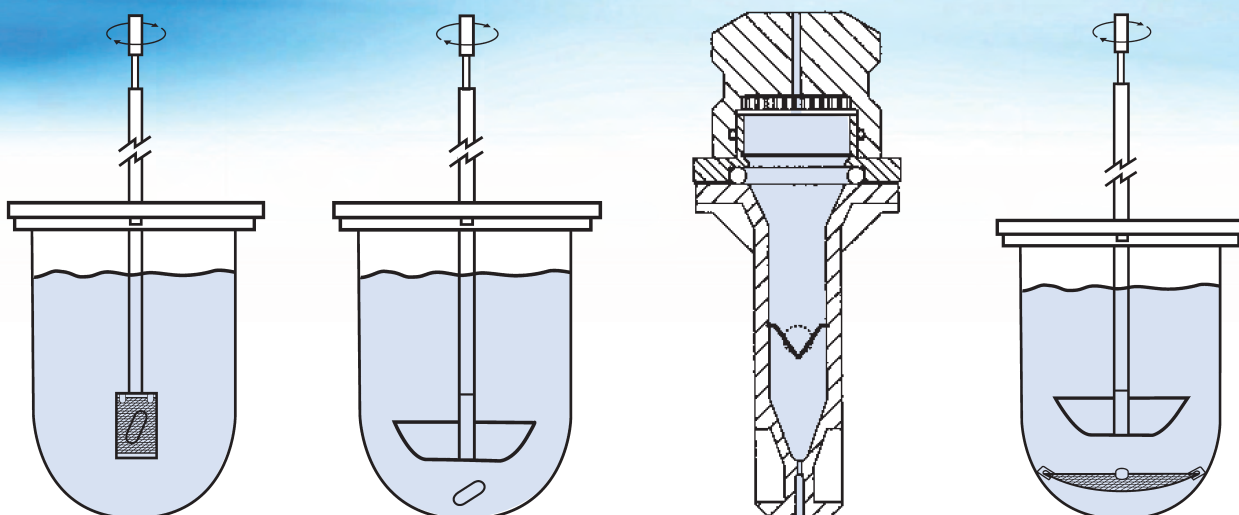
Collectively, these provide the guidelines for a new **Pharmaceutical Quality System (PQS)** described in ICH Q10.

The decision to include Development in the PQS by way of the QbD approach is described in more detail in **ICH Q8 (R2) Part II Pharmaceutical Development - Annex**.

This annex gives examples of many of the essential concepts employed in QbD including **Critical Quality Attributes (CQAs)**, Design Space and Control Strategy and its implementation through **Process Analytical Technology (PAT)** tools.

**Dissolution** or, perhaps more correctly, **Drug Release** is an essential Critical Quality Attribute (CQA) in the development, manufacture and QC of virtually all medicines available today.





Apparatus 1 - Basket

Apparatus 2 - Paddle

Apparatus 4 - Flow Through Cell

Apparatus 5 - Paddle over Disc

## THE ROLE OF THE REGULATOR

Tablets or capsules taken orally remain one of the most effective means of treatment available.

One of the problems facing the pharmaceutical industry is to optimise the amount of drug available to the body i.e., its **"bioavailability"**. Inadequacies in bioavailability can mean at best that the treatment is ineffective and at worst potentially dangerous (toxic overdose).

Drug release in the human body can be measured ***in vivo*** by measuring the plasma or urine concentrations in the subject concerned. However, there are certain obvious impracticalities involved in employing such techniques on a routine basis.

These difficulties have led to the introduction of official ***in vitro*** tests which are now rigorously and comprehensively defined in the respective Pharmacopoeias.

The principal function of the dissolution test may be summarised as follows:

- Optimisation of therapeutic effectiveness during development and stability assessment
- Routine assessment of production quality to ensure uniformity between production lots

- Prediction of *in vivo* availability i.e., bioavailability (where applicable)
- Assessment of **"bioequivalence"** (production of the same biological availability from discrete batches of products from one or different manufacturers) and its application in Scale-Up and Post Approval Changes (SUPAC)

Whether or not its numbers have been correlated *in vivo*, the standard dissolution test is a simple and inexpensive indicator of a product's physical consistency.

Initially developed for immediate release (IR) and then to extended / delayed or modified release (MR) oral dosage forms, the role of the "dissolution test" has now been expanded to the "drug release" of various other forms such as semi-solids, suppositories, topical and transdermal systems.

The term **"dissolution test"** is normally used to describe the testing of those forms, such as immediate release oral tablets or capsules intended to dissolve rapidly, in the test medium.

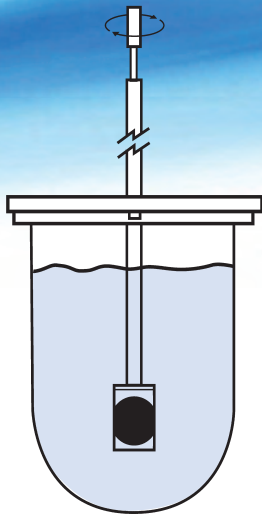
For non-oral dosage forms such as semi-solids, suppositories, topical and transdermal systems, the term **"drug release"** is normally employed.

From a regulatory perspective, the **Food and Drug Administration (FDA)** has published five main Guidances for Industry relating to dissolution:

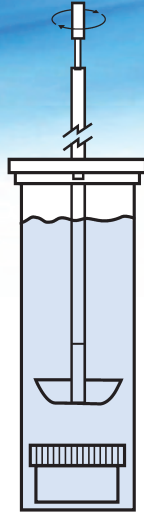
- Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997
- Extended Release Oral Dosage Forms: Development, Evaluation and Application of *In Vitro/In Vivo* Correlations, September 1997
- SUPAC-IR Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation, November 1995
- SUPAC-IR Modified-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation, June 1997
- The use of Mechanical Calibration of Dissolution Apparatus 1 and 2 - Good Manufacturing Practice (CGMP), January 2010

A similar function is provided by the **European Medicines Agency (EMA)** in the form of the **Committee for Medicinal Products for Human Use (CHMP)**.

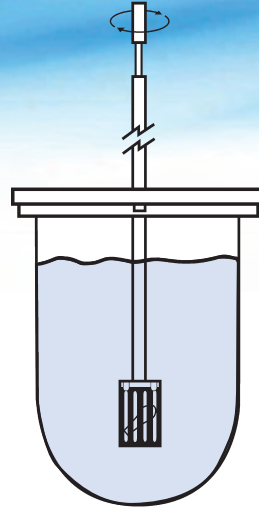




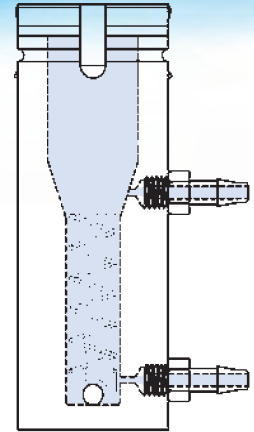
Apparatus 6 - Cylinder



Special Immersion Cell



Special Suppository Basket



Vertical Diffusion Cell (Franz Cell)

## PHARMACOPOEIAL REQUIREMENTS

The main role of the Pharmacopoeias is to lay down suitable quality standards, requirements and tests to ensure the safety and efficacy of the various drugs and excipients used in modern medicine.

As with the regulatory bodies, the main Pharmacopoeias lie with the European, Japanese and US bodies.

The value of the "dissolution test", or perhaps more correctly "drug release", as a tool in pharmaceutical development and quality control is reflected in the number of chapters bearing direct or indirect reference to it in the compendia.

In the **United States Pharmacopoeia (USP)** for example, there are no less than nine chapters referencing dissolution:

- <711> Dissolution
- <724> Drug Release
- <1058> Analytical Instrument Qualification
- <1087> Intrinsic Dissolution
- <1088> *In Vitro* and *In Vivo* Evaluation of Dosage Forms
- <1090> *In Vivo* Bioequivalence
- <1094> Liquid-Filled Capsules
- <1092> Dissolution Procedure: Development & Validation
- <2040> Dissolution of Dietary Supplements

Note: Chapter numbers less than <1000> are mandatory whilst those above <1000> are for guidance only.

A similar situation exists as far as test methods are concerned with seven methods currently listed:

- Apparatus 1 - Basket <711>
- Apparatus 2 - Paddle <711>
- Apparatus 3 - Reciprocating Cylinder <711>
- Apparatus 4 - Flow-Through Cell <711>
- Apparatus 5 - Paddle over Disk <724>
- Apparatus 6 - Cylinder <724>
- Apparatus 7 - Reciprocating Holder <724>

Attention should also be drawn to the **Vertical Diffusion Cell (Franz Cell)** whose inclusion in the Pharmacopoeias is currently under review for testing the *in vitro* release rate of semi-solid dosage forms such as creams, gels and ointments (USP Chapters <724> and <1724>).

The **European Pharmacopoeia (Ph. Eur.)** categorises its Dissolution Chapters in a similar manner, thus:

- 2.9.3 Dissolution test for solid dosage forms
- 2.9.4 Dissolution test for transdermal patches

- 2.9.25 Dissolution test for medicated chewing gum
- 2.9.29 Intrinsic Dissolution
- 2.9.42 Dissolution test for lipophilic solid dose forms (suppositories)
- 2.9.43 Apparent Dissolution

At first sight, this proliferation of equipment and procedures can appear confusing.

Suffice it to say, however, that the drug release of all but the most specialised of dosage forms can be tested with a combination of the following three apparatus:

1. **Apparatus 1 - Basket Method**
2. **Apparatus 2 - Paddle Method (plus appropriate accessories)**
3. **Vertical Diffusion Cell**

This includes tablets, gelatin capsules, oral suspensions, orally disintegrating and chewable tablets, transdermal patches, semi-solids such as creams, gels and ointments and suppositories (see Table opposite).

## Dissolution/Drug Release Apparatuses available from Copley and their Applications

### Apparatus 1 – Basket

The dosage form is contained within a 40 mesh basket attached to the stirring shaft, lowered into the medium and rotated typically at either 50 or 100 rpm ( $\geq 100$  rpm may be more suitable for modified release dosage forms).

- Beads (use a finer mesh basket where appropriate)
- Capsules (preferred over Apparatus 2)
- Orally disintegrating (orodispersibles)
- Tablets

### Apparatus 2 – Paddle

The dosage form is dropped directly into the medium which is stirred by means of a paddle attached to the stirring shaft rotated typically at 50 or 75 rpm ( $\geq 100$  rpm may be suitable for modified release forms).

- Capsules
- Hydrogels
- Liquid Filled Capsules
- Orally disintegrating (orodispersibles)
- Powders
- Suspensions
- Tablets (preferred over Apparatus 1)
- \* Soft Shell Capsules (Rupture Test 500 mL 50 rpm)

### Apparatus 5 – Paddle over Disk

A variation on Apparatus 2. The dosage form is applied to a stainless steel disk or watch glass which is then placed in the bottom of the vessel prior to being stirred in the conventional manner. Test at 32 degrees C and pH 5-6 to reflect skin conditions.

- Transdermal Patches (Drug Release Studies)
- Products involving delivery through the skin

### Apparatus 6 – Cylinder

A variation on Apparatus 2. The dosage form is applied to a rotating cylinder attached to the stirring shaft in the conventional manner.

- Transdermal Patches (Drug Release Studies)

### Apparatus pending - Vertical Diffusion Cell (Franz Cell)

For drug release studies on topical semi-solids. The VDC is a small volume heated/stirred cell with a donor chamber containing the dosage form to be tested, a synthetic membrane through which the drug permeates and a receptor chamber from which samples may be analysed for drug release. Test at 32 degrees C to reflect skin conditions.

- Creams
- Gels
- Implants
- Lotions
- Ointments
- Transdermal Patches (Permeation Studies)

## Accessories for Special Applications

### Suppository Basket

The dosage form is contained in a special polyurethane basket similar to that employed in Apparatus 1 but having 12 linear slots 2.5 mm wide in place of the conventional 40 mesh and used typically at 50 rpm using a phosphate buffer solution pH 7.4 at 37 degrees C.

- Suppositories (hydrophilic)

### Mini-Paddle Systems

A variation on Apparatus 2. Two systems, (a) 100 ml and (b) 200 mL are available based on scaled down versions of the standard apparatus.

- Low dosage strength forms

### Immersion Cell

A special form of Apparatus 2 using a mini paddle and 200 mL flat bottomed vessel designed for use with topical semi-solids. The dosage form is constrained within a cell placed at the bottom of the vessel. The cell serves to ensure that the surface area of the dosage form exposed to the dissolution media always remains constant.

- Creams
- Gels
- Implants
- Lotions
- Ointments
- Microparticulates

### Apparatus for testing the drug release of orally inhaled and nasal drug products

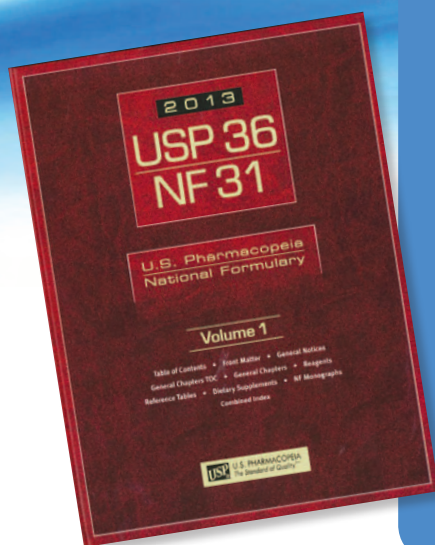
A variation on Apparatus 5. The inhaled dose is collected on a special dissolution cup by means of a cascade impactor whereupon, it is then transferred to a stainless steel disk or watch glass placed in the bottom of the vessel containing 300 mL of dissolution media stirred at 75 rpm.

- Orally inhaled and nasal drug products

### Intrinsic Dissolution (Rotating Disc)

A special kit designed to form a compact, the holder for which is then attached to the stirring shaft in the normal manner. The cell serves to ensure that the surface area of the dosage form exposed to the dissolution medium always remains constant.

- Pure drug compacts



### USP Studies into the sources of mechanical variation

A Design of Experiment (DOE) study reported by USP in 2007 (Joseph Eaton *et al.* Perturbation Study of Dissolution Apparatus Variables - A Design of Experiment Approach. *Dissolution Technologies*. February 2007, Volume 14, Issue 1) found three variables that were statistically significant as far as mean percent dissolved was concerned: level of deaeration, vessel type and rotation speed. When standard deviation results were taken into account, paddle height was also significant.

Vessel geometry constantly features as a source of concern. In the same issue as the article above, USP reported significant differences in the geometric dimensions and surface irregularities of eleven sets of six dissolution vessels selected from 10 commercial sources (Liddell *et al.* Evaluation of Glass Dissolution Vessel Dimensions and Irregularities. *Dissolution Technologies*. February 2007, Volume 14, Issue 1).

## CURRENT ISSUES

It is widely acknowledged that the rate at which, for example, a tablet or capsule dissolves is critical to its therapeutic effectiveness, that is to say, is a **Critical Quality Attribute (CGA)** in its *in vitro* characterisation.

Unfortunately, as with any *in vitro* test, there are outside variables other than those caused by the dosage form itself which may affect results.

A number of studies have been carried out by both the FDA and USP (see box above) to identify the different sources of mechanical variation within the USP Dissolution Apparatus that lead to variability in results.

This has resulted in calls from both regulators and industry alike for a tightening of the original mechanical specifications relating to Dissolution Testers laid down in the Pharmacopoeias to ensure that those tolerances that are critical to the process are maintained within known limits and policed by a process known as **Enhanced Mechanical Calibration (EMC)**.

Such suggested "enhancements" would not have been possible in the 1970s when the dissolution tester was first introduced. Fortunately, improvements in the precision of machine tools and metrology techniques used to manufacture and

qualify the modern-day dissolution tester means that, today, enhanced mechanical calibration is not only a possibility but a reality.

### MINIMISING VARIABILITY

Based on our own research, we quickly recognised that the critical elements of a dissolution tester, and therefore the most likely to affect the accuracy of results, were the ones making up the actual test station, namely the dissolution vessel itself and the associated stirring element.

It followed that if we could control the dimensions of these critical elements and their spatial relationship and then ensure that the speed of the stirring element, and the composition of the dissolution media (see Page 35) are maintained within equally tight limits, then any instrument's contribution to test method variability would be minimised.

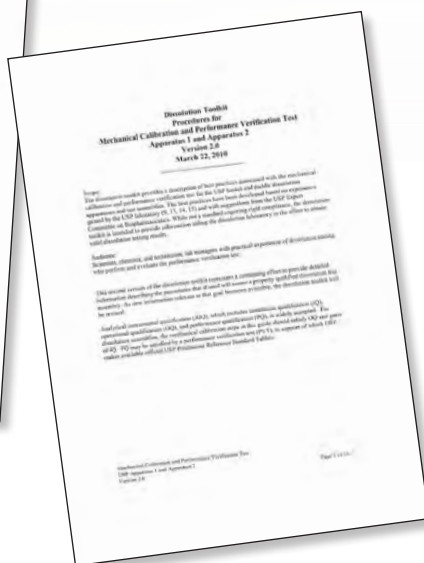
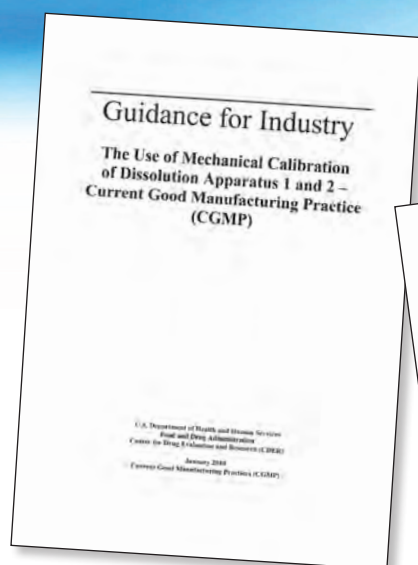
The dissolution community has long recognised that one of the major problems with respect to variability of results relates to **vessel dimensions and irregularities**. We determined from the outset that if we were able to resolve the problems arising from the vessel, then the problems emanating from the other element of the test station - the stirring element - could be easily resolved.

Traditionally, dissolution vessels have been made individually using manual glass blowing techniques from extruded glass tubing having a nominal tolerance of +/- 2 mm. Unfortunately, even by using "specially selected" tubing, it was not possible to obtain the tolerances we had set ourselves (twice as tight as those specified by the FDA) using this technique.

The solution, the **EMC Dissolution Vessel**, was to vacuum form the vessel as opposed to extrude it. In this method, the glass blank employed to produce the dissolution vessel is first heated to 2000 degrees C before being vacuum formed by shrinking it on to a precision ground mandrel. This technique not only guarantees the required dimensional tolerances but also a perfectly formed hemispherical bottom free of imperfections.

It is the EMC Dissolution Vessel that forms the basis of the new Copley Dissolution Tester Series DIS-EMC described on Page 25.





## CURRENT ISSUES

### CALIBRATION

The subject of calibration continues to stimulate considerable discussion amongst those organisations involved in dissolution testing.

Currently, the method of calibration adopted by USP in Chapter <711> has been to calibrate dissolution testers on a six-monthly basis using a combination of mechanical checks and performance verification reference tablets (formerly known as dissolution calibrators) to establish apparatus suitability.

**Performance Verification Testing (PVT)** is time consuming and concerns have been raised in some quarters about the wide acceptance ranges and variability of the results generated by the reference tablets used.

Consequently, there has been a general move towards **Enhanced Mechanical Calibration (EMC)** as an alternative or at least a precursor to chemical means.

The alternative approach was endorsed by the Food and Drug Administration (FDA) in their current guidance on the subject, "**The use of Mechanical Calibration of Dissolution Apparatus 1 and 2 - Current Good Manufacturing Practice (CGMP)**", published in January 2010.

This guidance suggests that "an **EMC** procedure (such as the one recommended in this guidance) can be used as an alternative to the current Apparatus Suitability procedure for Dissolution Apparatus 1 and 2 described in USP General Chapter <711> Dissolution".

USP, on the other hand, maintains that it is not possible to detect such problems as, for example, analyst error, dirty flow cells or insufficient degassing using mechanical calibration alone.

For that reason, USP argues that both mechanical calibration, based on the specifications laid down in USP Chapter <711> and PVT using USP Prednisone Reference Standard Tablets, are necessary to evaluate Apparatuses 1 and 2 and neither procedure is sufficient alone.

In March 2010, USP sought to further clarify its position on the subject by publishing details of a Dissolution Toolkit providing a description of best practices associated with its own enhanced mechanical calibration and performance verification testing of Apparatuses 1 and 2.

Whilst not a standard requiring rigid compliance, the "**Dissolution Toolkit. Procedures for Mechanical Calibration and Performance Verification Test Apparatus 1 and 2. Version 2.0. March 22, 2010**" represents, according to USP, its continuing effort to provide detailed information describing the procedures that, if used, will assure a properly qualified dissolution test assembly.

It is up to the dissolution laboratory itself to decide which calibration route to follow:

1. The conventional approach specified in USP Chapter <711> using a combination of less rigid mechanical checks supported by PVT testing.
2. The FDA approach based on a more rigid series of mechanical checks alone.
3. A combination of (1) and (2).

The comparison chart overleaf illustrates the differences between the current specifications and the suggested Enhanced Mechanical Calibration specifications from both the FDA and the USP.

