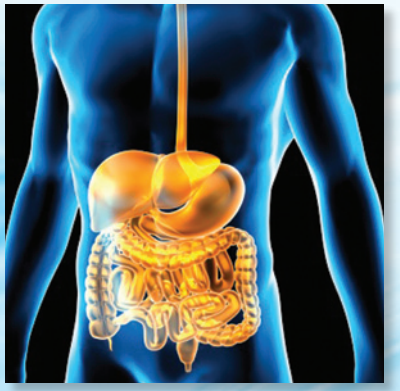
COPLEY SCIENTIFIC



Quality Solutions for the Testing of Pharmaceuticals

2016 EDITION

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

Who are Copley Scientific?

Copley Scientific was founded in 1946 in Nottingham, UK by Frank Copley to supply laboratory equipment to the local pharmaceutical industry.

Today, still family owned and managed, we are recognised as the world's leading manufacturer of inhaler test equipment, in addition to being a trusted provider of test instrumentation for other pharmaceutical dosage forms.

This focus on pharmaceutical test instrumentation began in 1957.

Subsequent decades saw marked expansion and today we manufacture a range of innovative equipment for tablet dissolution, disintegration, friability and hardness testing, and for testing creams, ointments, powders, suppositories and transdermal patches.

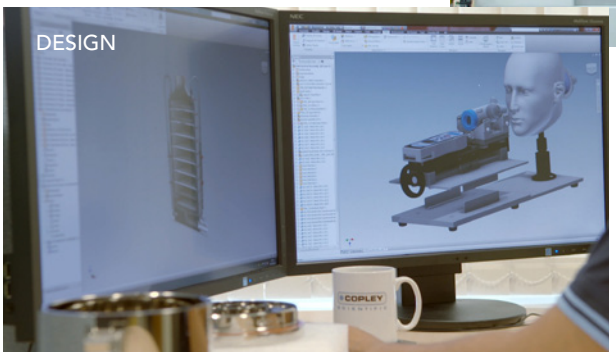
The 1980s saw respiratory drug delivery gain commercial momentum and, in parallel, the development of new solutions for the testing of orally inhaled and nasal drug products (OINDPs).

Early success was boosted in 2000, with the signing of a strategic partnership agreement with MSP Corporation, which enabled us to become the first company to offer the full range of cascade impactors specified by the European and US Pharmacopoeias for measuring the aerodynamic particle size distribution of all OINDPs.

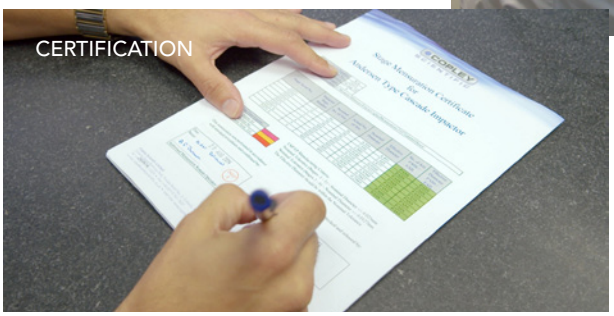
Our comprehensive range for inhaled product testing now extends to equipment, software and services for every stage of development and manufacture, of both innovator and generic products, topical and systemic.

We continue to work closely with industry groups and leading experts to bring relevant new products to market, with all equipment backed by expert training and lifetime support.

Company headquarters remain in Nottingham, in a purpose-built facility, but we also have a well-established sales and service company in Switzerland and secure partnerships in place to serve a growing number of dynamic international markets.



Designed, manufactured and tested in the UK



ISOQAR REGISTERED
UKAS MANAGEMENT SYSTEMS
0026
Certificate Number 7391
ISO 9001

Our Philosophy

Copley Scientific is a strong, stable company with a track record of success. Equally importantly, we are agile and forward-looking, with a philosphy closely aligned to the needs of the market we serve.

Accurate, precise, reproducible data drives pharmaceutical development and ensures product safety, but high productivity in testing is increasingly important.

Equipment that is rugged, robust and simple to use is essential.

To deliver instrumentation with the necessary accuracy and reproducibility hard-wired into its design we adopt the same Quality by Design principles that our customers rely on to control product performance.

Continuous improvement is a core element of this approach and we strive to exceed the expectations of the industry, not only by enhancing equipment performance but also through unrivalled service.

These commitments are exemplified by our investment in the **ISO 9001: 2008 Quality Management System** for which we have certification to the latest standard for all aspects of our business, including equipment design.