## Comparison between Compendial and Enhanced Mechanical Calibration Specifications

Calibration Parameter	Current Pharmacopoeia	Enhanced USP Specification	Enhanced FDA Specification
<b>Bench Horizontality</b>		≤ 1° from the horizontal	No Specification Given
<b>Vessel Support Horizontality</b>		≤ 0.5° from the horizontal in two orthogonal directions	No Specification Given
<b>Basket Conformance</b>	Must conform to <711> Free of "Gross Defects"	Must conform to <711> Mesh should be perpendicular to basket top and bottom (0.5 mm deviation over 37 mm is approx. equal to 1°). Free of "Gross Defects"	
<b>Paddle Conformance</b>	Must conform to <711> Free of "Gross Defects"	Must conform to <711> Free of "Gross Defects"	Must conform to <711> Free of "Gross Defects"
<b>Vessel Conformance</b>	Must conform to <711> Free of "Gross Defects"	Must conform to <711> Free of "Gross Defects"	Must conform to <711> Free of "Gross Defects"
<b>Shaft Wobble; Basket</b>	Rotate smoothly without significant wobble	Measure a full rotation at the bottom basket rim. Deflection of probe tip should be ≤ 1.0 mm	Gauge on top of the vessel plate, position the shaft such that the gauge is measuring a point 20 mm above the top of the basket. ≤ 1.0 mm total run-out
<b>Shaft Wobble; Paddle</b>	Rotate smoothly without significant wobble	Measure a full rotation. Deflection of probe tip should be ≤ 1.0 mm	Position the shaft such that the gauge is measuring a point 20 mm above the top of the paddle. ≤ 1.0 mm total run-out
<b>Shaft Verticality</b>	N/A	<0.5° from vertical. Check two positions	<0.5° from vertical. Check two orthogonal positions
<b>Wobble; Basket</b>	≤ 1.0 mm total run-out	Measure a full rotation at the bottom basket rim. Deflection of probe tip should be ≤ 1.0 mm	Gauge on top of the vessel plate. ≤ 1.0 mm total run-out at the bottom of the basket
<b>Wobble; Paddle</b>		At a position of 10 mm above paddle blade with the stirring element installed, total deflection of the probe tip during 360° rotation ≤ 1.0 mm	
<b>Shaft Centricity; Basket (Vessel Centring)</b>	≤ 2.0 mm from centreline	Measure the distance from the shaft to the vessel at no more than 20 mm below the vessel flange. Measure at 4 orthogonal locations. The difference between the highest and lowest reading must be ≤ 2.0 mm. Roughly translates to ≤ 1.0 mm away from centreline	≤ 1.0 mm at 2 mm and 60 mm above the basket. Basket at operational height (25 mm above the vessel bottom)
<b>Shaft Centricity; Paddle (Vessel Centring)</b>	≤ 2.0 mm from centreline	Measure the distance from the shaft to the vessel at no more than 20 mm below the vessel flange. Measure at 4 orthogonal locations. The difference between the highest and lowest reading must be ≤ 2.0 mm Roughly translates to ≤ 1.0 mm away from centreline	≤ 1.0 mm from the centreline. At 2 mm and 80 mm above the blade
<b>Vessel Verticality</b>	N/A	± 0.5° from vertical. Check two positions.	≤ 1.0° from vertical. Check two orthogonal positions
<b>Height Check; Basket Depth</b>	25 ± 2.0 mm	25.0 ± 2.0 mm - measure each position	25 ± 2.0 mm
<b>Height Check; Paddle Depth</b>	25 ± 2.0 mm	25.0 ± 2.0 mm - measure each position	25 ± 2.0 mm
<b>Rotational Speed</b>	± 4% from target	± 1 rpm evaluated at 50 and 100 rpm.	± 2 rpm
<b>Temperature</b>	37°C ± 0.5	37°C ± 0.5 (All vessels to be within 0.4°C of each other when filled with 500 mL of media)	37°C ± 0.5



Apparatus 1 (Basket) ▲



Apparatus 2 (Paddle) ▲

## COPLEY TABLET DISSOLUTION TESTERS

In the majority of cases, the effectiveness of tablets or capsules administered orally relies on the drug dissolving in the fluids of the gastrointestinal tract, prior to absorption through the walls of the gastrointestinal tract into the systemic circulation.

For this reason, the rate at which a tablet or capsule dissolves is therefore critical to its therapeutic efficiency and is a key factor in both the formulation process and final quality control.

The most common apparatus used to measure the dissolution rate of solid dose forms are the **basket** and **paddle**.

Both use the same basic configuration, are simple, robust and can be used to test a variety of different products.

The basic apparatus consists of a covered cylindrical vessel having a hemispherical bottom and capable of holding approx. 1000 mL of simulated gastric juice.

The vessel is partially immersed in a suitable water bath capable of maintaining the temperature of the vessel contents at 37 degrees C.

In the case of 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 by a 3-pronged retention spring and the shaft positioned in such a manner, that the bottom of the basket is at 25 mm from the bottom of the vessel.

In the case of 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 the test, a motor is used to rotate the drive shaft at the speed (normally 50, 75 or 100 rpm) specified in the pharmacopoeias.

Speeds outside 50 to 150 rpm are usually inappropriate because of hydrodynamic inconsistencies and problems with turbulence, respectively.

A sample of the dissolution medium is taken at predefined time intervals to determine the percentage of dissolved drug present – this is normally determined

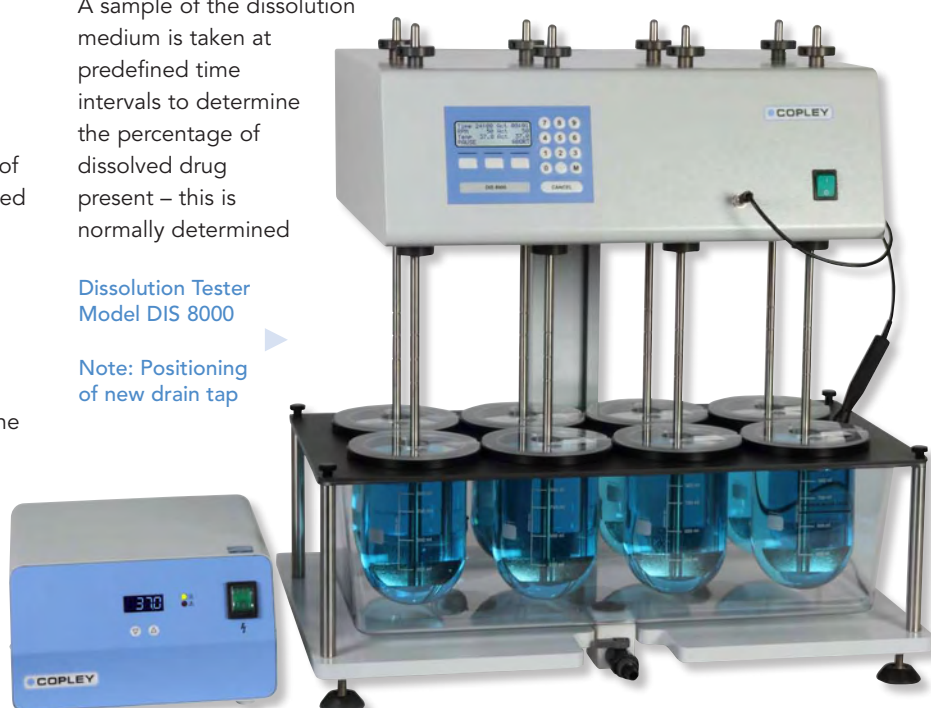
using a UV/Vis Spectrophotometer or High Pressure Liquid Chromatograph (HPLC).

All Copley Dissolution Testers feature:

- Sturdy, robust construction specifically designed to reduce clutter and maximise visibility and access in the critical sampling area above the water bath
- Simple, easy to use operation ensuring that the number of operations required to perform a test are kept to a minimum
- Full supporting documentation (including full IQ/OQ/MQ/PQ qualification documentation if required)

Dissolution Tester Model DIS 8000

Note: Positioning of new drain tap





## DISSOLUTION TESTER DIS 8000

The Dissolution Tester Series DIS represents the very latest in tablet testing technology. CNC production techniques combined with modern microprocessor design, guarantee the highest standards of performance and reliability.

All Copley Scientific dissolution testers meet the latest specifications as laid down in the European, United States and associated Pharmacopoeias.

Efficient and extremely compact, the **Tablet Dissolution Tester DIS 8000** is a rugged "no-nonsense" unit having **eight stirred** test vessels and simple, easy to use controls. It is ideal for both R&D and quality control applications.

The design of the unit has been based on those features that you, the user, advised us as being essential to the "ideal" dissolution tester.

### PHARMACOPOEIA COMPLIANCE AND QUALIFICATION

The most critical factors in the design of any dissolution tester are (a) that it complies with the respective Pharmacopoeias, (b) that this compliance can be proved or qualified and (c) that both compliance and qualification can be documented. Copley offer a three tier approach to address these points:

- **Certificate of Compliance to USP/Ph.Eur.:** Included with each unit. Written statement that the product, by design, complies with the current pharmacopoeial specifications.

Unfettered access to the critical sampling area above the water bath ▶



- **Laser Numbering and Certification:**

Identification and measurement of critical components to provide documented verification of compliance with current pharmacopoeial specifications. Available as an optional service.

- **IQ/OQ/PQ Qualification**

**Documentation:** Comprehensive documentation to guide the user through the installation, operating and performance checks of the equipment in its operating environment, using specified test protocols. It provides a comprehensive record of the suitability of the equipment to perform its specified task, to be created and archived.

Please see the ordering information for further details on our verification and qualification services.



### DESIGN AND CONSTRUCTION

In common with the rest of the series, the DIS 8000 has been specifically designed to reduce clutter and maximise visibility and access in the critical sampling area above the water bath.

Particular emphasis has been placed on those factors affecting the eccentricity, alignment and centring of the stirring elements in order to reduce the number of parts used and hence keep the machine variables at a minimum.

### BASKETS, PADDLES AND ROTATING CYLINDERS

All of the DIS series are equipped with precision-ground drive shafts that will accept any of the baskets, paddles or rotating cylinders described in the respective Pharmacopoeias.

Individual clutches enable each individual basket/paddle to be raised, lowered or engaged independent of the drive head.

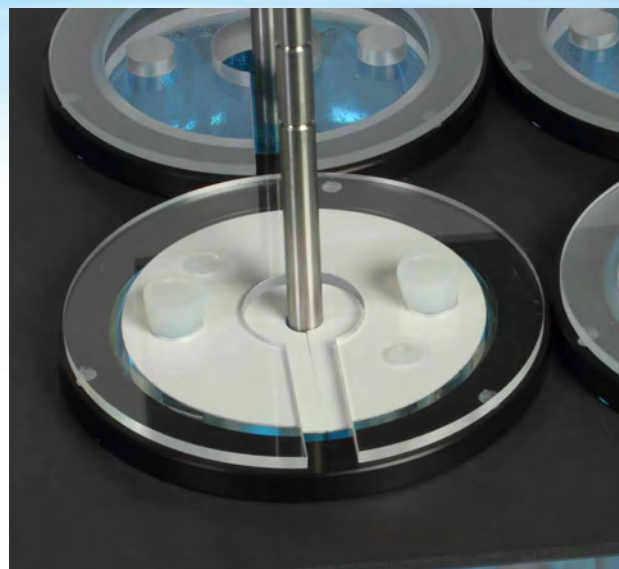
This feature is particularly useful in the case of staggered starts, and at the end of the test allows the baskets/paddles to be pushed upwards to gain maximum accessibility to the vessels.

Interchangeable Baskets/Paddles ▶





“Easy-Centre” Vessel Location ▲



Two-Part Membrane Sealed Lid ▲

## DISSOLUTION TESTER DIS 8000

All stirring elements can be laser numbered and certified on request.

The construction of the **baskets and paddles** are such that they are completely **interchangeable**. Simply screw in the appropriate element, with no further height adjustment necessary.

All of the elements can be supplied with a teflon coating for additional protection against aggressive media, if necessary.

### VESSELS, VESSEL CENTRING AND LIDS

All Copley dissolution testers are supplied with USP/Ph.Eur. compliant vessels and feature the unique “**Easy-Centre**” system to ensure that the vessels are perfectly centred every time.

The “Easy-Centre” system is based on a standard 1000 mL borosilicate glass vessel with a rim that has been precision ground and then centred accurately within a two-part acetal ring.

The acetal ring is provided with three bayonet fittings which locate in recesses provided in the vessel support plate. When turned clockwise these fittings lock the vessel into the correct position, relative to the drive shafts.

The fixture is designed such that once secured, the vessels will not become loose or float, even when empty.

All vessels can be numbered and certified on request. UV-resistant amber vessels are also available for those products sensitive to UV.

All vessels are supplied as standard with clear view acrylic lids. Special membrane-sealed two-part lids are available on request, where losses caused by evaporation may be an issue.

### CONTROL AND MONITORING OF SPEED AND TEMPERATURE

All of the DIS series of dissolution testers have a speed range of **50-200 rpm**.

The electronic speed control is provided with its own digital closed loop circuitry which guarantees an accuracy of **+/- 2%** by automatically checking and compensating for any drift from the nominal speed.

In the case of the DIS 8000, the temperature of the warming solution is controlled by means of a self-priming **1100 W external digital heater/circulator**, which allows for rapid heating of the test media from ambient to the desired temperature.

The digital heater/circulator has an accuracy of **+/- 0.1 degrees C** thus ensuring a constant and even distribution of heat throughout the bath. It is fitted with an **adjustable over-temperature cut-out** and alarm indicator,

together with a **low-level cut-out** which operates if there is insufficient water available in the bath.

The one-piece vacuum formed water bath is constructed in rigid PETG and has been specifically designed to eliminate leaks and to make it easier to clean. A fill-line is provided on each bath to indicate the level to which the bath must be filled.

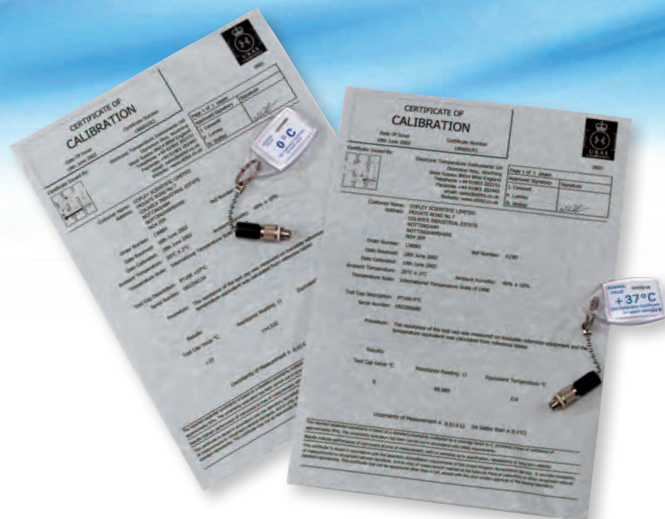
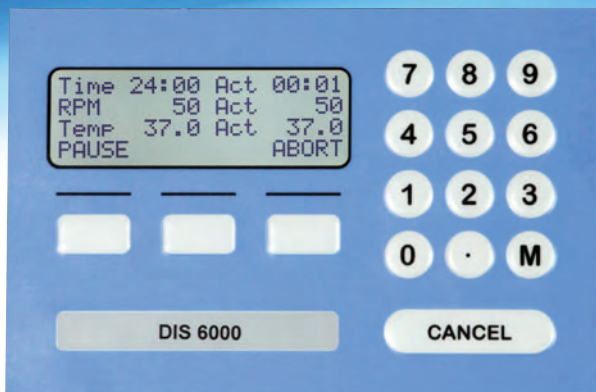
The water bath and the easy to clean teflon-coated 316 stainless steel vessel support plate are supported by means of four stainless steel pillars and secured by four thumb screws.

The bath and vessel temperatures can be constantly monitored using the **PT100 temperature probe** provided for this purpose. Provision is made for logging the actual speed and temperature at user-defined intervals throughout the test for subsequent printing.

### ▼ Digital Heater/Circulator







## DISSOLUTION TESTER DIS 8000

### OPERATION

The control of all models is provided by a membrane keypad linked to a 4-line 20 character backlit display, which together with the electronics is mounted in the head of the instrument so as to avoid any accidental spillages in the test area.

Many users have criticised the fact that their existing dissolution testers are overly complex with unnecessary software functionality for day-to-day use. For this reason, considerable attention was given in the design to ensuring that the number of actions necessary to perform a test was kept to a minimum.

Once the test sequence has been initiated, all that is necessary to start the test is to input the required rpm and nominal temperature, together with the duration of the test and the report interval (the time interval during the test at which the actual rpm and temperature is logged and subsequently reported), introduce the samples and press START.

During the test the following information is shown on the display:

- Nominal and actual rpm
- Nominal and actual temperature
- Preset test duration and time elapsed

An audible alarm alerts the user that the test is completed.

The dissolution tester is provided with both parallel and USB ports as standard for print-out of time, date, bath identification, serial number and date of calibration, together with the speed and temperature at operator selectable time intervals during the test.

### CALIBRATION

Routine calibration is an essential part of your operation. Therefore a special calibration menu guides the user through the various functions and provides a printed report at the end of the operation.

One unique feature in this respect is the electronic temperature calibration kit. Ordinarily, temperature calibration can prove to be a time consuming and inaccurate process involving iced water. Available as an option, the electronic temperature calibration kit comprises two **UKAS certified test keys (0 and 37 degrees C)** which are simply plugged into the PT100 temperature probe socket to perform the calibration.

We offer a wide range of tools for calibrating your dissolution tester. Please see the appropriate information in the Dissolution Accessories section on page 34.

### Temperature Calibration Kit ▲

### AUTOMATION

Manual dissolution testing is extremely time consuming and tedious. For this reason, many users are turning to complete automated systems to fulfill their requirements. As in the DIS 6000 and 8000, in most cases, the software involved also controls the dissolution tester.

The DIS 8000 has a bi-directional RS232 interface on the back panel which allows for communication with external devices and incorporation into automated systems.

### DIMENSIONS

The DIS 8000 measures: 650 x 450 x 640 mm (w x d x h) and the Heater/Circulator measures: 260 x 300 x 150 mm (w x d x h)



### Temperature Calibration Kit ►



## DISSOLUTION TESTER DIS 8000

### SUMMARY OF KEY FEATURES

#### Standard

- Rugged, compact and easy-to-use
- Conforms to all current Ph.Eur. and USP specifications
- User friendly operating procedure via membrane keypad and 4-line LCD screen
- Screw-in baskets/paddles allow method changes in seconds such that no further adjustments are necessary
- Individual clutches allow each basket/paddle to be raised, lowered and engaged independent of the drive head
- Uncluttered design allows maximum access to working area
- 316 stainless steel teflon coated vessel support plate
- "Easy-Centre" vessel centring system
- One piece PETG water bath with built-in drain tap; no leaks; easy to remove and clean

- Independent digital heater/circulator with over-temperature cut-out and indicator. Easily removed for maintenance
- Full printed test report on completion of the run (user selectable)
- RS232 bi-directional interface and USB/parallel printer port
- Menu guided calibration procedure (with print-out)

#### Options

- Laser numbering, certification and IQ/OQ/PQ documentation
- Teflon coated baskets/paddles for aggressive media
- Amber coated UV-Resistant vessels and lids
- Low evaporation membrane sealed vessel lids
- Electronic temperature calibration kit

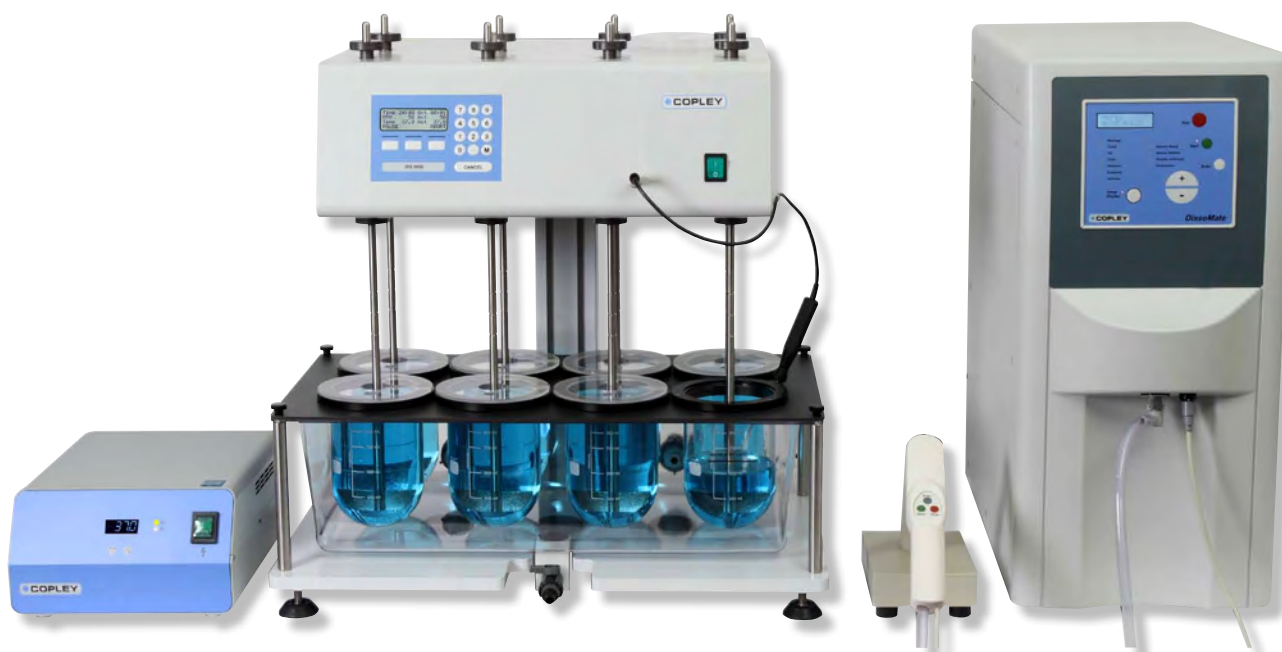
#### Cat. No. Description

1301	Dissolution Tester DIS 8000 (incl. 8 Drive Shafts)
1302A	Set of 8 Baskets (Ph.Eur./USP Method 1)
1304A	Set of 8 Paddles (Ph.Eur./USP Method 2)
1307	Printer (including USB Cable)
1207	Electronic Temperature Calibration Kit
1309	IQ/OQ/PQ Documentation Pack

#### Extra for Laser Numbering and Certification

See Page 32

▼ DIS 8000 with "Dissomate" Media Prep Station



## DISSOLUTION TESTER DIS 6000

In many laboratories, bench space is at a premium. The **DIS 6000** has been designed as a direct response to this problem. With a footprint of just 650 x 450 x 640 mm (w x d x h), the DIS 6000 is one of the most compact dissolution testers available on the market today.

The unit has **six stirred test vessels** arranged in two rows of three.

Heating is provided by an **independent digital 1250 W heater/circulator**, which obviates the need for priming and can be quickly removed for cleaning, without compromising the whole tester.

The digital heater/circulator is fitted with a special low vibration impellor which in comprehensive tests has proved to be equal to or less, in terms of vibration measurements than an independent heater/circulator.

**A low water-level and over-temperature cut-out** is provided as standard.

A common complaint from customers is that their existing tester is overly complex with unnecessary software functionality for day-to-day use. For this reason, considerable attention was given in the design to ensuring that the number of actions necessary to perform a test was kept to a minimum. Once the test sequence has been initiated, all that is necessary to start the test is to input the nominal rpm and nominal temperature required, together with the duration of the test and the report interval (the time interval during the test at which the actual rpm and temperature is logged and subsequently reported), introduce the samples and press START.

During the test the following information is shown on the display:

- Nominal and actual rpm
- Nominal and actual temperature
- Preset test duration and time elapsed



Dissolution Tester DIS 6000 ▲

An audible alarm alerts the user that the test is completed.

The dissolution tester is provided with both parallel and USB ports as standard for print-out of time, date, bath identification, serial number and date of calibration, together with the speed and temperature at operator selectable time intervals during the test.

A bi-directional RS232 Interface on the back panel allows communication with external devices and incorporation into automated systems. In all other respects, the Dissolution Tester DIS 6000 is similar in construction to the DIS 8000 described on the preceding pages.



### Cat. No. Description

1311	Dissolution Tester DIS 6000 (incl. 6 Drive Shafts)
1302B	Set of 6 Baskets (Ph.Eur./USP Method 1)
1304B	Set of 6 Paddles (Ph.Eur./USP Method 2)
1307	Printer (including USB Cable)
1207	Electronic Temperature Calibration Kit
1309	IQ/OQ/PQ Documentation Pack

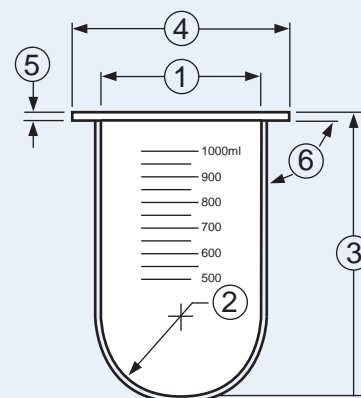
### Extra for Laser Numbering and Certification

See Page 32



#### EMC Ultra Precision Dissolution Vessel

1	Inside Diameter	101.19 +/- 0.13 mm
2	Inside Spherical Radius	50.59 +/- 0.13 mm
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 mm Max



## DISSOLUTION TESTER DIS-EMC

If you require the ultimate in a Dissolution Tester then the DIS-EMC is the dissolution tester for you.

The **Copley Dissolution Tester Series DIS-EMC** includes all the features of the standard DIS 6000 and 8000 units described on the preceding pages.

It goes without saying that the standard DIS 6000 and 8000 units already comply with the new EMC specifications as laid down by the FDA.

Where the DIS-EMC differs from the standard unit is the application of the latest state-of-the-art technologies to the manufacture of the Dissolution Vessel, which in combination with the precision ground stirring element brings you a new level of standard in terms of dimensions and tolerances.

It is the **Dissolution Vessel** in which the dosage form resides during testing and which consequently has the most potential to contribute variability.

Vessel geometry constantly features as a source of concern. A Design of Experiment (DOE) study reported by USP in 2007 (Joseph Eaton *et al.* Perturbation Study of Dissolution Apparatus Variables - A Design of Experiment Approach. Dissolution Technologies, February 2007, Volume 14 Issue 1) found three variables that were statistically significant as far as mean percent dissolved was concerned: level of deaeration, vessel type and rotation speed.

In the same issue as the article above, USP reported significant differences in the geometric dimensions and surface irregularities of eleven sets of six dissolution vessels selected from 10 commercial sources (Liddell *et al.* Evaluation of Glass Dissolution Vessel Dimensions and Irregularities. Dissolution Technologies).

It is little surprise therefore that the key to overcoming instrument induced variability lay in the development of the **EMC Ultra Precision Dissolution Vessel** described in the box above.

Traditionally, dissolution vessels have been made individually using manual glass blowing techniques from extruded glass tubing having a nominal diameter of +/- 2 mm.

The solution was to vacuum form the vessel as opposed to extrude it. In this method, a glass blank is first heated to

2000 degrees C before being vacuum formed by shrinking it on to a precision ground stainless steel mandrel. This method guarantees an inside diameter tolerance and blemish-free spherical radius of +/- 0.13 mm (compared with +/- 2 mm on the conventional unit) together with a flange perpendicularity tolerance of 0.50 mm TIR (Total Indicated Runout).

If one compares the FDA and USP Enhanced Mechanical Qualification Specifications outlined on Page 18 with the Dissolution Tester DIS-EMC fitted with the new EMC Ultra Precision Dissolution Vessels described above, it can be seen that the DIS-EMC better the dimensional tolerances specified in the FDA's Enhanced Mechanical Calibration by **a factor of 2**.

**All the relevant parts are individually serialised as standard.**

#### Cat. No. Description

1392	Dissolution Tester DIS-EMC 6000
1302B	Set of 6 Baskets (Ph.Eur./USP Method 1)
1304B	Set of 6 Paddles (Ph.Eur./USP Method 2)
1395	Dissolution Tester Model DIS-EMC 8000
1302A	Set of 8 Baskets (Ph.Eur./USP Method 1)
1304A	Set of 8 Paddles (Ph.Eur./USP Method 2)
1307	Printer (including USB Cable)
1207	Electronic Temperature Calibration Kit
1309	IQ/OQ/PQ Documentation Pack





## AUTOMATIC TABLET DROP

The first procedure at the start of any dissolution test is to drop the samples into the individual vessels.

This function can be performed manually if desired: indeed, when using the DIS series of dissolution testers, this is relatively easy since the baths have been deliberately designed to reduce clutter and maximise visibility and access in the critical sampling area above the water bath.

However, this approach does mean employing a staggered start since it is very difficult to introduce all the tablets and then take samples simultaneously. For this reason, a correction factor has to be applied to the final results in order to take into account the time-lag between introducing the tablets.

When using automated systems, where sampling from all vessels can be performed simultaneously, the dissolution tester can be fitted with an automatic tablet drop system. With this system, the tablets are placed in a series of chambers on the dissolution vessel lids and ejected into the vessels at the same time at the start of the test.

### Cat. No. Description

1312A	Automatic Tablet Drop (DIS 8000)
1312B	Automatic Tablet Drop (DIS 6000)

◀ Above and below:  
Automatic Tablet Drop

## SAMPLING

Four different dissolution sampling systems are available according to user requirements.

The simplest method is to sample from each vessel using a **manual sampling cannula**.

The manual sampling cannula (above) has a **luer fitting** to accept a 20 mL syringe supplied with it and is bent at the top to allow for easy positioning in the dissolution vessel.

Alternatively, we can offer **resident probes** designed to fit directly into the dissolution lid. Resident probes are designed to be left "in-situ" in the dissolution vessel for the duration



Manual Sampling Cannula ▲

of the test - they can, of course, be removed between tests for cleaning.

All of the resident sampling probes are height adjustable to take into account the differences in sampling position required by the differing methods described in the Pharmacopoeias.

Two types of resident sampling probe are available:

1. For manual sampling (with **luer fittings** for manual sampling).
2. For automated systems: fitted with '**Omnifit**' fittings and used in conjunction with the return line inserts for use in automated systems.

Note: See Page 33 for probe filters.

### 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)



▲ Resident Probe, left with luer fitting and centre with "Omnifit" fitting together with right, a Return Line Insert



## TRANSDERMAL PATCH TESTING (DRUG RELEASE)

### PADDLE OVER DISK

The "Paddle over Disk" is a modified version of Method 2 (Paddle Method) and is used for the determination of the drug release rate of **transdermal patches**.

It is described in the United States Pharmacopoeia (USP) under Chapter <724> as Method 5 and in the European Pharmacopoeia (Ph.Eur.) under Chapter 2.9.4. Method 1 as 'Disk Assembly Method'.

The **standard disk** comprises a 35 mm o.d. 40 mesh stainless steel screen mounted in a stainless steel holder having a diameter of 41.2 mm and is designed to hold the transdermal patch at the bottom of the vessel.

It is suitable for all transdermal patches up to a maximum of 16 mm outside diameter. The transdermal patch is mounted on the disk, release side up, using a suitable adhesive (Hollister Medical Adhesive or equivalent).

A second and larger version of the disk comprising a 90 mm diameter **watch glass-patch-PTFE** assembly is available to accommodate larger patches. It is this second and larger disk assembly that is normally considered the method of choice since experimentation dictates that this procedure gives almost identical results with that of other, more complicated apparatus.

The assembled disk is placed, with the patch release side up, at the bottom of the vessel, parallel with the bottom edge of the paddle and the height of the paddle adjusted such that its bottom edge is 25 mm from the surface of the disk assembly.

The following parameters are normally considered representative of skin conditions *in vivo*:

- Media pH: 5 to 6
- Media Temperature: 32 degrees C
- Paddle Speed: 100 rpm



### ROTATING CYLINDER

An alternative method for the testing of **transdermal patches**, USP Method 6 (Ph.Eur. Chapter 2.9.4. Method 3) employs the same dissolution equipment as Method 1 simply substituting a cylinder stirring element in place of the standard basket. The rotation speed normally employed is 100 rpm. The element is designed to accept various sizes of patches.

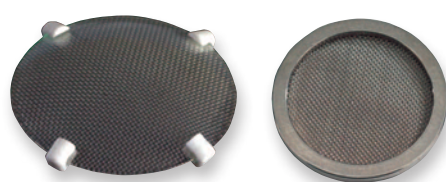
In this method, the protective liner of the transdermal patch is first removed and the adhesive side placed on a piece of inert, porous cellulosic material (Cuprophane Type 150) that is not less than 1 cm larger on all sides than the system.

The assembled system is then attached to the exterior of the cylinder using a suitable adhesive to the exposed borders of the Cuprophane support.

An **extension piece** (see above) is included in the kit for larger patches.

#### 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)



◀ Standard Disk

▲ Watch Glass / Patch / PTFE Assembly

#### Cat. No. Description

1386	Cylinder Stirring Element including Extension (USP Method 6)
1387	Cuprophane Flat Membrane 150 pm (10 Sheets)



## SPECIAL APPLICATIONS

### SMALL VOLUME CONVERSION KITS

Two conversion kits comprising special low volume vessels of either 100 or 200 mL capacity with appropriate mini-paddles are available for low dose formulations.

Some dosage forms such as patches or transplants require much lower concentrations than are usual in the standard 1000 mL vessel.

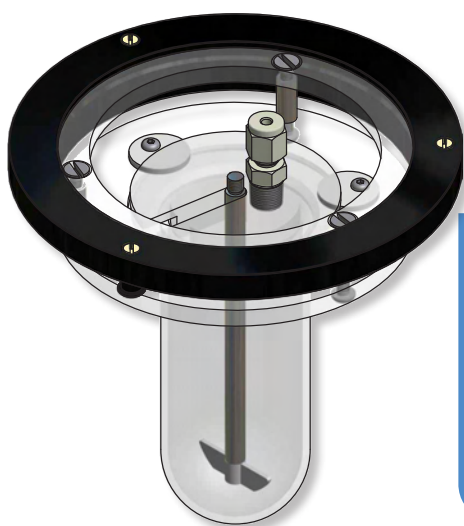
Each conversion kit comprises:

- 1 x Mini Vessel
- 1 x Mini Paddle
- 1 x Vessel Cover
- 1 x Centring Ring Assembly

A special flat bottomed vessel version of the mini-paddle and vessel is used with the ointment cell, a variation on USP Method 5 suitable for topical preparations such as liquids, suspensions, gels and ointments (see Page 63 for further details).

Special Coarse Mesh Basket ▶

Small Volume Conversion Kit ▼



▲ Small Volume Conversion Kit

### SPECIAL BASKETS

Some dosage forms have a tendency to block the standard 40 mesh basket and may require the substitution of a basket having a coarser mesh. The mesh size selected should be sufficient to retain the dosage form in the basket whilst allowing media penetration without clogging.

### BASKET FOR THE DISSOLUTION OF SUPPOSITORIES

Oil based suppositories give unacceptable and unreproducible results utilising the standard 40 mesh stainless steel dissolution basket, since the suppository base has a tendency to block the filter mesh.

The special basket for suppositories has the same basic basket specification as the standard USP basket but is constructed from polyurethane. The standard sieve mesh is replaced by 12 linear slots of 2.5 mm width providing a porosity of approx. 52% (approximately equivalent to 10 mesh).



◀ Special Suppository Basket

#### Cat. No. Description

1361	Basket only in 316 Stainless Steel (20 Mesh)
1362	Basket only in 316 Stainless Steel (10 Mesh)
1363	Special Suppository Basket
1371-100	Conversion Kit for Small Volumes - 100 mL
1371-200	Conversion Kit for Small Volumes - 200 mL



## SPECIAL APPLICATIONS

### INTRINSIC DISSOLUTION

Intrinsic dissolution may be defined as the dissolution rate of a substance under constant surface area conditions. It is normally measured in terms of "mg per minute per square centimetre".

It differs from the more conventional dissolution methods in that **only one 5 mm diameter surface is exposed to the solvent** (dissolution media).

The kit for intrinsic dissolution studies is based on the same principles as the **Rotating Disk** apparatus described in USP Chapter <1087> Apparent Intrinsic Dissolution - Dissolution Procedures for Rotating Disk and Stationary Disk.

Both Rotating and Stationary Disk methods share the same characteristics, namely:

- Both rely on compression of the test compound into a compact prior to testing
- Both use a tablet die to hold that compact
- The die is located in a fixed position within the vessel in order to maintain the same hydrodynamic conditions

The Intrinsic Dissolution Kit consists of six 5 mm diameter punches, six 5 mm diameter dies and a compression plate that allows the compression of the material into a compact.

The compaction process is relatively simple.

Turn the Die Displacement Screw anti-clockwise until the screw is fully extended.

Slide one of the Dies into the recess provided on the compression plate for this purpose until the side of the Die rests against the end of the Displacement Screw.

Place a measured amount of powdered drug into the die cavity (the hole in the centre of the Die).

#### Intrinsic Dissolution Kit



Now place one of the punches on top of the powder (flat surface down).

Place the entire assembly into a suitable bench mounted press (**not** supplied) and with the force transmitted to the top of the punch, apply the appropriate pressure to compact the powder.

Compression at 1 Newton per square mm for 1 minute is usually sufficient for most compounds.

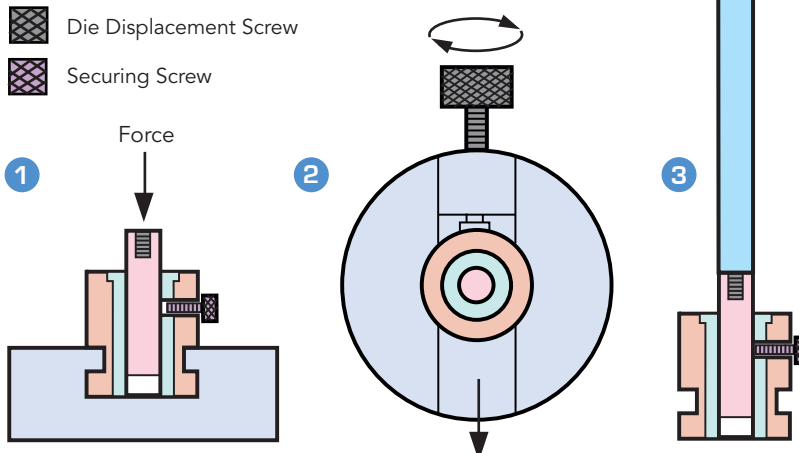
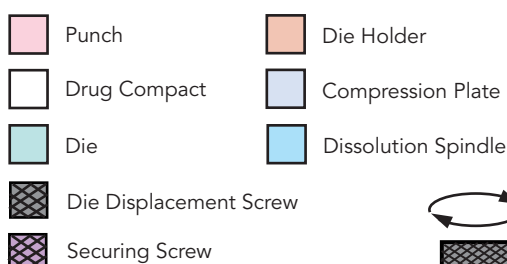
Release the assembly from the press and tighten the securing screw to lock the compacted punch firmly in position within the die.

Remove the assembly from the compression plate by screwing in the Die Displacement Screw.

Now with the punch still in place, screw the assembly on to the dissolution shaft and adjust the shaft such that when in the fully lowered position the surface of the compact is not less than 1 cm from the bottom of the vessel.

Repeat the exercise for the other five assemblies.

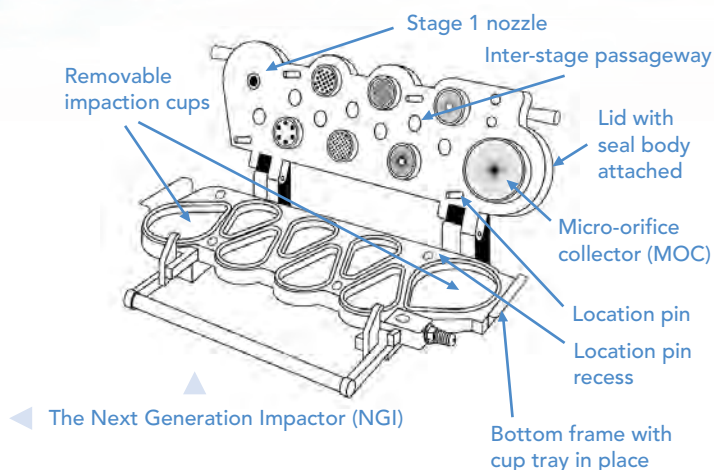
Rotate the shafts at 200 rpm - the dissolution rate depends on the rotation speed used.



#### Cat. No. Description

1364

Kit for Intrinsic Dissolution Studies



## SPECIAL APPLICATIONS - INHALED DRUGS

### INTRODUCTION

Dissolution is a critical quality attribute in the development and manufacture of oral dosage forms such as tablets and capsules, which rely on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation.

Indeed, dissolution testing is widely used for optimising efficacy during development (often by using modified or controlled release techniques), ensuring quality during batch to batch manufacture and in some cases to predict bioavailability *in vivo* and assess bioequivalence.

In the case of inhaled and nasal drug delivery products, the first prerequisite is to deliver an appropriate amount of drug to the target site. For that reason, *in vitro* testing is concentrated on drug delivery (emitted dose) and lung or nasal deposition (aerodynamic particle size distribution) using a cascade impactor such as the Next Generation Impactor (NGI) or Andersen Cascade Impactor (ACI) as opposed to dissolution or drug release.

Once deposited, the absorption or lung uptake, and hence the therapeutic effectiveness of the drug, depends on the active dissolving in the small amounts of aqueous fluid and lung surfactant available at the target site.

At present, there are no official dissolution test methods described

applicable to inhaled products. One of the main problems facing the developers of such methods is the identification and segregation of that part of the total emitted dose actually reaching the target site (as opposed to the whole dose) in a form readily adaptable to conventional dissolution testing techniques.



Membrane Holder in Dissolution Vessel ▶



## SPECIAL APPLICATIONS - INHALED DRUGS

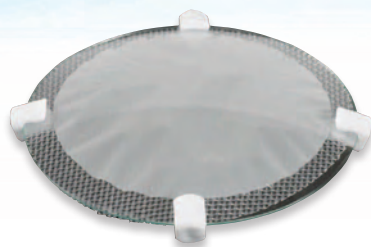
### DESCRIPTION

Based on a concept developed by Professor Jason McConville at the College of Pharmacy, University of Texas, the NGI Dissolution Cup and Membrane Holder incorporates a modification of the standard NGI collection cup. It allows size-fractionated particles from an aerosol cloud to be collected and then tested in a conventional dissolution tester.

The Dissolution Cup only differs from the standard cup in that it has a 50 mm removable insert in the impaction area. Particle sizing is carried out in the conventional manner. Once collection is complete, the insert is carefully removed from the cup, covered with a pre-punched 55 mm diameter polycarbonate membrane and secured in position in a Membrane Holder, using a ring, to form a sealed "disk" or "sandwich".

The Membrane Holder can now be placed in a conventional Dissolution Tester such as the Copley DIS 6/8000 and tested in a manner similar to the "Paddle over Disk" Method described in USP Method 5 and Ph.Eur. 2.9.4 using ca. 300 ml of dissolution medium and the paddle at 75 rpm.

A similar technique can be employed using the Andersen Cascade Impactor, in this case, by applying a 76 mm polycarbonate filter to the collection plates prior to analysis, such that the drug is captured directly on the



Watchglass/PTFE ▲  
Assembly for use with ACI

membrane, and then sandwiching the inverted membrane between the glass and PTFE surfaces of the Watch Glass/PTFE Assembly, normally used for transdermal patches.

The small amount of aqueous fluid and surfactant found in the lung make it extremely difficult to mimic *in vitro*.

Marques, Loebenberg and Almukainzi list five of the most used simulated lung fluids in Table 11\* of their article, "Simulated Biological Fluids with Possible Application in Dissolution Testing".

The first of these, SLF1, has been used to evaluate different interstitial conditions in the lung following exposure to various environmental emissions.

▼ NGI Dissolution Cup and Membrane Holder



▲ Andersen Cascade Impactor (60 L/min Version) with Induction Port

SLF2 was designed to model the interaction of particles with extracellular lung fluids, in this case, exposure to Hg due to the inhalation of airborne calcines from mine waste.