Introduction

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Equipment Selection Guide

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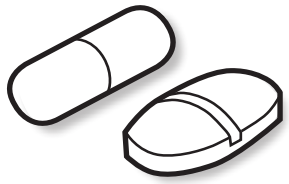
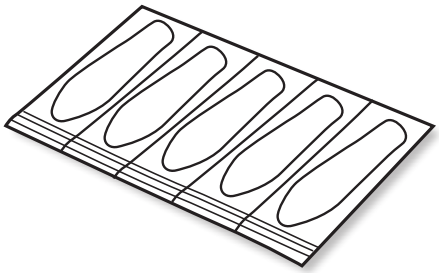
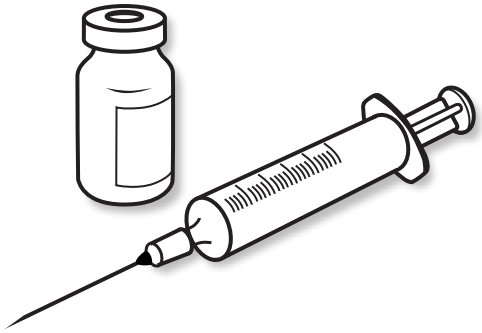
Services

Classification of Medicines

INTRODUCTION







One of the clearest taxonomic guides for the classification of pharmaceutical dosage forms is to be found in Chapter <1151> of the US Pharmacopeia (USP) entitled "Pharmaceutical Dosage Forms".

The guide is depicted in "Figure 1. Compendial taxonomy for pharmaceutical dosage forms", a modified version of which appears below.

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 urethal), skin surface (topical, transdermal), injection including implants (parenteral) or nasal/lungs (pulmonary).

The second tier describes the dosage form concerned, e.g. tablet, capsule, suppository, cream, ointment, transdermal patch, injection, inhaler, etc., whilst the third tier describes whether the dosage form concerned is designed for immediate, extended or delayed release.

It is the first tier classification which has been used as the basis for the Equipment Selection Guide to be found on page 7.

This lists the route of administration, 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 relevant test instrumentation can be found.

TIER 1
Route of Administration
GASTROINTESTINAL / MUCOSAL / INHALATION / INJECTION / TOPICAL (DERMAL)
TIER 2
Dosage Form
AEROSOLS / CAPSULES / CREAMS / EMULSIONS / FILMS / FOAMS / GASES / GELS
GRANULES / GUMS / IMPLANTS / INJECTIONS / INSERTS / IRRIGATIONS / LIQUIDS
LOZENGES / OINTMENTS / PASTES / PELLETS / PILLS / PLASTERS / POWDERS / SOAPS
/ SHAMPOOS / SOLUTIONS / SPRAYS / STRIPS / SUPPOSITORIES / SUSPENSIONS /
SYSTEMS / TABLETS / TAPES
TIER 3
Release Pattern
IMMEDIATE / EXTENDED / DELAYED

EQUIPMENT SELECTION GUIDE

ROUTE OF ADMINSTRATION - Dosage Form	European Pharmacopoeia	United States Pharmacopeia	Page No. (in this brochure)
GASTROINTESTINAL - Tablets & Capsules - Disintegration	Chapter 2.9.1	Chapter 701	Pages 12-16
GASTROINTESTINAL - Tablets & Capsules - Dissolution	Chapter 2.9.3	Chapter 711	Pages 17-47
GASTROINTESTINAL - Tablets & Capsules - Friability	Chapter 2.9.7	Chapter 1216	Pages 48-50
GASTROINTESTINAL - Tablets & Capsules - Breaking Force	Chapter 2.9.8	Chapter 1217	Pages 53-58
GASTROINTESTINAL - Tablets & Capsules - Weight & Thickness	Chapter 2.9.5	Chapter 905	Page 58
GASTROINTESTINAL - Powders - Bulk & Tapped Density	Chapter 2.9.34	Chapter 616	Pages 64-65
GASTROINTESTINAL - Powders - Flowability	Chapter 2.9.16 & 2.9.36	Chapter 1174	Pages 59-63
GASTRONINTESTINAL - Granules & Pellets - Friability	Chapter 2.9.41	----	Pages 51-52
MUCOSAL MEMBRANE - Rectal - Drug Release	Chapter 2.9.2	----	Pages 72-73
MUCOSAL MEMBRANE - Oropharyngeal, Opthalmic, Otic & Urethal	Outside the scope of this brochure		
MUCOSAL MEMBRANE - Vaginal - Drug Release	Chapter 2.9.22	----	Pages 72-73
SKIN SURFACE - Semisolids - Drug Release - Permeation	----	Chapter 1724	Pages 66-71
SKIN SURFACE - Transdermal Patches - Drug Release	Chapter 2.9.4	Chapter 724	Page 34
INJECTION - Injections & Implants	Outside the scope of this brochure		
LUNGS - Inhalers	Chapter 2.9.18 & 0671	Chapter 601	Pages 36-37
LUNGS - Nebulisers	Chapter 2.9.44	Chapter 1601	Pages 36-37
NASAL - Inhalers & Sprays	Chapter 2.9.18 & 0676	Chapter 601	See seperate brochure
ANALYTICAL INSTRUMENT QUALIFICATION - Guidelines	----	Chapter 1058	Page 78

Organisations and their roles

INTRODUCTION

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

In Europe, Japan and in the USA this function is performed by the **European Medicines Agency (EMA),** the **Ministry of Health, Welfare and Labor (MHWL)** and the **Food and Drug Administration (FDA)** respectively.

The regulatory authorities are supported in this role by the **Pharmacopoeias** whose job is to define the standards with which the drug formulation shall comply and the methods by which compliance will be adjudged.

In October 1999, the **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)*** published a single set of global specifications covering the **Test Procedures and Acceptance Criteria for new drug substances and products**.

The guidance takes the form of a number of universal tests/criteria considered generally applicable to:

a) new drug substances and
b) new drug products

together with a number of additional tests and acceptance criteria for specific substances and dosage forms, including solid oral drug products, liquid oral drug products and parenterals.

The additional tests for tablets (coated and uncoated) and hard capsules, for example, include:

a) Dissolution
b) Disintegration
c) Hardness/Friability
d) Uniformity of dosage units
e) Water content and
f) Microbial limits

The guideline on quality concerned (Q6A) was subsequently agreed and adopted by all of the parties involved, including the EMA, FDA and MHWL.

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

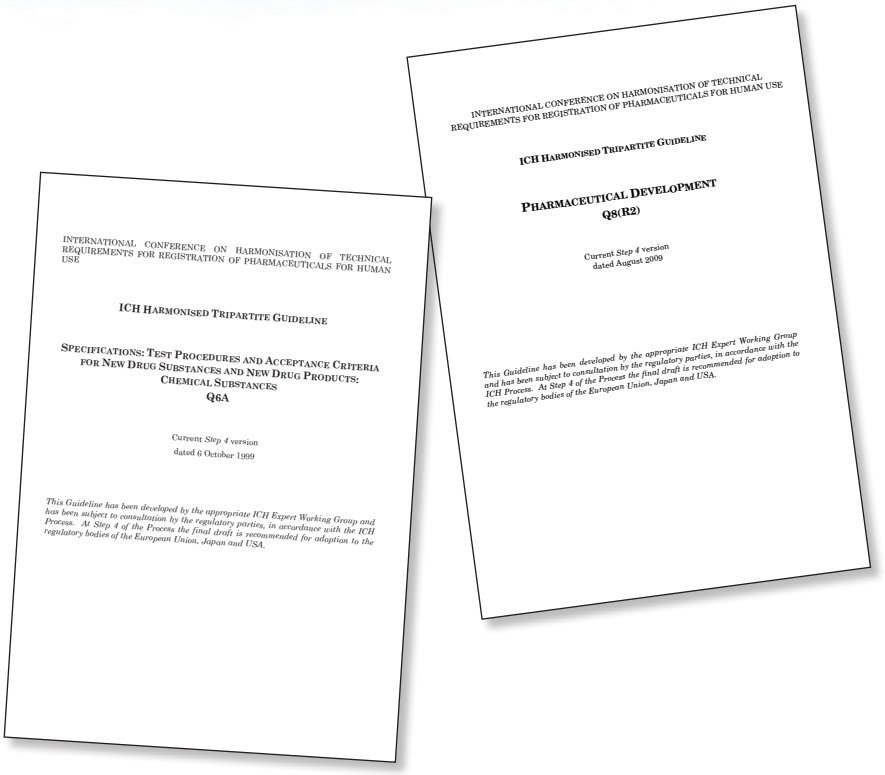
This initiative gave birth to **Process Analytical Technology (PAT)**, a framework for understanding and improving the processes involved in pharmaceutical development, manufacturing and quality control, described in FDA's Guidance of September 2004.

PAT operates on the premise that quality cannot be tested into products; rather, it should be built-in or by design.

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

ICH Quality Guidelines	
Q1A - Q1F Stability	Q7 - Good Manufacturing Practice
Q2 - Analytical Validation	Q8 - Pharmaceutical Development
Q3A - Q4B Impurities	Q9 - Quality Risk Management
Q4 - Q4B Pharmacopoeias	Q10 - Pharmaceutical Quality System
Q5A - Q5E Quality of Biotechnological Products	Q11 - Development and Manufacture of Drug Substances
Q6A - Q6B Specifications	Q12 - Lifecycle Management

* *See Page 9 for further details*



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

Current Step 4 version
dated August 2009

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES
Q6A

Current Step 4 version
dated 6 October 1999

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

The **Quality by Design (QbD)** approach agreed and now adopted by the EMA, FDA and the Japanese MWHL in the form of the five quality related guidelines, ICH Q8, Q9, Q10 and Q11, extends this philosophy to all parts of the product life cycle from product development, transfer through to manufacturing, manufacturing and finally product end.