Another fluid replicating interstitial fluid, SLF3, was used to evaluate the *in vitro* release of insulin following pulmonary delivery.

In the method described here, Son and McConville suggested the use of two standardised fluids, described in the article under the designation, SL3, and its modified version, SL4.

Finally, SLF5 was used to measure the dissolution of titanium tritide particles used as components of neutron generators.

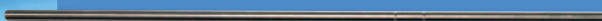
\*Margareth R.C.Marques, Raimar Loebenberg and May Almukainzi, *Simulated Biological Fluids with Possible Application in Dissolution Testing. Dissolution Technologies (August 2011) p. 15-23.*

### Cat. No. Description

6001	NGI Dissolution Cup and Membrane Holder (each)
6002	55 mm Punch
6003	Watch Glass/PTFE Assembly for use with ACI (each)
6004	Pack of 100 Polycarbonate Filters (0.1 micron x 76 mm diameter)



Dissolution Drive Shaft

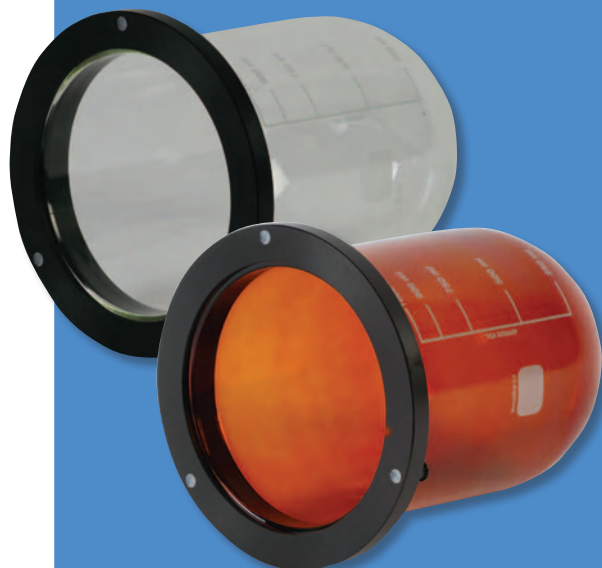


316 SS Basket



3 Prong Spring & Basket Holder

316 Stainless Steel & Teflon Coated Paddles



Standard & Amber Coated Vessels



316 SS & Plastic Sinkers



**Cat. No. Description**

**DISSOLUTION DRIVE SHAFTS**

1329 316 Stainless Steel Drive Shaft only

**BASKET STIRRING ELEMENTS (USP/Ph.Eur. Method 1)**

1302 Basket **only** in 316 Stainless Steel (40 Mesh)  
 1338 Basket Holder in 316 Stainless steel  
 1336 3-Prong Retention Spring in 316 Stainless Steel  
 1333 Basket Stirring Element **complete** with Drive Shaft

**PADDLE STIRRING ELEMENTS (USP/Ph.Eur. Method 2)**

1304 Paddle **only** in 316 Stainless Steel  
 1341 Paddle Stirring Element **complete** with Drive Shaft  
 1343 Paddle Stirring Element **complete** - Teflon Coated

**VESSELS**

1346 Vessel, 1000 mL, with "Easy-Centre"  
 1349 Amber Vessel, 1000 mL, with "Easy-Centre"  
 1398 EMC Dissolution Vessel, 1000 mL, with "Easy-Centre"

**VESSEL COVERS**

1351 Vessel Cover, **Standard**  
 1353 Vessel Cover, Two-part Membrane Sealed  
 1355 Plug for Catalogue number 1353

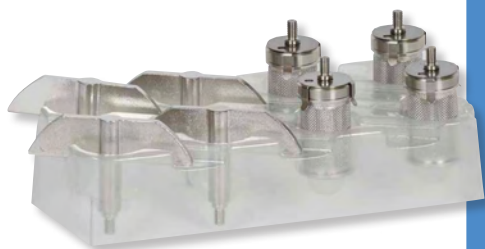
**CAPSULE SINKERS AND WEIGHTS**

1356 Set of 6 316 Stainless Steel Sinkers  
 1345 Set of 6 USP/Ph.Eur. Alternative Sinkers  
 1348 Wire, 316 Stainless Steel (50 ft length)

**LASER NUMBERING AND CERTIFICATION (each)**

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, with "Easy-Centre"

## SPARE PARTS AND ACCESSORIES



Storage Rack for 8 Baskets or Paddles ▲

Carrying Rack for 4 Vessels ▶



## 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

## PERFORMANCE VERIFICATION TESTING (PVT)

These standardised drug forms supplied by USP (Rockville, Maryland, USA) have been formulated to produce reproducible results under standard dissolution test conditions.

Thus, if the results using the reference standards prove satisfactory, it can be assumed that the physical and mechanical variables of the system are within the specified limits and that any anomalies are due to the dosage form under test.

USP holds that both mechanical calibration and performance verification testing are necessary to evaluate both USP Apparatus 1 and 2, and neither procedure is sufficient alone.

## Cat. No. Description

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



## 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)



## HYGIENE: ANTI-BACTERIAL/ALGAE TABLETS

Bacterial or algal growth in dissolution tester water baths can be hazardous, malodorous and inconvenient. The addition of just one mL of Aqua-Stabil per month will prevent the build-up of bacteria and algae keeping the water clear, safe and odour free.

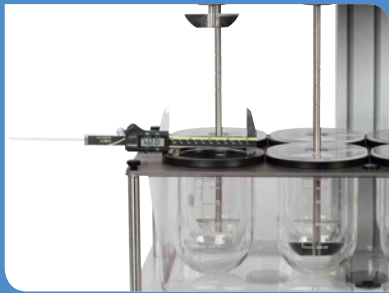
Each bottle contains 100 mL of Aqua-Stabil to maintain the clarity and quality of your water bath systems.

## Cat. No. Description

1372	100 mL Bottle of Aqua-Stabil
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CALIBRATION TOOLS



Basket, Paddle & Vessel Conformance



Horizontal & Vertical Levelling



Vessel Centricity



Basket/Paddle Wobble



Shaft Rotational Speed (Tachometer)



Cat. No. Description

- 1501 Digital Caliper Model 500
- 1502 Wobble Checker
- 1378 Height Checker
- 1503 Level Checker (Spirit Level)
- 1380 Temperature Checker (Digital Thermometer)
- 1381 Speed Checker (Tachometer)
- 1505 Stopwatch
- 1507 Centricity Checker
- 1508 Calibration Tool Kit complete (includes above tools)
- 1509 Verification Rig for Wobble & Centricity Checkers\*
- 1320 Vibration Meter\*



1378

\* Not included in Calibration Tool Kit



Note: All items UKAS calibrated as appropriate.



## MEDIA PREPARATION (DEAERATION - THE PRINCIPLES)

The effects of air bubbles and other dissolved gases in the media used to conduct dissolution tests are legion and can be significant.

A Design of Experiment (DOE) study reported by USP in 2007 (Joseph Eaton *et al.* Perturbation Study of Dissolution Apparatus Variables - A Design of Experiment Approach. Dissolution Technologies. February 2007 Volume 14 Issue 1) found that of the 9 variables and 36 two-factor variables studied, three variables stood out as being statistically significant as far as mean percent dissolved was concerned: **level of deaeration, vessel type and rotation speed**, with the level of deaeration contributing to **52.3%** of the total reported effects.

The major influence of gas or air in dissolution work seems to be physical. Air bubbles may collect on the dosage form, the basket containing the dosage form or the sampling probe or their filters used to draw off samples for analysis. Their presence in spectrophotometer flow cells or on fibre optic probes may lead to incorrect absorbance readings. They may also accumulate on the membranes employed in the vertical diffusion cells used in transdermal and percutaneous absorption tests.

"Dissomate" with  
Dissolution Tester



### THE REGULATIONS

The Pharmacopoeias recognise that "dissolved gases in the dissolution medium may affect dissolution test results and recommends that gases be removed before the test is performed".

They advocate the following procedure as one method of deaeration:

"Heat the medium, while stirring gently, to about 41 degrees C, immediately filter under vacuum using a filter having a porosity of 0.45 microns or less, with vigorous stirring and continue stirring under vacuum for about 5 minutes".

This "**filtering, warming and stirring under vacuum**" approach is echoed by the FDA (Terry W. Moore. Dissolution Testing: A Fast, Efficient Procedure for Degassing Dissolution Medium' Dissolution Technologies. May 1996).

The Pharmacopoeias also state "Place the **stated volume of the the Dissolution Medium (+/- 1%)** in the vessel of the specified apparatus given in the individual monograph, assemble the apparatus, equilibrate the Dissolution Medium to 37 +/- 0.5 degrees C, and remove the thermometer".

The temperature of the medium is critical to volumetric precision. The volume of the dissolution medium at the stated temperature of 25 degrees C is different for that at 37 degrees C, at which point the volume would be greater because the medium expands as the temperature rises.

It is for this reason that USP suggests that a more accurate and temperature independent measure of the media volume is gravimetric i.e., by **weight**.

### USER REQUIREMENTS

In addition to conformity to the compendial and regulatory requirements, there are a number of user requirements which must be taken into account:

- Simple, easy-to-use operation
- Proven time savings in comparison with manual methods
- Compact (space saving)
- Accurate and reproducible
- Capable of validation

#### "Dissomate" Media Station

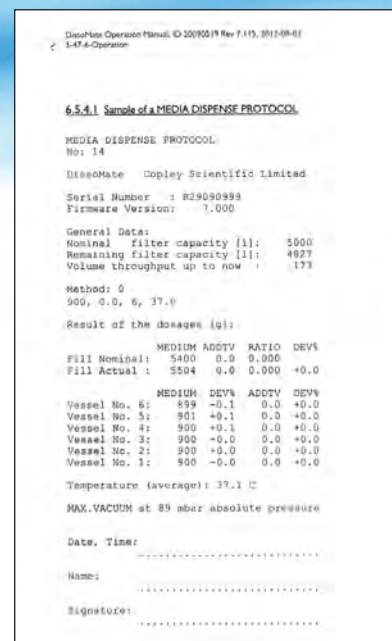
Warms	✓	Weighs	✓
Deaerates	✓	Dispenses	✓





Dispense Nozzle ▲

"Dissomate" Protocol Print-Out ►



## MEDIA PREPARATION - THE "DISSOMATE"

The "Dissomate" Media Preparation Station combines degassing and dispensing to provide a fresh source of pre-warmed, deaerated and dosed dissolution medium thus substantially reducing down times between dissolution tests.

There is no necessity to premix the dissolution medium in advance. The "Dissomate" automatically adds the appropriate volume of acid, buffer or surfactant to the prewarmed medium prior to mixing and dispensing.

### PRINCIPLE OF OPERATION

The principle of operation is extremely simple. The "Dissomate" operates on the same "**filtering, warming and stirring under vacuum**" approach as recommended by the Pharmacopoeias and FDA.

On initiation, dissolution medium is withdrawn under vacuum from the media reservoir (**not** provided) through the heater which warms the medium to the desired temperature and into the polypropylene mixing chamber.

An easily exchangeable filter cartridge located in-line within the fill tube filters the medium prior to use. The life of the filter is constantly monitored in terms of total elapsed volume filtered and the user prompted to change the filter when required. The default setting is 5000 litres.

The medium is preheated to the appropriate temperature (adjustable between 20 and 45 degrees C in 0.1 increments) en route to the mixing chamber by means of a special continuous-flow water heater, before degassing takes place. This enhances the degassing process and saves considerable time in testing.

If the "Additive" function has been selected, then the acid, buffer or surfactant is automatically added to the mixing chamber at this point. Dilution ratios of between 1:3 and 1:100 can be accommodated.

An in-built magnetic stirrer ensures an homogenous mix within the mixing chamber (Accuracy: < 0.5%, typically < 0.2%).

The efficiency of the degassing process is dependent on:

- the vacuum applied, in this case, <250 mbar (typically 95 mbar) pressure absolute
- the time the medium is exposed to the vacuum
- the temperature of the medium
- the stirring of the medium

All of these factors assist in the deaeration process. In the case of the "Dissomate", the interaction of heating, mixing and degassing generates a typical effective deaeration level of 3-5 ppm dissolved oxygen (measured after filling into the vessel).

The mixing chamber has a maximum total capacity of 11 litres. This allows for 8 litres of **fresh** medium (sufficient to fill all the vessels of one dissolution bath) plus an additional 3 litres (to accommodate the dead volume created by the tubes, etc., and also provide a flush sequence at the start of the dispense cycle).

Note: The importance of fresh medium cannot be overestimated. An investigation into the overnight re-aeration of unused previously deaerated media found that the concentrations of dissolved oxygen almost doubled during the period concerned (Owen S. Degenhardt *et al.* Comparison of the Effectiveness of Various Deaeration Techniques. Dissolution Technologies. February 2004).

The prewarmed and deaerated medium is dispensed directly into the dissolution vessels by means of a hand-held dispense nozzle (Dispense rate: 2 L/min/Accuracy < 1%).

Tip: A single "Dissomate" could possibly service all of your Dissolution and Disintegration Testing needs

"Dissomate" with Disintegration Tester ▶

## MEDIA PREPARATION - THE "DISSOMATE"

It typically takes 15 minutes from start to prepare 8 litres of medium and about 30 seconds per vessel to dispense. This means that a single "Dissomate" will handle several dissolution testers concurrently.

Accuracy is paramount in any drug release study. One of the unique features of the "Dissomate" is that both fill and dispense volumes employed are determined gravimetrically, i.e. by weight using the in-built load cell provided for this purpose. Different media have different volumes dependent on their temperature and pressure conditions - only weight remains constant under such changing conditions.

The use of a load cell means that all the processes involved can be documented and output to an external printer or PC. The "Dissomate" provides a full report detailing, weights, mixing ratios, vacuum and temperature after each "Dispense" Cycle. A "Calibration" protocol is also provided.

Extremely compact, the "Dissomate" measures 30 x 59 x 66 cm (w x d x h) and weighs 26 kilos.



### OPERATION

Immerse the inlet tubes from the "Dissomate" into the medium and additive (if used) reservoirs.

### Set Up

**Volume Vessel** - Enter the weight of the volume of medium to be dispensed into each vessel e.g. 897 g = 900 ml per vessel. (Range = 150 g to 8 kg).

**Volume Additive (if used)** - Enter the weight of the volume of additive to be dispensed into each vessel, e.g. 10 g.

**Number of Vessels** - Enter the number of vessels to be filled e.g. 6 or 8.

**Temperature** - Enter the media temperature required, e.g. 37 deg C

Press START key to save as the primary method.

### "Dissomate" Media Station

Warms	✓	Weighs	✓
Deaerates	✓	Dispenses	✓

### Preparation

Press START key.

- **Prefill**

Unit prefills system with sufficient medium to prime it.

- **Fill**

Unit fills the mixing chamber with the selected volume(s) of media =  $Vessel\ Volume \times Number\ of\ Vessels$ . The prewarming and degassing are performed at this stage.

### Dispense

Position the hand-held dispense nozzle over a waste container and press the START key.

- **Flush**

Unit flushes out and primes the dispense tube.

- **Dispense**

Position nozzle over first dissolution vessel and press ENTER. Unit dispenses appropriate volume into vessel. Repeat for remaining vessels. Unit returns to *Fill* Mode.

- **Print**

Unit prints out report.

Separate functions are available for *Emptying*, *Autowashing* and *Calibration*.



### Cat. No. Description

1322	"Dissomate" Media Preparation Station complete
1323	Printer (including cable)
1324	Validation Logbook
1510	Validation Tools





▲ Typical "Off-Line" System including Dissolution Tester DIS 6000, "Dissomate" Media Prep Station and "Dissofract" Sampling System

## AUTOMATION

### INTRODUCTION

The acceptance criteria quoted in the USP Chapters on Dissolution and Drug Release mean that a minimum of 6 and possibly up to 24 individual tests may be required per batch of formulation in order to meet pharmacopoeial requirements. Furthermore, the increasing use of extended and delayed-release preparations means that such tests may extend over 12, 24 hour or longer periods.

These demands, together with the rise in multi-point testing brought about by the need for *in vitro* - *in vivo* correlation mean that the dissolution or drug release test has now become one of the most common analyses employed in the pharmaceutical industry.

Manual dissolution testing is time consuming and labour intensive. As a result, an increasing number of laboratories are turning to automated tablet dissolution systems as a means of improving efficiency and reproducibility.

The advantages of automated systems are well documented, i.e. improved methodology, accuracy, reproducibility and throughput, better use of human resources, etc.

One should balance against these advantages the costs involved in setting up, programming, validating, operating and most importantly maintaining the automated system concerned, for example, in the event of breakdown.

Semi-automated systems that sample, filter, collect or UV/HPLC analyse can provide a valuable trade-off between manual and fully automated systems.

These can be classified into three categories:

#### 1. "OFF-LINE" SYSTEMS (COLLECT ONLY)

Normally comprises a sample collector containing test tubes or vials, a peristaltic or syringe pump to provide the motive force to transport the samples from the dissolution tester to the collector and a PC and interface box to control the system during operation.

The principle of operation is simple - medium from each of the dissolution vessels is circulated via an 8-line peristaltic pump through 8 switching valves prior to being returned to the dissolution vessel.

At user-defined intervals the valves operate, diverting a preset volume of sample into the sample collection lines, whereupon the samples are dispensed into either test tubes or open HPLC vials (or injected directly into sealed septum vials by means of an electrically operated vial piercing head provided for that purpose).

The pump is then reversed to clear the sampling lines prior to the next sampling interval, whereupon the operation is repeated. The whole operation is controlled and monitored by a PC. The exact status of the test at any given time can be determined from the software.

In the case of test tubes, the samples must be handled manually, for example by presenting them to the "sipper" accessory of a suitable spectrophotometer.

HPLC vials containing samples can be removed at any time and placed directly into an HPLC Autosampler.

This version is particularly useful where analytical techniques other than UV/Vis or HPLC are employed or where the samples require a degree of manipulation, for example, to be diluted or mixed with a reagent prior to analysis.

## AUTOMATION

### 2. "ON-LINE" DISSOLUTION SYSTEMS (UV/Vis)

Traditionally based on "continuous flow" methods, "on-line" dissolution systems incorporating UV/Vis analysis are understandably the most popular approach to automated dissolution testing.

Such systems are simple, clean, easy to set up and maintain.

In this technique, medium from each individual test vessel is circulated continuously through each of a series of flow cells (nominally 6-8) located in the cell compartment of a suitable UV/Vis Spectrophotometer by means of a peristaltic pump.

A cell changer mechanism moves each cell in turn into the light beam of the spectrophotometer and the absorbance of each solution is measured. Measurements are made at user-specified intervals. The whole system is controlled by an external PC whose software collects and analyses the results. For highly absorbing drug formulations, the systems can be supplied with 1, 2 or 5 mm pathlength flow cells in place of the standard 10 mm giving effective dilution ratios of 10:1, 5:1 and 2:1 respectively.

The choice of spectrophotometer will depend to a large extent on cost and the degree of sophistication required, i.e. single beam, double beam, etc.

Most UV/Vis continuous flow systems come "ready-to-run" and are particularly easy to use; the operator being guided throughout the performance of the test by a series of on-screen prompts.

### 3. "ON-LINE" DISSOLUTION SYSTEMS (HPLC)

Although UV is suitable for the analysis of the high proportion of drugs which exhibit active chromophore activity, in the case of certain dosage forms this approach is not practical. Furthermore, many formulations, for example, contain multiple components or excipients or coatings that interfere with UV analysis.

In these cases, **High Pressure Liquid Chromatography (HPLC)** may well provide the solution. The excellent specificity of HPLC makes it more sensitive than UV/Vis techniques for the analysis of sustained release products and of low dosage formulations.

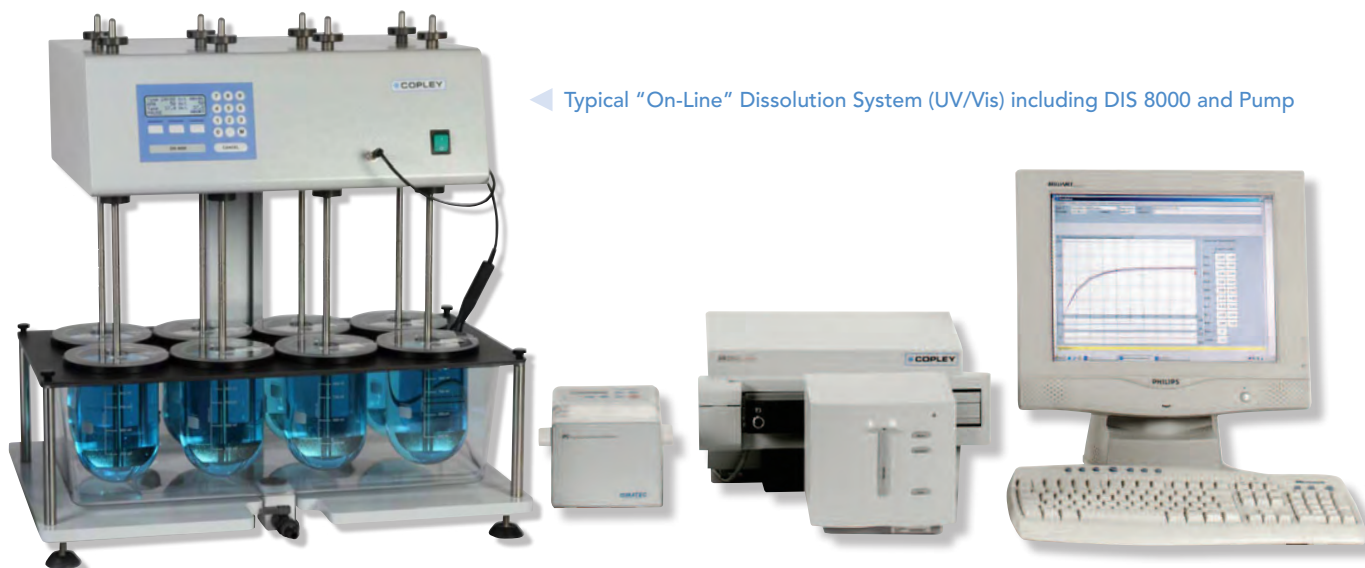
However, these techniques tend to bring a new set of problems. Many of these problems emanate from the fact that the samples are collected in multiples of 6, 7 or 8 simultaneously, whereas the HPLC detector will only accept samples one at a time.

Furthermore, the time taken to perform the test may prohibit the immediate "on-line" HPLC analysis of the collected samples, that is to say, there is insufficient time between the dissolution sampling intervals to allow for the analysis of 6-8 samples.

Modern "on-line" HPLC systems are specifically designed to meet this eventuality in so much that the sampling station acts simply as a temporary storage vehicle for the dissolution samples; the collected samples are then aspirated sequentially to the appropriate detector.

Such systems provide for maximum flexibility in the sample/inject control sequence allowing separate timing of sample withdrawal and analysis whilst optimising throughput.

**Our technical staff will be happy to discuss the various options available to you.**



◀ Typical "On-Line" Dissolution System (UV/Vis) including DIS 8000 and Pump



"Off-Line" Dissolution System comprising Dissolution Tester DIS 6000 and "Dissofract" Sampling System

## AUTOMATION - THE "DISSOFRACT"

### INTRODUCTION

The "Dissofract" is an "Off-Line" Dissolution Sampling System specifically designed to automatically remove samples from either 6 or 8 Dissolution Vessels at predetermined time intervals and deposit them in test tubes or HPLC vials for subsequent analysis (see No.1. on Page 38).

The system employs a series of 6 or 8 dedicated bidirectional small volume diaphragm pumps (one per line/vessel) to facilitate the *flush-sample-purge* functions.

As well as being extremely accurate (Volumetric Precision < 0.25 mL, typically 0.1 mL), the bidirectional pumps have a number of advantages over the more conventional peristaltic or syringe pumps employed in such systems, namely:

- First In/First Out (FIFO) principle
- Low dead volume
- Eliminates need for media replacement
- Low cross contamination
- Short sampling interval times (2 min)

The First In/First Out (FIFO) principle employed in the system is the same as that found in manual testing.

The low dead volumes employed in the system ensure that flush, sample and purge times are kept to a minimum whilst flush media recycling makes media replacement obsolete and dissolution calculations simple. Cross contamination is <1% at 2 minute sampling intervals.

The short interval time is particularly important when testing quick release formulations in so much that it allows sampling at intervals hitherto unachievable by more conventional methods.

The user interface is simple, functional and easy to use.

The unit is supplied as standard with two collection racks, one to accept 2 mL HPLC vials and the other 8 mL test tubes.

Each rack accommodates 10 rows of 8 lines and an additional row with test tubes for waste.

In order to eliminate any cross contamination, the standard sampling procedure is always *flush-sample-purge*.

The "Dissofract" has three main menus:

1. Start menu (the START button)
2. Method menu (the SET UP button)
3. Functions menu (the ENTER button)

### 1. START MENU

The Start menu is activated by pressing the START button.

This allows you to select and run a previously stored method.

The system first checks to ensure that the correct rack has been loaded into the collector to meet the method requirements.

It then checks to ensure that the sample lines are clear and initiates a *purge* if this is not the case.

The message now appears *Start Dissolution*. The sampling process is initiated by pressing the START button.

During sampling, the number of the next step, the elapsed time and the remaining time to the next step are indicated on the display.

At the end of the sampling process, a message appears on the display to indicate that the method has been completed and the sampling protocol automatically stored and printed.



## AUTOMATION - THE "DISSOFRACT"

### 2. METHOD MENU

The Method Menu is activated by pressing the SET UP button.

The Method entry comprises two parts, an initial part relating to the system parameters to be employed and a second part relating to the actual sampling procedure to be followed.

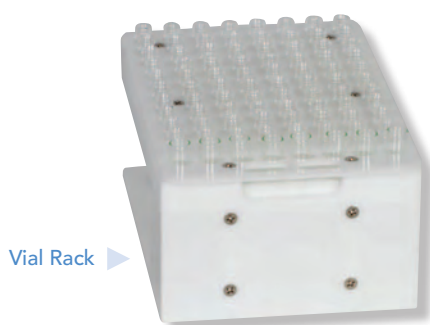
The **System Parameters** comprise as follows:

- *Rack Type*: Vials or Test Tubes
- *Lines*: No. of sample lines/vessels
- *Collection Flow Rate*: 1-15 mL/min
- *Flush Volume*: 1-8 mL
- *Purge Flow Rate*: 1-15 mL/min
- *Stagger Interval*: The required interval between lines when employing staggered starts (0-99 sec)
- *Double Sampling*: Samples into two rows at each step
- *UV/HPLC Transfer* (Option)
- *UV/HPLC Transfer Volume* (Option)
- *Rack Cooling/Heating Temperature*: (5-37 degrees C). Only available with Peltier option

Once the System Parameters have been entered correctly, the ENTER button is now pressed in order to set up the **Sampling Procedure** required:

- *Step*: Selects the Step Number.
- *Time - Seconds*: Time in seconds
- *Time - Minutes*: Time in minutes
- *Time - Hours*: Time in Hours  
Note: Maximum is 99:59:59
- *Collection Volume*:  
Vials - 0.1 - 1.8 mL in 0.1 digits  
Tubes - 0.5 - 8.0 mL in 0.5 digits

Press the START button.



Vial Rack ▶

### 3. FUNCTIONS MENU

The Functions Menu is activated by pressing the ENTER button.

This provides access to no less than 8 separate sub-menus:

#### 3.1 Print Menu

Used to print (a) Test (b) Performance and (c) Calibration Protocols as well as Method Data.

#### 3.2 Purge

Empty all lines back to the vessels/backflush.

#### 3.3 Flush

Perform a manual flush to flush out the system.

#### 3.4 Single Sample

Perform a single sample.

#### 3.5 Autowash

Regular cleaning procedure designed to keep the system in good working order.



▶ "Dissofract" open to illustrate sample needles and collection rack

#### 3.6 Drying

Used in conjunction with the Peltier Rack Cooling/Heating option to reduce condensate following cooling.

#### 3.7 Calibration Menu

Complete guidance on the IQ/OQ/PQ procedures required to validate and document your system.

#### 3.8 System Menu

Allows you to set up your system parameters in order to meet your own individual needs. The "Dissofract" measures 30 x 58 x 35 cm (w x d x h) and weighs 23 kg.

◀ "Dissofract" Sampling Station

### Cat. No. Description

1325	Set of 6 Resident Probes with Omnifit fitting
1326	"Dissofract" 6-Line Sampling System
1327	Additional Lines incl. Resident Probe - max. 8 (each)
1328	HPLC Vial Rack (spare)
1511	Test Tube Rack (spare)
1330	Printer (including USB cable)
1319	Validation Logbook
1512	Validation Tools

# Friability

## INTRODUCTION ▶▶▶

Friability is the tendency for a tablet to chip, crumble or break following compression. This tendency is normally confined to uncoated tablets and surfaces during handling or subsequent storage.

It can be caused by a number of factors including poor tablet design (too sharp edges), low moisture content, insufficient binder, etc.

For obvious reasons, tablets need to be hard enough such that they do not break up in the bottle but friable enough that they disintegrate in the gastrointestinal tract.

The basic apparatus comprises a drum and a motor capable of rotating the drum at 25 rpm. The standard friability drum has an inside diameter of 287 mm and a depth of 38 mm and is fitted with a curved baffle which subjects the tablets to be tested to a drop of 156 mm.

The sample (normally 10 tablets) to be tested is first weighed and then placed into the drum. The drum is then rotated 100 times, any loose dust from the sample removed and the sample re-weighed.

The friability of the sample is given in terms of % weight loss (loss in weight expressed as a percentage of the original sample weight). A maximum weight loss of not more than 1% is considered acceptable for most tablets.

Abrasion drums for carrying out tests into the attrition of tablets caused by the product rubbing together during transit are also available on request.

In some cases, such as coated tablets, granules and spheroids, it is not possible to determine the friability of the product using a conventional friability tester since the dosage form is simply too hard for meaningful weight losses to be generated.

The Friabimat described on Pages 45 and 46 is a new instrument that has been specifically designed to address this problem: it operates by oscillating the sample container at high frequencies causing the sample contents to collide with each other and/or the internal surfaces of the container.

All Copley Friability Testers feature:

- Simple, easy-to-use operation; ensures that the number of operations required to perform a test is kept to a minimum
- Full supporting documentation (including full IQ/OQ/PQ qualification documentation where applicable)

### Copley Philosophy

Robust	✓	Reliable	✓
Easy to use	✓	Compliant	✓

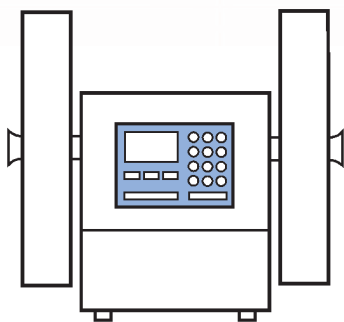


## FRIABILITY TESTER SERIES FR

Based on an original design by Roche, the friability tester has now become an accepted standard throughout the pharmaceutical industry for determining the resistance of uncoated tablets to the abrasion and shock experienced in manufacturing, packing and shipping operations.

Such stresses can lead to capping, chipping, abrasion or even breakage of the tablets.

Whilst the basic design remains unchanged, considerable advances have been made in terms of reliability and ease of use which have now been incorporated into current units.



### PHARMACOPOEIAL COMPLIANCE AND VALIDATION

In order to meet your individual requirements, Copley provide a three tier approach to regulatory compliance and validation:

- **Certificate of Compliance to USP/ Ph.Eur.:** Included with each unit. Written statement that the product, by design, complies with the current pharmacopoeial specifications.
- **Laser Numbering and Certification:** Identification and measurement of critical components (i.e. the friability drum) to provide **documented verification** of compliance with pharmacopoeial requirements. Available as an optional service.
- **IQ/OQ/PQ Qualification Documentation:** Comprehensive documentation to guide the user through the installation, operating and performance checks of the equipment, in its operating environment, using specified test protocols. It provides a comprehensive record of the suitability of the equipment to perform its specified task, to be created and archived. Available as an optional service.

Please see the ordering information for further details on our verification and IQ/OQ/PQ services.

### DESIGN AND CONSTRUCTION

Designed in accordance with the specifications as laid down in **Eur. Ph. Chapter 2.9.7** and **USP Chapter <1216>**, the FR Series forms the basis of our range of friability testers for **uncoated tablets**.

The standard FR Series operates at a **constant speed of 25 rpm +/- 1**.

It is available in two variants, that is to say, with either one (Model FR 1000) or two test drums (Model FR 2000).

Similar in construction to the fixed speed FR Series, the **Friability Series FRV** differs only in having **variable speed between 20 and 60 rpm**.

The speed is controlled via the membrane keypad in steps of 1 rpm. The variable speed allows the operator to subject the tablets under test to varying stresses and therefore determine an optimum for each type.

As on the FR Series, the duration of the test can be selected in either revolutions of the drum (1 - 999,999) or time (up to 99 hours, 59 minutes, 59 seconds).

During the test run, the nominal test duration and remaining test duration, in either revolutions or time, is indicated on the LCD screen, together with the selected speed.

The control of all models is provided by a membrane keypad linked to a 4-line 20 character back-lit LCD screen.



◀ Friability Tester FR 1000 (for Uncoated Tablets)



## FRIABILITY (UNCOATED TABLETS)

### DRUMS

The friability drum has been designed for testing the rolling and impact durability of tablets and has a single curved baffle which allows the tablets to be tested to rise and then drop through a distance of approx. 156 mm. Premature fracture or sign of wear at the edges indicates that such tablets may not withstand the rigours of transportation.

All friability drums are now fitted with an aperture such that **it is no longer necessary to remove and open the friability drum in order to load and remove the samples.** At the start of the test, the drum automatically revolves until the aperture(s) faces the operator so that the tablets can be loaded. On completion of the test, the drum stops and then reverses automatically emptying the contents of the drum into the waiting collection tray(s). All friability drums are completely **interchangeable**, i.e. they will fit either side of the tester.

Abrasion drums for carrying out tests into attrition are also available as an optional extra. The Abrasion drum comprises of a drum 20 cm diameter with a series of baffles which carry the tablets to a predetermined height before sliding off and reproduces the action of the tablets rubbing against each other during transport.

All testers can be equipped with a choice of either USP friability drums and/or abrasion test drums. Dual drum units can for example be fitted with one friability and one abrasion drum thus allowing comparisons to be made between the two parameters under identical test conditions.

Friability Tester  
FR 2000 with  
1 Friability Drum  
& 1 Abrasion Drum ▶



### OPERATION

Considerable attention was paid to the design of the FR and FRV series to ensure that the number of actions necessary to perform a test are kept to a minimum. Consequently, once the method (number of revolutions or time) has been selected and the test duration set, it is only necessary to press the START key to initiate the test.

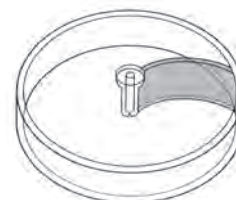
The standard test procedure is to take a sample of 10 tablets (a sample equivalent to 6.5 grams should be taken if the tablets weigh less than 650 mg), the weight of which has already been determined (W1). The tablets should be de-dusted prior to weighing.

The tablets are then placed into the test drum and allowed to rotate 100 times. The tablets are then re-weighed (W2) having first removed any accumulated dust and the results calculated in terms of % weight loss utilising the formula  $(W1-W2) \times 100$  divided by W1. In general, a maximum

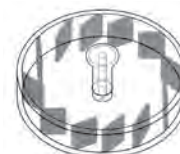
weight loss of not more than 1% is acceptable for most tablets. If necessary, repeat the test twice more basing the result on the mean of the three tests.

Dimensions (mm):  
FR 1000 / FRV 1000 =  
290 x 360 x 350 mm (w x d x h)

FR 2000 / FRV 2000 =  
342 x 360 x 350 mm (w x d x h)



Schematic of Friability Drum



Schematic of Abrasion Drum

### Cat. No. Description

1401	Friability Tester FR 1000 (Fixed Speed - 1 Drum)
1402	Friability Tester FR 2000 (Fixed Speed - 2 Drums)
1403	Friability Tester FRV 1000 (Variable Speed - 1 Drum)
1404	Friability Tester FRV 2000 (Variable Speed - 2 Drums)
1405	Extra for Numbering & Certification (per Drum)
1406	IQ/OQ/PQ Documentation Pack
1407	Abrasion Drum (Optional extra)
1408	Friability Drum (Spare)
1409	Device for angling friability tester at 10 degrees
1410	Qualification Tools (Certified Stopwatch, Tachometer and Rule)

## FRIABILITY (GRANULES AND SPHEROIDS)

### INTRODUCTION

In many cases, such as with hard coated and uncoated tablets, granules and spheroids, it is impossible to determine the friability of the dosage form using a conventional tablet friability tester (based on the Roche friability drum) even if the test time is extended, simply because the resistance is such that no measurable attrition is obtained. The energy imparted by the friability tester is just not sufficient to generate quantifiable changes in surface mass.

The **Friabimat SA-400** is a new instrument specifically designed to address this particular problem by offering a method of friability measurement suitable for the hardest and most robust of solid dosage forms.

### DESIGN AND CONSTRUCTION

The Friabimat was originally designed as a method to effectively determine (under precisely defined, controlled and reproducible conditions) the friability of hard pellets and granules prior to further processing, for example, drum coating.

The instrument is particularly useful in detecting variations in mechanical properties between different formulations and batches and is a convenient tool in both research and development and quality control applications.

Following review, the instrument has now been included in the 7th edition of the European Pharmacopoeia under **Chapter No. 2.9.41 Friability of Granules and Spheroids**.

This describes the Friabimat under Method B Oscillating Apparatus 2.9.41.-2.

The Friabimat's range of application has since been extended to include hard coated and uncoated tablets and other dosage forms which fall outside the scope of the standard friability tester.

For the purpose of the test, the sample to be tested is confined within a standard 105 mL glass bottle (measuring approx. 85 mm high x 49 mm i.d. with twist-off cap) which serves as the sample container.

During operation, this sample container is secured by means of a

spring clip to the sample container holder horizontally mounted on the end of an oscillating arm having an arc of 37 degrees at a radius of 152 mm from the centre of oscillation.

The abrasive action is generated by the horizontal shaking movement of the oscillating arm which causes the samples to rub against and collide with each other and/or the internal surfaces of the sample container.

The intensity of the abrasive action and the duration of the test can be adjusted via the controls mounted on the front panel between 0 and 400 oscillations per minute and 0 and 9999 seconds respectively.

This enables the user to optimise the test conditions applicable to each formulation and reproduce it at will.

Average test times are between 2 and 4 minutes. The combination of these short test run times, together with the use of inexpensive, commercially available glass bottles as the sample container, means that it is possible to carry out tests economically in batches, as opposed to singularly on an infrequent basis.

The Friabimat measures 440 x 300 x 220 mm (w x d x h) and weighs 13 kg.



◀ Friabimat (with Safety Lid Open)



▲ Friabimat (with Safety Lid Closed)

## FRIABIMAT

### OPERATION

Adjust the number of oscillations to the desired frequency by adjusting the thumb wheel switches on the rotary speed adjuster mounted on the front panel to the appropriate setting (between 0 and 400 oscillations per minute).

Now set the test duration using the push button timer (between 0 and 9999 seconds).

Note: Shake for about 240 seconds at approx. 400 oscillations per minute for hard dosage forms, or, for example, 120 seconds at 140 oscillations per minute for soft dose forms. Optimise these settings according to the dosage form concerned.

The Friabimat is now ready for operation.

Take a sample of the formulation to be tested and remove any fine particles present in the sample using a 355 micron sieve.

Weigh out approx. 10 grams (m1) of the product into a sample container ensuring that the twist-off cap is well secured. Now place the sample container into the spring clip fastening on the Friabimat provided, to secure it and close the safety lid.

Start the test by pressing the appropriate key on the timer. The unit will switch off automatically on expiration of the preset time. The time remaining to the end of the test is displayed on the timer during operation.

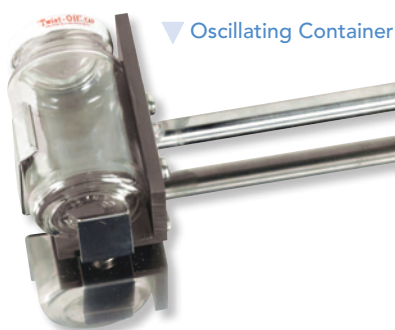
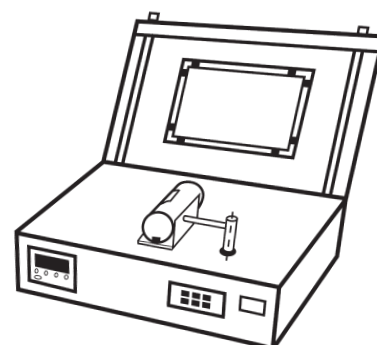
Note: The Friabimat is fitted with a **safety interlock** which automatically pauses operation if the safety cover is opened during a test. The test can be re-started once again by simply closing the lid.

At the end of the test, sieve as at the start of the test and re-weigh (m2). Perform three tests and calculate the mean value.

Express the results in terms of % weight loss using the formula  $(m1-m2) \times 100$  divided by m1.

### KEY FEATURES

- Quantifiable friability of hard tablets, granules and pellets
- Horizontal shaking action
- Programmable shaking rate (0-400 oscillations per minute)
- Programmable test times (0-9999 seconds)
- Stainless steel case for production environments
- Clear acrylic lid with magnetic interlock for safe operation
- Interchangeable glass sample containers for rapid throughput
- Oscillation frequency verification certificate (optional)



▼ Oscillating Container

### Cat. No. Description

- |      |  |
|------|--|
| 1450 | Friabimat Model SA-400 including 1 Glass Container |
| 1451 | Oscillation Frequency Verification Chart           |
| 1452 | Pack of 100 Spare Glass Containers                 |



# Hardness

## INTRODUCTION ▶▶▶

Copley Philosophy			
Robust	✓	Reliable	✓
Easy to use	✓	Compliant	✓

Modern day tablets come in a variety of forms – uncoated, coated, dispersible, effervescent, gastro-resistant, modified release, soluble, rapidly disintegrating, slowly disintegrating, etc. Each type places different demands on the formulation concerned.

Manufacturing processes such as coating, printing, packaging and rigours of handling and transport place additional demands on the mechanical integrity of the finished product.

Together with friability testing, the testing of a tablet's **hardness (or more correctly breaking force)** plays a vital role in both product development and subsequent quality control.

In this test method, the tablet is placed between two platens (jaws), one of which is attached to a load cell and the other to a motor which provides the mechanical drive. During testing, the motorised jaw drives forward pressing the tablet against the fixed jaw until such time as the tablet breaks whereupon the motorised jaw retracts and the load required to break the tablet is recorded.

High hardness values may indicate, for example, increased disintegration times and reduced dissolution values. On the other hand, if hardness is too low then friability, and hence % defective, may well be too high. By exploiting the correlation between hardness, disintegration, dissolution, friability, percentage defective and weight variation, the various parameters can be manipulated to produce a dosage form with optimum characteristics.

Significant advances have been made in the field of tablet hardness testing in recent years. Copley Scientific offers a range of semi and fully automatic electronic testers incorporating these advances and varying in sophistication from simple hand-held units for use on the production floor to fully automatic units incorporating print-out and data input/output facilities.

All Copley Hardness Testers feature:

- Simple, easy to use operation ensures that the number of operations required to perform a test is kept to a minimum
- Full supporting documentation (including full IQ/OQ/PQ qualification documentation where applicable)



### Notes on the Terminology and Units of Measurement employed in Tablet Hardness Testing

Traditionally, the **breaking force** of tablets has always been referred to as hardness. However, as the United States Pharmacopoeia (USP) points out, this term is really a misnomer since **hardness** refers to the resistance of a surface to penetration or indentation by a probe, e.g. penetrometer.

For this reason, in its Chapter <1217>, USP refers to **Tablet Breaking Force** not hardness describing the breaking force of a tablet as being the force required to cause it to fail (i.e. break) in a specific plane.

The European Pharmacopoeia (Ph.Eur.), on the other hand, in its Chapter 2.9.8 uses the term **crushing strength**. Purists would, no doubt, argue that, in many cases, the tablet is not actually crushed, merely fractured, and that the term **strength** implies tensile strength as opposed to compressive load. Suffice it to say, all Copley Testers comply with the relevant Pharmacopoeia irrespective of the terminology employed.

The units of force normally employed to quantify breaking force are Kiloponds or Newtons.

Comparative values for these are as follows:

**1 kilopond (kp) = 1 kilogram-force (kgf) = 9.80665 Newtons (N)**

A kilopond is the force exerted by a mass of one kilogram in earth's gravity.



Tablet Hardness Tester Model TH3 ▲

## TABLET HARDNESS TESTER TH3

A portable semi-automatic electronic tester with LCD display designed to accept tablets up to 30 mm in diameter - ideal for the tablet production area as a quick check as to compression force settings.

The tablet is placed on the test platform between the test jaw and the load cell plunger.

A multi-turn, low-friction hand-wheel similar to the type used on machine tools, is used to apply load to the tablet until it fractures. The resulting breaking force is displayed on the LCD display in either newtons (N), grams (g), pounds (lbs) or ounces (oz).

To test another tablet, simply press <Zero> to zero the load cell and proceed as above.

Two models are available, the TH3/200 having a range of 200 Newtons +/- 0.04N or the TH3/500 having a range of 500 Newtons +/- 0.1 N respectively.

The TH3 is provided with RS232, Mitutoyo and analogue data output facilities as standard. All displayed readings can be transmitted to peripheral devices, for example, a PC or printer, by pressing the <TXD> key. Alternatively, a PC can request data from the unit by sending a <?> character via the RS232 interface.

The unit measures 450 x 70 x 80 mm and weighs approx. 2 kig and can be operated in either mains or battery modes. It includes a calibration certificate and mains adaptor/charger as standard.

The instrument performs an automatic self test (zero calibration routine) on switch on.



### Cat. No. Description

7801	Tablet Hardness Tester Model TH3/200
7802	Tablet Hardness Tester Model TH3/500
7803	Re-Calibration Certificate
7804	Calibration Verification Hanger & Weight

## TABLET HARDNESS TESTER TBF 1000

The Tablet Hardness Tester Model TBF 1000 combines the economy of a simple easy to use tester with the performance and accuracy of microprocessor-controlled data collection.

It was designed in accordance with the specifications as laid down in **Ph.Eur. Chapter 2.9.8 Resistance to crushing of tablets and USP Chapter <1217> Tablet Breaking Force.**

Foremost in the design specification were those features that you, the user, identified as being essential to the **"ideal"** hardness tester.

You told us, for example, that the unit must be as **compact** as possible such that it could be used in the confines of the tablet press booth.

Measuring only 283 mm x 235 mm x 160 mm (w x d x h) (including **in-built printer** and **optional keyboard**) and weighing 8.5 kg, the TBF 1000 has the smallest footprint of any hardness tester of its type on the market, making it ideal for this purpose.

You told us that the unit should be **simple to operate** - the TBF 1000 employs just three touch sensitive keys located on the front panel to set up, perform a test and provide a print-out of the results, namely <New Size>, <Test> and <Stats>.

At the same time, you asked for a number of **advanced and sophisticated features** - so, we provided them plus a small QWERTY keyboard located in the base of the instrument to access them.

The 4-line on-screen menu leads you through the measuring process. Attach a balance and/or thickness gauge and the TBF 1000 will collect **weight and thickness data** as well.

On completion of the test, the TBF 1000 automatically prints out the results and **statistical analysis** including time, date, min, max, mean and standard deviation together with the batch number and size.

Finally, you asked us whether it would be possible to **output data** to an external PC or printer - so, on the back of the unit, in addition to the interfaces for balance and thickness gauge, we have provided two further ports, one RS232 and one USB, to satisfy this request.

### PRINCIPLES OF OPERATION

The principle of measurement is based on proven electronic load cell technology used in conjunction with a mechanical drive and electronic signal processing.

In practice, the tablet is placed on a platform between two precision ground platens (jaws), one of which is attached to the load cell and the other to a motor which provides the mechanical drive.

During testing, the motorised jaw drives forward pressing the tablet against the fixed jaw until such time as the tablet fractures whereupon the motorised jaw retracts and the change in the resistance of the strain gauge employed on the load cell (the breaking force) is measured.

The pressure to the tablet can be applied in two ways. Most modern testers including the TBF 1000 work on the principle of **constant speed** (that is to say, the rate of jaw movement). Other units, mainly earlier models, monitor the rate at which the compressive force is applied i.e. **constant loading**.

Irrespective of which method is employed, it is essential that the uniformity and rate of loading be constant in order to assure comparability of results.

Tab No.	Weight (mg)	Thick (mm)	Hard (kg)
1	379	3.25	5.19
2	379	3.25	5.31
3	380	3.24	5.54
4	380	3.24	5.47
5	379	3.26	5.02
6	378	3.25	4.98
7	381	3.25	5.28
8	380	3.26	5.05
9	379	3.23	4.92
10	380	3.25	5.30

BATCH STATISTICS	
Batch No.	1
Batch Size:	10
Min:	4.92 kg
Max:	5.54 kg
Mean:	5.21 kg
Std. Dev:	0.21
Time:	HH:MM DAY DD/MM/YY
Calibration No:	00004

Typical Printout ▲

Tablet Debris  
Collection Tray ▶







Tablet Hardness Tester TBF 1000 ▲

TBF 1000 (with Keyboard Option) ►

## TABLET HARDNESS TESTER TBF 1000

In general, the lower the speed or load, the more consistent the results. The **US Pharmacopoeia**, for example, suggests a constant platen movement of less than 3 mm per second.

The TBF 1000 offers a choice of speeds between 0.06 and 0.5 mm per second with a default setting at 0.1 mm per second, all of which exceed the pharmacopoeial requirement by a considerable margin.

The standard TBF 1000 has a measuring range of **0 - 520 Newtons (+/- 0.1N)**. Other ranges, for example 50 N and 1000 N are available on request - please consult our technical staff for further details.

The unit will accept tablets up to **36 mm in diameter**.

Results can be expressed in either **kilograms-force (kgf), kiloponds (kp), newtons (N) or pounds (lbs)**.

The TBF 1000 has a **throughput** of approx. 5-8 tablets per minute dependent on the hardness and diameter of the tablets under test.

The TBF 1000 is also available with a **polished stainless steel case**, as an option, for use in a tablet production environment. Please see ordering information for details.

### OPERATION

#### 1. Setting up for a new tablet

Press the <New Size> key - the motorised jaw will retract allowing the operator to insert the new tablet between the jaws before advancing once again to press the tablet lightly against the fixed jaw.

This contact is detected by the load cell electronics which in turn instructs the motorised jaw to retract to the Test position approx. 5 mm wider than that of the diameter of the tablet.

The **diameter** of the new tablet is printed out on the in-built printer.

The unit is now ready to carry out a test.

#### 2. Carrying out a test

Place a tablet on the test platform, lower the guard and press <Test> twice. The moving jaw will fast forward (2 mm per second) until it reaches a position approx. 0.2 mm from the tablet and then change to the test speed (default 0.1 mm per second).

The increase in load once the moving jaw reaches the tablet is displayed on the LCD display together with the tablet count, the time and date.

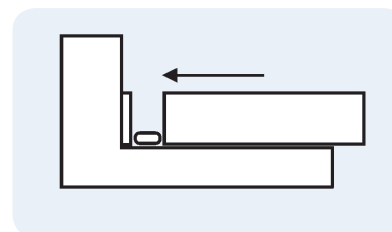
Tablet fracture is detected automatically - once detected, the result is printed out on the printer and the moving jaw retracts back to the Test position ready for the next sample.

Testing of the next sample can be initiated in two ways depending on the set-up mode (a) by pressing the <Test> key or (b) by lowering the guard.

The tablet testing position is arranged for horizontal loading and incorporates a removable tray in order to dispose of any **tablet debris**.

**3. End of Batch - Statistical Analysis**  
**Ph.Eur.** and **USP** recommend that 10 and at least 6 samples are tested respectively.

At the end of the test, to initiate the print-out and re-zero the tablet count, press <Stats>. A further batch of tablets can now be tested.





Rear Panel ▲



Calibration ►

## TABLET HARDNESS TESTER TBF 1000

### ADVANCED FEATURES

The TBF 1000 has been specifically designed such that all basic day-to-day operations can be performed using the four touch sensitive keys located on the front panel. Other features like the safety guard system which prohibits operation unless closed, the tablet debris collection tray, the **integral 30 column printer** and keyboard drawer are included as standard.

This outward simplicity disguises the many special sophisticated and advanced features available to the user via the setup menu which may be accessed through the optional keyboard. This feature is passcode protected to prevent unauthorised changes to operational settings.

In the original design brief for the TBF 1000, considerable emphasis was placed on providing the user with the ability to configure the unit to their own specific needs.

This emphasis is reflected in the setup menu. In addition to basic settings such as time and date, units (kgf, kp, N or lb), test speed (4, 6, 10, 16 or 30 mm/min), PC interface (RS232 or USB) and LCD backlight functions, the user can also configure the way in which the unit actually operates: the print format, the way in which the unit interfaces with other peripherals and the calibration of the instrument.

Operational settings include the ability to change the way in which batches are counted and incremented, whether a test is instigated via the <Test> key or simply closing the safety guard and the fracture detect percentage, a particularly useful feature for soft crumbly or extra hard tablets.

During a test, the load cell constantly monitors the increasing force applied to the tablet. The breaking point of the tablet is said to have been reached when the force falls to a set % (the fracture detect percentage) of the maximum (peak) load reached during that particular test. The default setting for this percentage is 70% - it can however be adjusted if circumstances dictate between 30 and 90%.

Print format settings include options available to enable or disable start-up messages, the print-out of individual tablet results and diameter print-out, together with the provision to enter product names and operator identities (requires optional keyboard).

Peripheral and calibration settings allow the user to connect the hardness tester to a balance and/or a micrometer for measuring thickness and to calibrate the instrument, respectively.

### SYSTEM SUITABILITY

The TBF 1000 incorporates an automatic load check routine that runs automatically every time the unit is switched on.

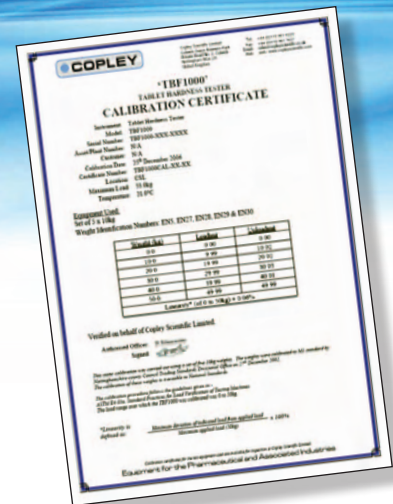
This routine imposes a simulated load of known proportions. The simulated load and the difference between this and the value stored at the last full calibration are displayed on the LCD.

A difference of > 0.1 kg, for example, would suggest a potential problem and the need for recalibration (see below).

### CALIBRATION

All tablet hardness testers should be calibrated on a periodic basis, for example, monthly or quarterly.

Calibration on the TBF 1000 can be carried out "in-house" and takes only a few minutes using the calibration rig provided for this purpose. It is based on a "static" calibration technique using calibrated weights.



Calibration Certificate ▲

## ▲ Weight and Thickness Measurement

**TABLET HARDNESS TESTER TBF 1000**

The user is guided through the passcode protected calibration process by a series of prompts from the in-built software accessible from the setup menu.

A full report is printed out at the end of the calibration process.

An individual calibration number is generated on each occasion the unit is calibrated and reiterated on subsequent test printouts - this ensures that any test printout is traceable to a specific calibration certificate.

**IQ/OQ/PQ QUALIFICATION DOCUMENTATION**

Analytical Instrument Qualification is no doubt an essential element of your quality control procedures. The following documentation is available in helping you to meet these obligations:

- **Certificate of Compliance to USP/Ph.Eur.:** Included with each unit. Written statement that the product, by design, complies with the current pharmacopoeial specifications.
- **IQ/OQ/PQ Qualification Documentation:** (option)  
Comprehensive documentation to guide the user through the installation, operating and performance checks of the

equipment, in its operating environment, using specified test protocols. It provides a comprehensive record of the suitability of the equipment to perform its specified task, to be completed and archived.

**WEIGHT & THICKNESS MEASUREMENT**

The versatility of the TBF 1000 does not end with the measurement of hardness - simply add a balance and/or a Mitutoyo micrometer for measuring thickness and you have a complete system for measuring the hardness, weight and thickness of tablets with the same capabilities as many of the more sophisticated systems that are commercially available.

A list of compatible balances (by make and model) may be found in the setup menu - please consult our technical staff for further details.

Weight and thickness measurements are conducted in a similar manner to that of hardness (see section on OPERATION on Page 50).

If, for example, both weight and thickness are enabled, then at the start of the test the LCD display will show Weight - the operator should then place the tablet on the balance, wait for the weight to stabilise and then press <Test>. The weight of the tablet will now be displayed and the LCD will show Thickness to request a thickness measurement. Remove the tablet from the balance pan, place it in the micrometer and press <Test>. Repeat the exercise for hardness.

At the end of the individual tests, the results relating to all three parameters are printed out on the printer.

**Cat. No. Description**

2501	Tablet Hardness Tester Model TBF 1000
2501A	Tablet Hardness Tester TBF 1000 with polished stainless steel case
2502	Compact Keyboard (optional)
2503	Calibration Rig
2504	Set of Calibration Weights for TBF 1000 (4 x 10 kg, 2 x 5 kg)
2510	Other Qualification Tools (Certified Stopwatch, Gauge Blocks)
2505	IQ/OQ/PQ Documentation Pack
2506	Pack of 10 Paper Rolls
2511	Re-Calibration Certificate
2507	Sartorius Balance Model CPA324S including cable
2508	Mitutoyo Thickness Measuring Gauge



# Powders

## INTRODUCTION ▶▶▶



The widespread use of powders in the pharmaceutical industry has led to a proliferation of test methods for measuring **powder flow** and **density**.

The new harmonised chapters in the Pharmacopoeias on Powder Flow (USP Chapter <1174> and Ph.Eur. Chapter 2.9.36) list four well-defined methods for powder testing, aimed at trying to bring about some degree of standardisation within the test methodology:

- Flow through an orifice
- Angle of Repose
- Shear Cell
- Compressibility Index and Hausner Ratio

The new Flowability Tester BEP2 from Copley Scientific provides a range of options for testing pharmaceutical powders including three of the four methods quoted in the Pharmacopoeias – flow through an orifice, angle of repose and shear cell – in a single, cost effective unit.

The BEP2 is an easy to use, small footprint instrument with interchangeable cylinder, funnel, angle of repose and shear cell attachments.

In addition to providing the test methods detailed in USP <1174> and Ph.Eur. 2.9.36, the unit can also be used to carry out tests described in the separate European Pharmacopoeia Chapter on Flowability 2.9.16.

An optional balance/timer simplifies time vs mass testing.

For compressibility index and Hausner ratio testing, the fourth specified methodology, Copley Scientific offers a series of tapped density testers and the bulk density tester (Scott Volumeter), detailed monographs for which feature in USP Chapter <616> and Ph.Eur. Chapter 2.9.15.

### Copley Philosophy

Robust	✓	Reliable	✓
Easy to use	✓	Compliant	✓



BEP2 with  
Cylinder  
Attachment

## FLOWABILITY TESTER MODEL BEP2

### INTRODUCTION

The Flowability Tester BEP2 has been specifically designed to address the specifications in and comments raised by the **European Pharmacopoeia Chapter 2.9.36** and **US Pharmacopoeia Chapter <1174>** on **Powder Flow**.

The widespread use of powders in the pharmaceutical industry has led to a proliferation of test methods for measuring powder flow.

The new harmonised chapters in the Pharmacopoeias on Powder Flow (USP Chapter <1174> and Ph.Eur. Chapter 2.9.36) list four well-defined methods for powder testing aimed at trying to bring about some degree of standardisation within the existing test methodology:

- Flow through an orifice
- Angle of Repose
- Shear Cell
- Compressibility Index and Hausner Ratio

The new Flowability Tester BEP2 from Copley Scientific provides a range of options for testing pharmaceutical powders including three of the four methods quoted in the Pharmacopoeias – flow through an orifice, angle of repose and shear cell – in a single, cost effective unit. In addition to providing the test methods detailed in the harmonised pharmacopoeia chapters, it is also suitable for flowability testing according to Ph.Eur. 2.9.16. An optional balance/timer simplifies time vs mass testing.

The BEP2 is an easy to use, small footprint instrument with interchangeable cylinder, funnel, angle-of-repose and shear cell attachments. A description of each attachment can be found below.



Interchangeable Disks

### CYLINDER ATTACHMENT (FLOW THROUGH AN ORIFICE)

Measuring the ability and the time taken for a powder to flow through an orifice of known size is a useful method of quantifying powder flow.

At the same time, it is important to recognise that the ability of the powder to flow through the orifice can be affected by factors other than the characteristics of the powder itself. Such factors include the shape and material employed in the construction of the powder container, the diameter and height of the powder bed and the shape of the orifice concerned.

The Pharmacopoeias suggest that the use of a circular cylinder as the powder container encourages powder over powder flow as opposed to powder over container wall, minimising any effect brought about by differences in the material used to produce the powder container.

As the title suggests, this technique is only suitable for materials that flow – **not** cohesive materials. Assuming this to be the case, then the Pharmacopoeias suggests that providing:

- a) The height of the powder bed (the "head") is much greater than that of the orifice
- b) The diameter of the opening is greater than 6 times the diameter of the particles and
- c) The diameter of the cylinder is greater than 2 times the diameter of the opening

then any difference in results brought about by either powder bed or orifice can be considered negligible.

The cylinder attachment has been designed to take all of these factors into account.

The **cylinder attachment** comprises a stainless steel cylinder measuring 76 mm long x 57 mm i.d. and having a capacity of 200 mL. The bottom of the cylinder is sealed with a collar designed to accept disks having various orifice diameters.

The attachment comes complete with a set of 20 interchangeable stainless steel disks each containing a precision drilled hole in the centre covering the following sizes: 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34 and 36 mm. A shutter covers the hole during filling. This can be smoothly removed without vibration to allow the powder to flow through the selected hole.

The cylinder attachment can be used in two ways (a) to carry out **quantitative flowability tests** based on mass vs time or (b) to determine the **intrinsic flowability** of the powder concerned in the form of a flowability index based on comparative measurements.

### a) Mass vs Time

Operation is extremely simple.

Select a disk having the appropriate orifice size for the powder concerned (start with 18 mm and work up or down accordingly if size unknown) and secure it to the bottom of the cylinder using the collar provided for this purpose. Adjust the shutter so that the hole in the bottom of the cylinder nozzle is covered.

Introduce the test sample (100 grams unless inappropriate) into the flow cylinder. Now open the shutter and measure the time required for the entire sample to flow out of the funnel using a suitable stopwatch.

Carry out three measurements: express the flow rate results in terms of mass vs time i.e. grams per second.

BEP2 with Cylinder and Balance/Timer Attachments ▶



### b) Intrinsic Flowability

The cylinder attachment provides a simple and repeatable technique for the determination of powder flow characteristics. As such, it takes into account most of the physical characteristics affecting flowability such as particle size, shape, fines, unit surface, actual and bulk density, porosity, settling, and electrostatic charge without a direct quantitative measurement of any of these parameters.

The determination of Intrinsic Flowability is based upon the ability of a powder to fall freely through a hole in a plate. The results are expressed in terms of a Flowability Index given as the diameter (in mm) of the smallest hole the powder falls through freely on three successive attempts.

For new formulations, it is recommended to start with the 18 mm disk. Once the disk is in position and with the shutter in the closed position, a 50 gram sample is introduced into the test cylinder using the funnel provided for this purpose.

After waiting for approx. 30 seconds to allow for any possible formulation of flocculi, the shutter is opened. The test is positive if the powder flows through the hole leaving a residue in the form of an upside-down truncated cone. A powder that flocculates in bulk will on the other hand fall abruptly forming a cylindrical cavity. In this instance, as is the case if the powder refuses to flow through the hole, the test is adjudged to be negative.

In the case of a positive result, the test must be repeated with smaller and smaller disk holes until the result is negative. For negative results, increase the size of the disc hole until the test is positive.

The Flowability Index has been used successfully to establish dry powder characteristics prior to setting up filling equipment such as capsule fillers, tablet presses and dry packaging

machines thus avoiding high coefficients of variation. It can also be used in purchasing specifications to ensure consistent flow characteristics of materials received as well as general quality control procedures.

Anti-static Grounding Kit for BEP2 ▶







◀ BEP2 with Funnel and Balance/Timer Attachment

BEP2 with Funnel and Angle of Repose Attachment ▶

▲ BEP2 with Funnel Attachment

## FLOWABILITY TESTER MODEL BEP2

### FUNNEL ATTACHMENT (FLOW THROUGH AN ORIFICE)

In certain instances where, for example, the purpose of the test is to simulate flow in a hopper or other production situation, it may be preferable to use a funnel in the form of a truncated cone.

The **funnel attachment** is based on the stainless steel flow funnel and nozzle described in the European Pharmacopoeia Chapter 2.9.16 for Flowability. It has a capacity of approx. 400 mL.

The attachment is supplied with three nozzles corresponding to aperture sizes of 10, 15 and 25 mm respectively. Both funnel and nozzles are manufactured from pharmaceutical grade 316 stainless steel. The nozzles can be quickly interchanged using the connecting nut provided for that purpose.

The opening at the bottom of the funnel is secured by means of an adjustable shutter which is closed during the filling operation. The test is carried out in a similar manner to that of Method A (Mass vs Time) of the cylinder attachment (see page 55).

Manually Operated Stirrer ▶

### BALANCE / TIMER ATTACHMENT

By adding a balance and a timer linked to a microswitch located on the shutter mechanism, it is now possible to conduct time vs mass tests using either cylinder or funnel methods without the need for an external stopwatch.

The balance/timer option allows the use of the unit in 4 modes:

- Determination of the flow time of a predetermined sample weight
- Determination of the flow time of a predetermined sample volume
- Determination of the weight of sample in a predetermined time
- Plot of time against sample weight (weight/time)



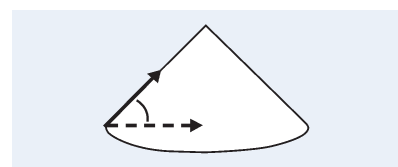
### ANGLE OF REPOSE ATTACHMENT

The angle of repose is the angle (relative to the horizontal base) of the conical pile produced when a granular material is poured onto a horizontal surface. It is related to the density, surface area and coefficient of friction of the material concerned.

The **angle of repose attachment** comprises a 100 mm diameter circular test platform together with a digital height gauge, having a range of 0-300 mm and an accuracy of 0.03 mm. The test platform has a protruding outer lip in order to retain a layer of powder upon which the cone is formed. Surplus powder is collected in a tray below the test platform.

For this particular test, the funnel is normally equipped with a special 10 mm i.d. nozzle mounted 75 mm above the test platform. If necessary, the contents may be stirred to assist in the powder flow (see left).

The tangent of the angle of repose (in degrees) can be determined by reading off the height of the powder cone in mm from the digital display of the height gauge and dividing it by 50. The Table on Page 57 indicates the flow properties associated with corresponding Angles of Repose.





BEP2 with  
Funnel and  
Shear Cell  
Attachment

Shear Cell

## FLOWABILITY TESTER MODEL BEP2

### SHEAR CELL ATTACHMENT

Shear cell methodology is widely used in the pharmaceutical industry to determine the flow properties of fine grained powders and bulk solids and how they will behave in bins, hoppers, feeders and other handling equipment.

The ability of a material to flow through such devices is dependent on the bulk density of the material and its shear strength.

The **Shear Cell** employed with the BEP2 comprises a cylindrical chamber (manufactured from clear acrylic) measuring 140 mm i.d. and 32.5 mm high and capable of holding 500 ml of the sample. In the floor of the chamber, there is a 100 mm hole which can be sealed during the consolidation process using an acrylic disk provided for this purpose.

The test is based on measuring the force required to shear a circular disk through a prepared sample of bulk material. It comprises two stages (a) sample consolidation (bulk density measurement) and (b) failure inducement (shear strength).

The sample is first subjected to a consolidated load such that the

bulk density of the material can be determined – ideally, this should be similar to the loads experienced by the material in practice. Alternatively, a standard reference can be employed e.g. 10 kilos.

The acrylic disc sealing the bottom of the test cell is now removed and load steadily applied to the test sample by

pouring sand through a funnel into a container of appropriate proportions resting on top of the sample until such time as the sample fails (shears).

The results should be expressed in terms of bulk density, shear strength and if appropriate, estimate of device outlet required.

### Flow Properties & Angle of Repose

Flow Property	Angle of Repose
Excellent	25 - 30
Good	31 - 35
Fair - aid not needed	36 - 40
Passable - may hang up	41 - 45
Poor - must agitate, vibrate	46 - 55
Very poor	56 - 65
Very, very poor	> 66

### Cat. No. Description

1650	Flowability Tester Model BEP2 Stand and Upright
1651	Cylinder Attachment (Flow through an Orifice)
1652	Funnel Attachment (Flow through an Orifice)
1656	Manually operated Stirrer for Funnel Attachment
1653	Balance/Timer Attachment
1654	Angle of Repose Attachment*
1655	Shear Cell Attachment
1657	Anti-static Grounding Kit for BEP2

\* Note: Requires the Funnel Attachment Cat.No.1652 to operate.



▲ 18-mesh and 10-mesh screen filter inserts

## BULK DENSITY TESTER

### THE SCOTT VOLUMETER

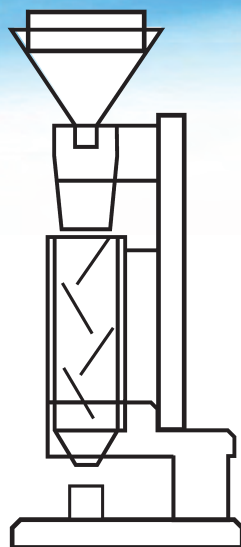
The bulk density of powders can be extremely difficult to measure since the slightest disturbance may result in a change in the results.

This is the result of the relationship between the particles that constitute the powder bulk. This same relationship affects the ability of the powder to flow.

The **bulk density** of a powder may be described as the density of the powder "as poured" into a measuring vessel.

**Tapped density**, on the other hand, is the density attained after "tamping down": this is normally measured using an instrument that lifts and then drops a measuring cylinder containing the powder through a fixed distance (see the Tapped Density Tester described on the next page).

A comparison of the bulk and tapped densities of powders can give an indication of the type of interaction present between the various particles making up the powder mass and hence provide an index of powder flowability (see **Compressibility Index** and **Hausner Ratio** described on the next page).



Schematic of Scott Volumeter ▲

The **Bulk Density Tester (Scott Volumeter)** is described in **USP Chapter <616> Method 2** and is designed for measuring the **bulk density of fine powders** and similar products.

### CONSTRUCTION

The apparatus comprises:

- A stainless steel top funnel having an integral 18-mesh stainless steel screen
- A baffle box containing four glass baffle plates over which the powder slides and bounces as it passes
- A stainless steel bottom funnel to direct the powder into the receiving cup
- A cylindrical receiving cup having a capacity of 25 +/- 0.05 mL
- A stand to support the apparatus and its constituent parts.

An alternative funnel having an integral 10-mesh screen is available on request.



Scott Volumeter ▲

### MODE OF OPERATION

- 1) Weigh the empty receiving cup and place it in position
- 2) Slowly pour the powder through the upper funnel until it overflows the receiving cup. (Note: Use a minimum of 35 cm<sup>3</sup>)
- 3) Level the top of the receiving cup with a spatula such that it is completely full being careful not to compress or shake the powder
- 4) Re-weigh the receiving cup and its contents
- 5) Calculate the bulk density in terms of grams per mL by dividing the weight of the powder by the volume of the cup

### Cat. No. Description

6301	Scott Volumeter with 18-mesh screen (USP <616> Method 2)
6302	Alternative filter insert with 10-mesh screen
6303	Volume Certification of the Receiving Cup
6305	Spare Receiving Cup
6306	Spare Set of Glassware (4 x Baffles + 1 Front and Rear Plate)



## TAPPED DENSITY TESTERS

The Tapped Density Testers Series JV have been designed to measure the tapped density of powders, granules and similar products in accordance with **USP Chapter <616> Method 2 and European Pharmacopoeia Chapter 2.9.15.**

This technique is particularly useful in powder flowability studies and also in determining the amount of settlement during transit, to optimise pack sizes e.g. washing powders.

Tapped density is achieved by mechanically tapping a measuring cylinder (i.e. raising the cylinder and allowing it to drop a specified distance under its own weight) containing the sample under test.

**Two versions of the tester** (JV 1000 and JV 2000) are available dependent on the number of test stations required (1 or 2). Both versions utilise 250 mL measuring cylinders as standard, however 100 mL cylinders (and smaller) together with appropriate platforms are also available if required.

Both of the instruments concerned are equipped with membrane keypads for setting the number of strokes or time and an LCD screen to set the appropriate parameters and monitor the progress of the test.

### MODE OF OPERATION

The mode of operation is identical on both models.

Weigh out a predetermined amount of the sample, say 100 g +/- 0.1%, place it in the graduated cylinder provided and note the unsettled volume. Secure the graduated cylinder to the test platform of the tester using the bayonet fitting provided for this purpose.

Unless otherwise specified, set the number of taps via the membrane keypad on the front of the instrument to 500 and operate the device making a note of the resulting tapped volume.



▲ JV 1000 with 1 x 250 mL Measuring Cylinder



▲ JV 2000 with 1 x 100 mL and 1 x 250 mL Measuring Cylinder

Repeat this operation for a further 750 taps noting the volume once again. Continue repeating the test in increments of 1250 taps until the difference in tapped volume is less than 2%. Note the final reading.

### The tapped density in grams per mL

can now be calculated by dividing the sample weight by the final tapped volume.

Measures of the ability of the powder to flow and its compressibility can now be given in the form of the Hausner ratio (Tapped Density/Bulk Density) and the Compressibility Index ((Tapped Density - Bulk Density/Tapped Density) x 100).

In a free flowing powder, inter-particulate interaction is less significant and unsettled and tapped densities will be closer in value. In poorly flowing powders, the inverse is to be expected. It follows that the closer the Hausner ratio is to 1, the better the flow. Powders with poor flow generally have a ratio of greater than 1.25.

A special **acoustic cabinet** capable of reducing the noise level of the volumeter from about 80 db to 58 db is available on request. The tapped density testers measure 280 x 250 x 670 mm (w x d x h).

### Scale of Flowability

Compressibility Index (%)	Flow Character	Hausner Ratio
< 10	Excellent	1.00 - 1.11
11-15	Good	1.12 - 1.18
16-20	Fair	1.19 - 1.25
21-25	Passable	1.26 - 1.34
26-31	Poor	1.35 - 1.45
32-37	Very poor	1.46 - 1.59
> 38	Very, very poor	> 1.60

### Cat. No. Description

1601	Tapped Density Tester JV 1000 (1 Cylinder)
1602	Tapped Density Tester JV 2000 (2 Cylinders)
1603	IQ/OQ/PQ Documentation Pack
1604	250 mL Measuring Cylinder (spare)
1605	100 mL Measuring Cylinder (option)
1605A	Special Platform for use with 100 mL Cylinder (option)
1616	Set of Certified Qualification Tools
1606	Acoustic Cabinet

# Semisolids

## INTRODUCTION ▶▶▶

### Copley Philosophy

Robust	✓	Reliable	✓
Easy to use	✓	Compliant	✓

Note: The EMA Draft "Guideline on quality of transdermal patches" published 23/08/2012 suggests the use of the VDC for permeation studies on transdermal patches

Creams, ointments, lotions and gels are topical drugs normally described as **semisolid dosage forms**. Unlike transdermal drug systems (see Note) which are applied to the skin for systemic effects (the drug penetrates the skin whereupon it is then absorbed into the blood stream), topical drugs are applied to the skin for local action principally to counter dermatological problems.

Current USP thinking suggests two types of test to characterise semisolids, **product quality tests (USP Chapter <3>)** and **product performance tests (the proposed USP Chapter <1724>)**.

USP Chapter <1724> *Semisolid Drug Products - Performance Tests* currently under revision suggests 3 apparatuses that may be used to determine the drug release from semisolids, the:

1. Vertical Diffusion Cell
2. Immersion Cell
3. Flow Through Cell (Apparatus 4)

### VERTICAL DIFFUSION CELL

The **Vertical Diffusion Cell** or **Franz Cell** is a simple, reproducible test for measuring the drug release from creams, ointments and gels. It is rapidly emerging as the apparatus of choice for the *in vitro* testing of drug release of topical semisolid dosage forms.

The cell comprises two parts (a) the sample holder containing either 250 mg or 425 mg of the sample to be tested and (b) the reservoir of the diffusion cell itself containing the receptor medium.

The two parts are separated by a membrane designed to act as a conduit for diffusion to take place and which serves to contain the test sample whilst ensuring that it remains in contact with the receptor medium.

The receptor temperature is usually set to 32 degrees C to approximate normal skin conditions. Normally, no fewer than 6 samples are taken over a 6 hour period, say, 0.5, 1, 2, 4, 5 and 6 hours and analysed using HPLC or similar analytical technique. The results are expressed as the amount of drug released per unit membrane area ( $\text{mcg}/\text{cm}^2$ ) vs square root of time (minutes) which should yield a straight line. The slope of the line (regression) represents the release rate of the product.

The **Copley Vertical Diffusion Cell System** features a unique clamping system to simplify equipment set up and has been carefully designed to eliminate the "spaghetti" of tubing associated with the use of more conventional water-jacketed cells.



## VERTICAL DIFFUSION (FRANZ) CELL

At the present time, there are no compendial methods relating to the *in vitro* release testing of topical semi-solid dosage forms such as **creams, ointments and gels** or for **permeation studies on transdermal patches** described in the Pharmacopoeias.

However, there does appear to be a growing body of opinion in support of the **vertical diffusion cell** system (sometimes called the "**Franz Cell**" after its originator, Dr. T. J. Franz) to fulfill these roles.

The vertical diffusion cell is, for example, already the system of choice for the FDA's "Guidance for Industry on Scale Up and Post Approval Changes for Semisolid (SUPAC-SS) Dosage Forms" and is currently under review by the USP Advisory Panel as the apparatus of choice in its new Chapter <1724> *Semisolid Drug Products - Performance Tests*.

The EMA Draft "Guideline on quality of transdermal patches" published in August 2012 also suggests its use for permeation studies on transdermal patches.



Vertical Diffusion Cells ▲

### Design

The design of the vertical diffusion cell is illustrated in the schematic below. It is occluded to avoid air bubbles that may affect the test.

Two sizes of cell are available.

**The standard** cell has a surface diameter of 15 mm and a receptor medium volume of approx. 7 mL. A **larger cell** is available with a 20 mm orifice and a volume of 20 mL.

Both cells are fitted with ports to facilitate sample withdrawal and media replacement. The cell contents are continuously stirred during operation by means of a magnetic stirring bar to ensure homogeneous distribution of temperature and adequate mixing of the contents.

The **sample holder** comprises a three part sandwich made up of:

- Clear view sample support disc
- PTFE sample chamber ring and
- 25 mm diameter membrane

The three part sandwich is held together by means of a three pronged spring clip which also serves to clip the assembled sample holder to the cell.

### Sample Preparation

Sample preparation is quick, easy, and precise. Insert the clear view sample support disc and PTFE sample

chamber ring into the three pronged spring clip and place the inverted assembly on to the worktop. Now, fill the sample chamber with the sample cream or ointment to be tested (approx.

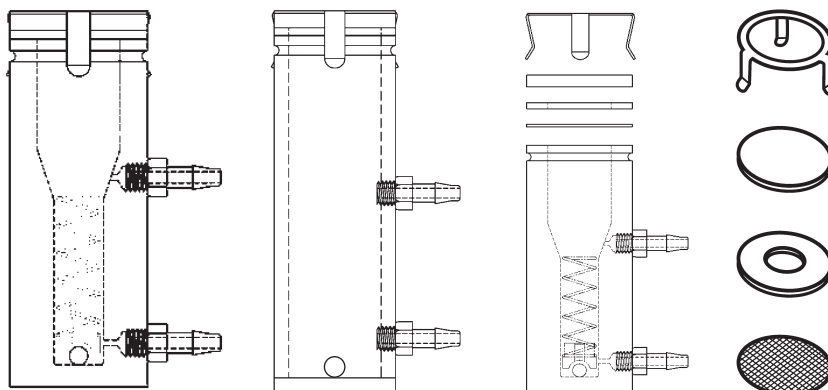
250 mg or 425 mg according to cell) removing any excess with the aid of a spatula. Finally, place the artificial membrane (or excised skin if you prefer) over the top of the sample holder with the membrane or visceral side of the dermis (the underneath of the skin sample) uppermost, such that when the holder is inverted and placed on the cell this side is bathed with receptor medium.

Note: the membrane should be thoroughly wetted with a suitable wetting agent prior to use unless Strat-M membranes, which do not require wetting, are employed. **The sample sandwich is now complete.**

Now, fill the **Franz Cell** with the specified receptor media e.g. isotonic saline solution at pH 7.4, suitably de-gassed to remove air bubbles and prewarm using suitable means to 32 degrees C to reflect normal skin temperature (37 degrees C for vaginal preparations). Note: It is helpful to marginally overfill the cell with medium to ensure contact between medium and membrane once the cell and sample holder are assembled.

### Running a Test

Once the desired temperature has been reached, **start the test** by securing the prepared sample holder to the cell and activating the stirrer (it is important to stir the cell contents during testing to ensure homogeneity of its contents). Precautions should be taken to remove any air bubbles from the cell which may affect the test.



7 and 20 mL Vertical Diffusion Cells ▲

Exploded Cell and Sample Holder ▲





◀ Single Cell VDC Test System HDT 1



▲ 10 Cell VDC Test System HDT 10

## VERTICAL DIFFUSION (FRANZ) CELL

### Sampling

Take samples as appropriate.

The vertical diffusion cell is equipped with two ports for sampling and media replacement respectively.

It is essential, whilst sampling, to ensure that the volume of receptor medium and hence contact between medium and the membrane is maintained. One of the most effective ways of achieving this is to use a syringe in conjunction with a check valve inserted in the replacement media line. The purpose of this valve is to allow replacement medium to be introduced into the cell whilst prohibiting medium flowing back once the syringe is removed.

The action of introducing the replacement medium displaces an equal volume of aliquot concurrently pushing it out of the sampling port for collection.

### Stirring and Heating

The **HDT 10 Vertical Diffusion Cell Test System** has been specifically designed to accommodate **ten diffusion cells**. It comprises a heated aluminium block accepting two rows of five cells. A powerful magnetic stirrer is mounted beneath each test station.

The heating block approach to heating the diffusion cells eradicates the difficulties in use and spaghetti of tubing associated with its water jacketed cell predecessors.

Temperature and stirrer speed are set, controlled and displayed from a single control panel on the front of the unit.

The HDT 10 will accommodate either end-point, discrete manual or fully automatic sampling techniques. Please ask our technical staff for further details.

The HDT 10 is incredibly compact measuring only 243 x 160 x 135 mm (w x d x h) - a footprint less than an A4 sheet of paper.

A second and less expensive Test System (the **HDT 1**) is available to accommodate a **single diffusion cell**.

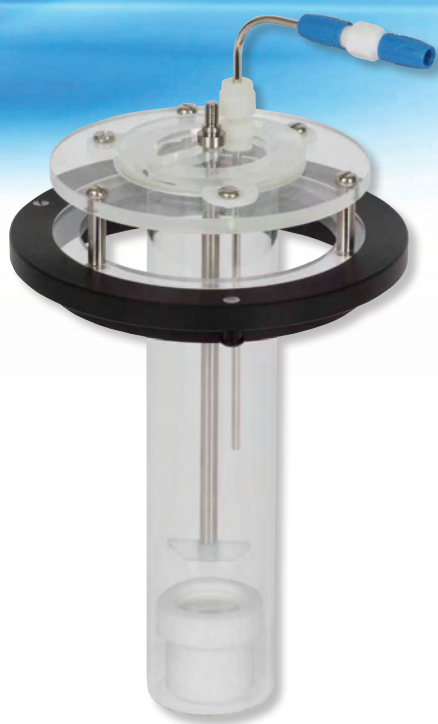
### Strat-M Membranes

The Strat-M Membrane is a new synthetic transdermal test model predictive of diffusion in human skin **without the wetting**, lot-to-lot variability, safety and storage limitations of the original.

Like human skin, Strat-M has multiple layers with varied diffusivity. It is constructed of two layers of polyether-sulfone (more resistant to diffusion) on top of one layer of polyolefin (more open and diffusive) to create a porous structure with a gradient across the membrane in terms of pore size and diffusivity. The porous structure is impregnated with a proprietary blend of synthetic lipids imparting additional skin-like properties to the membrane.

### Cat. No. Description

7265	Vertical Diffusion Cell 15 mm x 7 mL (in Acrylic)
7269	Vertical Diffusion Cell 20 mm x 20 mL (in Acrylic)
7278	Vertical Diffusion Cell 15 mm x 7 mL (in Glass)
7279	Vertical Diffusion Cell 20 mm x 20 mL (in Glass)
7270	Pack of 100 PVDF Membranes 25 mm o.d.
7274	Pack of 100 Tuffryn Polysulfone Membranes 25 mm o.d.
7275	Pack of 60 Strat-M Membranes 25 mm o.d.
7277	IQ/OQ/PQ Documentation Pack
7271	10 Cell Vertical Diffusion Cell Test System HDT 10 (excl. cells)
7276	Single Cell Vertical Diffusion Cell Test System HDT 1 (excl. cells)



## IMMERSION CELL

### Design

Another alternative to the Vertical Diffusion or Franz Cell for testing semisolids is the Immersion Cell.

The **Immersion Cell** is used with the conventional USP Apparatus 2 described on Page 19.

The PTFE Immersion Cell is designed to accommodate a 25 mm diameter membrane. It comprises four main parts:

1. A retaining ring which secures the membrane to the cell body
2. A washer which holds the membrane in contact with the sample
3. The membrane or skin
4. The cell body which contains the compartment in which the sample to be tested is placed

The cell is also provided with an alignment tool and an adjustment tool that allows the user to vary the volume of the reservoir within the cell.

The Immersion Cell is used with a special flat bottomed version of the **200 mL Small Volume Conversion Kit** (described on Page 28) in order to avoid the issue of dead space under the cell, were a round bottomed vessel to be used.



◀ ▲ Immersion Cell with 200 mL Small Volume Conversion Kit

### Sample Preparation

Replace the conventional 1000 mL Vessels on the Dissolution Tester with the 200 mL Small Volume equivalents, adjust the height of the mini-paddles to 25 mm above the surface of the membrane and the temperature to 32 +/- 0.5 degrees C (37 +/- 0.5 degrees C in the case of vaginal preparations).

Adjust the reservoir of the cell body to the volume required using the Adjustment Tool provided for this purpose.

Now fill the reservoir with the sample under test, removing any excess with the aid of a spatula.

Finally, place the artificial membrane (or excised skin) over the top of the sample with the membrane or visceral side of the dermis (the underneath of the skin sample) facing upwards, such that when the cell is placed in the vessel this side is bathed with receptor medium and secure it with the washer and retaining ring.

Note: the membrane should be thoroughly wetted with a suitable wetting agent prior to use unless Strat-M membranes which do not require wetting are employed.

### Running a Test

Place the assembled cell into the bottom of the vessel with the membrane facing up.

Add the appropriate amount of preheated and degassed dissolution medium (see Page 35) and start the test.

Normally, no fewer than 6 samples are taken over a 6 hour period, say, 0.5, 1, 2, 4, 5 and 6 hours and analysed using HPLC or similar analytical technique. The results are expressed as the amount of drug released per unit membrane area (mcg/cm<sup>2</sup>) vs square root of time (minutes) which should yield a straight line. The slope of the line (regression) represents the release rate of the product.



▲ Immersion Cell

### Cat. No. Description

7280	Immersion Cell
7281	200 mL Small Volume Conversion Kit for Immersion Cell
7270	Pack of 100 PVDF Membranes 25 mm o.d.
7274	Pack of 100 Tuffryn Polysulfone Membranes 25 mm o.d.
7275	Pack of 60 Strat-M Membranes 25 mm o.d.

# Suppositories

## INTRODUCTION ▶▶▶

The suppository is a more common and accepted dosage form in Europe than in the USA. This probably explains why pharmacopoeial references to specific test methods relating to suppositories and associated dosage forms, are in the main, confined to the European Pharmacopoeia.

With regard to **drug release (dissolution)**, various trials indicate that no single method of dissolution testing is suitable for all types and formulations of suppositories.

**Hydrophilic** suppositories are made from a water-soluble base such as polyethylene glycol, which dissolves in the rectal or vaginal fluids. The rate of drug release (dissolution) of such suppositories can be measured using the standard basket, paddle or flow through methods described in USP Chapter <711> and Ph.Eur. 2.9.3 (see Page 19).

**Lipophilic** suppositories, on the other hand, are made from a greasy base, such as cocoa butter, which melts at body temperature. Various methods have been described

to measure the rate of drug release (dissolution) from lipophilic suppositories, including a modified basket method (see Page 28), a paddle method (see Page 32) and a modified flow cell method with dual chambers described in Ph.Eur. 2.9.42.

Normally the dissolution medium temperature employed should be at 37 degrees C, however with lipophilic suppositories, the test temperature may need to be raised to ensure that it is above the melting point of the suppository concerned.

In addition, the European Pharmacopoeia 7th Edition makes reference to two other technical procedures relating to the **disintegration** and **softening time** of suppositories, namely:

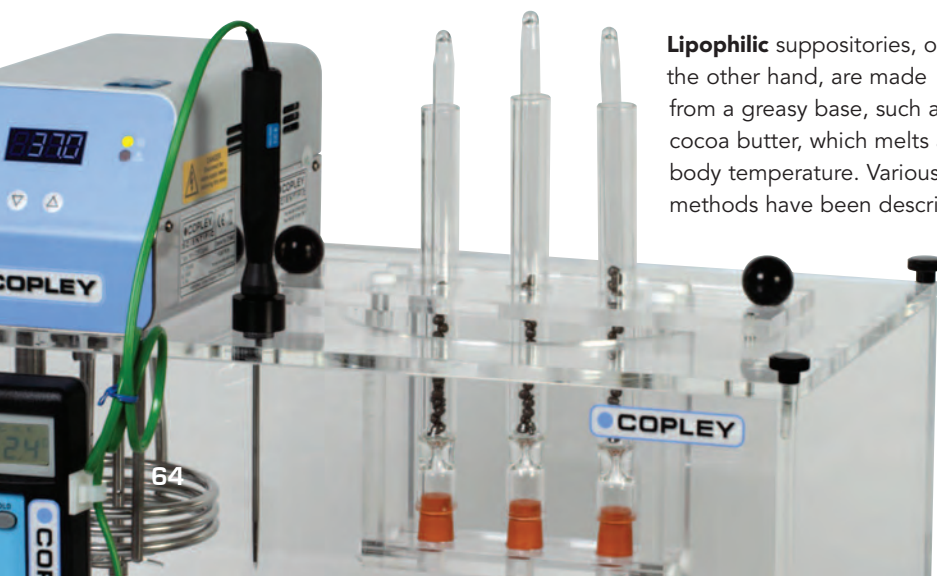
2.9.2 Disintegration of suppositories and pessaries

2.9.22 Softening time determination of lipophilic suppositories

This section describes the apparatus and test methods to be employed in measuring the disintegration of suppositories and pessaries and the softening time of lipophilic suppositories in these two sections.

Copley Philosophy			
Robust	✓	Reliable	✓
Easy to use	✓	Compliant	✓

Softening Time Attachment ▼



▲ Digital Timer





The Suppository Tester SDT 1000 is a single stage unit which has been designed in accordance with the specifications as laid down in the **Ph.Eur. Test 2.9.2 for the disintegration of suppositories, pessaries and vaginal tablets** and with suitable attachments **2.9.22.-2 Apparatus 2 for measuring the softening time of lipophilic suppositories.**

The **disintegration test station** is made up of a 60 mm long acrylic cylinder having an internal diameter of 52 mm into which is inserted the sample holder containing the sample under test. The sample holder comprises two stainless metal disks, 50 mm in diameter and containing 39 x 4 mm holes held 30 mm apart by three spring clips.

Consistent heating of the medium is achieved by immersing the test station into a 4 litre glass vessel contained within a plexiglass water bath. The temperature of the medium is controlled at 36-37 degrees C by an immersion thermostat and measured in the water bath using a PT100 probe connected to a digital display.

During operation, the black knob is rotated through half a turn at 10 minute intervals, which automatically inverts the sample holder through 180 degrees using a water resistant pulley system. The whole test station can be quickly removed from the beaker for cleaning.

Agitation of the test medium is achieved through an electro-magnetic stirrer which, located on a sliding drawer, sits beneath the water bath, directly below the centre of the test station.

The drawer can be withdrawn to allow the setting of the stirrer speed and then retracted during the test. The stirrer speed can be varied between 80 and 2000 rpm at 10 rpm intervals. The stirrer can be removed and used for other purposes if required.

#### MODE OF OPERATION

Preheat the test medium to 36-37 degrees C using the combination of the immersion thermostat provided and the slow speed stirrer (optional).



Removing the Test Station ▲

#### Suppository Disintegration Tester Model SDT 1000

Place a **suppository** or **pessary** in the sample holder, place the latter in the perspex cylinder and secure. Run the test for the time prescribed in the appropriate monograph, inverting the apparatus every 10 minutes using the black knob provided for this purpose. Repeat the test for two more suppositories or pessaries - all samples should disintegrate within the stated time.

The tester can also be used for testing **vaginal tablets**. In this case, only the sample holder is employed. The test station used for suppositories and pessaries should therefore be removed. Place the sample holder on the base of the beaker and adjust the level of the test medium (preheated to 36-37 degrees C) such that it just covers the perforations on the upper plate. Place a tablet on the latter and cover with a suitable glass plate to maintain appropriate conditions of humidity. Repeat the test for two more tablets - all samples should disintegrate within the stated time.

A special attachment designed to be used in place of the disintegration test station and 4 litre beaker containing three glass rods (C1) is available for measuring the **softening time of lipophilic suppositories** (2.9.22.-2).

The unit measures 510 x 280 x 500 mm (w x d x h).



#### Cat. No. Description

1704	Suppository Disintegration Tester SDT 1000
1705	Electro-Magnetic Stirrer for SDT 1000 (see photo left)
1706	Softening Time Attachment (Ph.Eur. 2.9.22.-2)
1709	Glass Plate for use with Vaginal Tablets
1708	IQ/OQ/PQ Documentation Pack
1710	Digital Timer with Audible Alarm (including calibration)

# Tergotometer

## INTRODUCTION ▶▶▶

### Copley Philosophy

Robust	✓	Reliable	✓
Easy to use	✓	Compliant	✓

The testing of detergents and associated products can be extremely time consuming, requiring multiple testing to generate the statistical data required to justify any claims as to the efficacy of the product by the formulator.

The Copley Tergotometer has been specifically designed for the multiple processing of textile samples, prior to analysis for colour fastness by grey scale or instrumental methods as typified by the International Organisation for Standardisation (ISO) Methods ISO 105-A01 to ISO 105-A05, and similar methods published by the American Society for Testing Materials (ASTM) and American Association of Textile Chemists and Colorists (AATCC).

The ability of a detergent product to remove stains or affect colour changes within a fabric is dependent on a number of factors: the fabric under test, the degree and type of soiling or staining, the temperature and sometimes pH and hardness of the water used in the test, the stirrer speed and the wash and rinse times employed. A wide range of standard soiled/stained samples are available. Please contact us for further information.

The Tergotometer combines eight miniature washing machine simulators within a single benchtop instrument allowing eight samples to be processed simultaneously under identical conditions of speed, time and temperature.

Once processed, the samples can be analysed by comparison with a grey scale or by measuring the reflectance of the samples concerned using a suitable colorimeter. In the case of the latter, results are normally expressed in terms of % stain removal using the formula:

$$\%SR = [ (Rw - Ru) / (Rn - Ru) ] * 100$$

where:

R = reflectance

n = normal unstained unwashed fabric

u = stained unwashed fabric

w = stained washed fabric

Whiteness and Yellowness Indices can also be employed. The whiteness scale ranges from 0 (black) to 100 (white), the yellowness scale from positive (yellow) to negative (blue).

A product or surfactant can be considered successful when both criteria, stain removal and whiteness, can be said to have been met.





## TERGOTOMETER (DETERGENT TESTER)

The **Tergotometer** is a versatile laboratory-scale multiple washing machine which simulates the action of a domestic washing machine.

Typical applications include:

- Evaluation of the effectiveness of soap, detergents, etc
- Washability and colour fastness of fabrics and other materials
- Optimisation of temperature, speed and water hardness parameters applicable to different detergents
- Routine screening for dirt removal, brightening, softening, foaming

The unit has eight test stations each comprising a 1000 mL test vessel in glass, located in a clear view acrylic water bath (stainless steel options available). The temperature of the water bath is controlled by an external digital heater/circulator which is adjustable between ambient and 70 degrees C. A refrigeration unit can be provided as an optional extra if temperatures are required below ambient (down to 10 degrees C). In this case, the number of test stations is reduced to 7.

Agitation (50 - 200 rpm) is provided by a series of eight stirrers located in each vessel which produce a scaled down version of larger machines. Provision is made for controlling and monitoring the speed and temperature during the test. Plain 316 stainless steel paddles are available as an option, or paddles which allow pieces of fabric to be attached to them are available on request.



Standard Stirrers ▲



Tergotometer ▲

A special modification to allow for reverse rotation of the paddle to the following specification is available on request: stirrer rotation 10 revolutions (360 degrees) clockwise followed by 10 revolutions anti-clockwise *ad infinitum* throughout the test.

### OPERATION

The detergency value of any washing material is normally determined by washing standardised soiled fabrics and measuring the amount of soiling removed, by comparison with a grey scale, or measuring the reflectance before and after the washing process.

Operation is simple. Adjust the water bath to the desired temperature, add 1000 mL of water to each test vessel and allow to equilibrate until the desired temperature has been attained. Add the pre-weighed volume of soap or detergent to each test vessel and operate the paddles at the prerequisite speed until homogenisation is complete.

Add the test sample to each test station and operate at the speed required for the time specified. At the end of this phase, remove the samples and empty and refill the vessels with clean water. Wring the samples out and return them to the vessels for rinsing at the temperature and for the time specified in the protocol. Repeat the washing and rinsing operations as required.

Any number of variables can be tested in this manner: not only the temperature, agitation speed and period of test but also composition of the wash solution, degree of water hardness, pH, bleach, etc.



Vessels (Stainless Steel/Glass) ▲

### Cat. No. Description

6401	Tergotometer (Ambient to 70 degrees C)
6402	Refrigeration Unit (Ambient to 10 degrees C)
6403	Modification to allow for reverse rotation of the Stirrers
6404	Set of 8 Stainless Steel Paddles (option)
6404A	Set of 8 SS Paddles with holes for fabric attachment (option)
6405	Vessel, Glass, Flat Bottomed, 1000 mL with "Easy-Centre"
6406	Vessel, Stainless Steel, 1000 mL with "Easy-Centre" (option)
6407	Stainless Steel Bath (option)



# Thickness

## INTRODUCTION ▶▶▶

### Copley Philosophy

Robust	✓	Reliable	✓
Easy to use	✓	Compliant	✓



Tablet Thickness Tester 547 ▲

The thickness of tablets is critical to their therapeutic effectiveness.

All tablets, where the active ingredient comprises a major part of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity, are required to meet a weight variation test. It is assumed that providing the weight of the tablet is kept within defined limits that the amount of active drug available to the user will remain the same.

The weight of a compressed tablet is dependent on three factors: density, diameter and thickness. In theory, the modern tablet press should provide a good measure of uniformity.

However, in practice, there are several potential sources of variation, the most important of which is powder flow and its effect on the uniformity with which the die is filled before compaction. Other, but smaller, variations may be introduced by wear or simply mechanical imperfections in the press or tooling. Finally, build-up of granulation on the punch face or die wall during a run may reduce the effective volume of the die and hence the tablet weight.

Again, in theory, the density and diameter (which is dictated by the die wall) of the tablet should remain unchanged: it follows that by monitoring thickness at regular intervals, potential problems relating to tablet weight, and hence content uniformity, can be detected at an early stage.

The calipers and thickness testers featured in this section are simple, easy to use instruments designed for use by the press operator on the compression floor.

The **Digital Caliper Model 500** is an inexpensive hand-held electronic caliper and is particularly useful for the press operator as being extremely easy to use and completely dust resistant. The data produced by the caliper can be down loaded to a Statistical Data Processor or PC if so desired.

The **Model 700 Tablet Thickness Tester** is an inexpensive hand-held thickness tester designed to slip easily into the pocket. The **Model 547** is a rather more sophisticated unit which like the Digital Caliper Model 500 may be linked to a Data Processor or PC if so desired.

## DIGITAL CALIPER FOR MEASURING TABLETS

### DIGITAL CALIPER MODEL 500

The instrument is designed to accept tablets and similar samples up to a **maximum of 150 mm (6")** and to an accuracy of 0.01 mm (0.0005").

The convenient one-handed operation could not be simpler.

Holding the gauge in the right hand, use the thumb to move the display head of the caliper to the right in order to open the jaw of the gauge, insert the tablet with the left hand between the jaws.

Then by moving the display head to the left to close the jaws, read off the measured value from the digital display.

Provision is made to measure in either metric or imperial at a single push of a button with a **resolution of 0.01 mm** or 0.0005". The gauge can be zero set at any point thus enabling the display to show a +/- variance.

The gauge can be used in **four modes**, that is to say, to measure outside, inside, depth or step measurements.

The unit comes complete in a handy plastic storage case to prevent inadvertent damage. A 6-pin socket is provided as standard such that the unit can be connected to a data processor for statistical process control.

The **Digimatic Mini Processor Model 264** is a powerful and compact data processor which provides a wide variety of calculations for generating X-R control charts, histograms and data displacement charts.



Digital Caliper 500 ▲

## TABLET THICKNESS TESTER

### TABLET THICKNESS TESTER 700

The least expensive of the two units, the **Tablet Thickness Tester Model 700** is designed to accept tablets up to 12 mm (0.5") thick to an accuracy of **0.01 mm** (0.0005").

Operation is simplicity itself.

Press "on" button to switch the unit on and to zero the gauge, select the appropriate unit of measurement (mm or inches), depress the red button to open the jaw, insert sample, release the red button and read off the result on the clear LCD display.

This unit is truly hand held, measuring only 94 mm long x 45 mm wide.

### Mini Processor for SPC 264 ▼



### TABLET THICKNESS TESTER 547

The **Tablet Thickness Tester Model 547** is a rather more sophisticated unit designed to accept tablets and similar samples up to **10 mm** (0.4") thick to an accuracy of **0.01 mm** (0.0005"). The gauge has a throat of 30 mm (1.2").

The convenient one-handed operation could not be simpler.

Holding the gauge in the right hand, depress the thumb-lever with the right thumb in order to open the jaw of the gauge, insert the tablet with the left hand between the jaws and then releasing the thumb-lever to close the jaws, read off the measured value from the digital display.

Provision is made to measure in either metric or imperial at a single push of a button with a resolution of 0.01 mm or 0.0005".

The gauge can be used in two modes, that is to say, either in "direct measurement" mode whereupon the actual thickness value is displayed or in "comparator" mode whereby a +/- variance from a preset norm is indicated on the display. The unit comes complete in a handy plastic storage case to prevent inadvertent damage.

Model 547 is also provided with a 6-pin socket as standard such that it can be connected to the **Digimatic Mini Processor Model 264**.

### Cat. No. Description

4901	Digital Caliper 500
4902	Mini Processor for SPC 264
4903	Tablet Thickness Tester 700
4904	Tablet Thickness Tester 547
4901A	UKAS Calibration of Digital Caliper 500
4903A	UKAS Calibration of Tablet Thickness Tester 700
4904A	UKAS Calibration of Tablet Thickness Tester 547





## QUALIFYING ANALYTICAL INSTRUMENTS

### SOURCES OF ERROR

The pharmaceutical industry employs a wide variety of analytical instrumentation to help ensure the efficacy and safety of its products.

Unfortunately, in many cases, the validity of the results produced by this instrumentation can be influenced by factors other than the product itself.

The source of these potential errors are two-fold:

- Human (inappropriate method development or execution)
- Instrumental (errors in instrument and/or ancillary equipment)

If these sources of error can be eliminated then it is fair to assume that any anomalies in results are reliable and are a direct result of the formulation itself.

### <1058> ANALYTICAL INSTRUMENT QUALIFICATION

The Good Manufacturing Practices (GMP) regulations require that:

- the **test methods** used to monitor pharmaceuticals must meet proper standards of accuracy and reliability and
- that companies should establish procedures to ensure the fitness for use of **instruments** that generate data supporting product testing.

However, the GMP regulations do not provide definitive guidance as to how these goals are to be achieved.

The United States Pharmacopoeia (USP) has sought to address this problem by the introduction of a series of chapters as follows:

- <1225> Validation of Compendial Procedures
- <1226> Verification of Compendial Procedures
- <1058> Analytical Instrument Qualification

Attention is drawn at this point to the terms "validation" and "qualification" above. Hitherto, these terms have been used on an interchangeable basis creating a degree of ambiguity in the scientific community.

For this reason, USP have suggested that:

- the term "**qualification**" be applied to instrumentation and
- the term "**validation**" to processes and software

Hence, the term "**analytical instrument qualification**" (AIQ) is used for the process of ensuring that an instrument and the term "**analytical method validation**" for ensuring that the analytical and software procedures employed is suitable for its intended application.

### The USP Chapter <1058> Analytical Instrument Qualification

describes in detail the four phase approach to Qualification based on design (DQ), installation (IQ), operational (OQ) and performance (PQ) qualification.

Copley Scientific recognises the regulatory importance of these new initiatives. For this reason, for a wide selection of our products, you can request full supporting documentation in the form of full **IQ/OQ/PQ manuals** (Installation, Operation and Performance Qualification) to guide you through the qualification process.

It is important to note that the purpose of analytical instrument qualification and analytical method validation is to ensure the quality of analysis **before** conducting the tests whereas system suitability tests and quality control checks ensure the quality of analytical results **immediately before** or **during** sample analysis.





## SERVICING/TRAINING

### SERVICING

Copley Scientific offers a comprehensive range of both in-house and on-site service contract options tailored to individual customer needs and designed to provide quality maintenance and calibration procedures at really competitive prices.

Contracts can be prepared for **individual instruments** or complete **calibration management** systems.

The creation of a typical service contract follows a structured format: "discussion" to establish a User Requirement Specification (URS), "quotation" to establish costs, "implementation" to implement the contract and "review" to ensure compliance with the initial specification.

Our skilled team of engineers and technicians are trained to a high standard on the complete range of Copley Scientific and other related products and are well versed in all aspects of calibration and qualification (IQ/OQ/PQ) procedures, from actual performance to document control and storage.

All documentation supplied conforms to **GxP standards** as required by the international regulatory authorities.

Similarly, the instrumentation used by our service engineers for critical calibration of equipment is certified to a traceable standard. Such instruments are calibrated by, or traceable to, an accredited **UKAS** calibration company in the UK or equivalent international standards.

Such calibration companies encompass all the relevant requirements of EN and ISO. Certificates for the instruments used to calibrate the customer's equipment are available for viewing on request.

We will be pleased to discuss your individual requirements and quote accordingly.

### TRAINING

As a world leader in the provision of equipment for testing pharmaceutical dosage forms Copley Scientific offers a range of tailored training packages for both analysts and laboratory managers of pharmaceutical companies developing such products.

Training courses vary depending on existing levels of knowledge and can be conducted at Copley Scientific's training facility in Nottingham, UK, or at the customer's facility (in most cases).

Typical training programmes include:

- Presentation on dosage form types, test equipment, regulatory requirements, monographs and methodology and new industry developments
- Provision for the supply of technical papers and documents where appropriate
- Audit of current system set-up and procedures used (on-site training courses only)
- Training of users in operation of the equipment supplied
- Troubleshooting, Questions and Answers

Please feel free to contact us to discuss your own requirements. We will be pleased to provide you with a quotation for a training programme designed to meet your particular needs.



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