ICH Q8 Pharmaceutical Development describes the suggested contents of a regulatory submission based on the QbD format.

ICH Q9 details a systematic approach to quality risk management, whilst ICH Q10 describes a new quality management system based on the complete product life cycle and referred to as the Pharmaceutical Quality System.

ICH Q11 provides a Guideline to the "Development and Manufacture of Drug Substances", including the type and extent of information to be submitted in regulatory dossiers.

1. REGULATORY BODIES IN THE EUROPEAN UNION, JAPAN AND THE USA

In the USA, the regulatory function is performed by the **Food and Drug Administration (FDA)** with technical and scientific support being provided through two centers - the Center for Drug Evaluation and Research (CDER) in respect of medicines and the Center for Devices and Radiologic Health (CDRH) in respect of medical devices.

A similar function to the FDA is provided by the **Ministry of Health, Welfare and Labor (MHWL)** in Japan and the **European Medicines Agency (EMA),** with support in the form of the **Committee for Medicinal Products for Human Use (CHMP),** representing the various states making up the European Union (EU).

Other prominent bodies include the **Central Drugs Standard Control Organisation (CDSCO)** of India, the **China Food and Drug Administration (CFDA)**, **Health Canada** and **Swissmedic**.

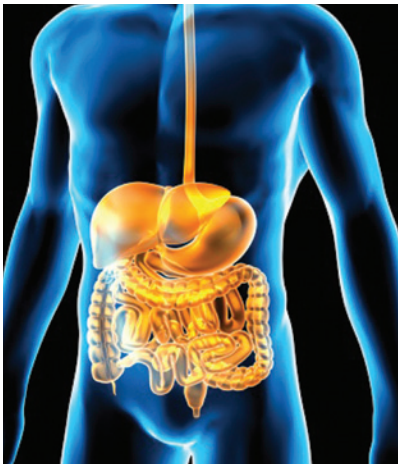
2. INTERNATIONAL REGULATION AND HARMONISATION

The **International Centre for Harmonisation (ICH)** mentioned on Page 8 is a unique organisation consisting of representatives from the regulatory authorities in the European Union (EMA), Japan (MHLW) and the USA (FDA), and experts from the pharmaceutical industry in the three regions, in a single forum.

The purpose of the ICH is to promote greater harmonisation in the ways in which the individual regulatory bodies regulate new drugs such that the medicine reaches the patient economically and with the minimum delay whilst maintaining the standards of safety, quality and efficacy necessary to safeguard public health.

Current goals include finalisation of ICH Q12, which is intended to link with ICH Q8-Q11 guidelines to provide a framework to facilitate the management of the entire "Pharmaceutical Product Lifecycle".

(Note: A similar organisation, the **Global Harmonisation Task Force (GHTF), exists for medical devices).**



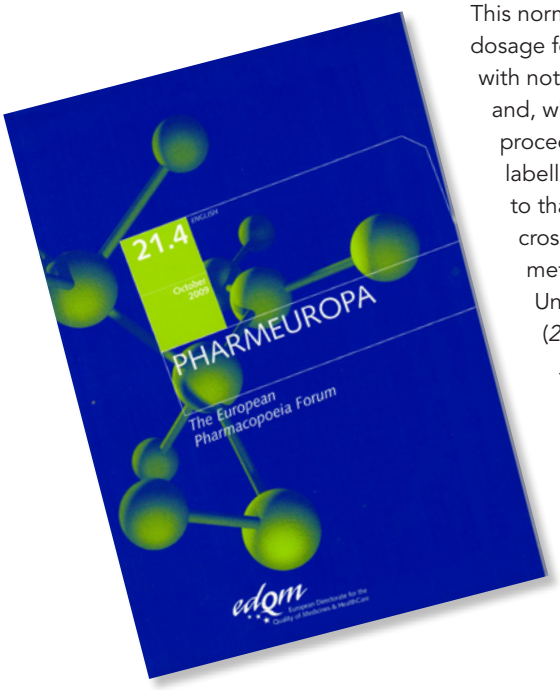
Current Ph.Eur.

ORGANISATIONS AND THEIR ROLES

3. DRUG SAFETY, QUALITY AND EFFICACY – THE PHARMACOPOEIAS

The main role of the Pharmacopoeias is to define the standards with which medicines must comply and the methods by which compliance will be adjudged.

As with the regulatory groups, the leading Pharmacopoeias tend to be those of the European Union, Japan and the USA.



Pharmeuropa

a) European Pharmacopoeia

This is published by the Directorate for the Quality of Medicines and Healthcare of the Council of Europe (EDQM).

In the **European Pharmacopoeia (Ph. Eur.)**, the main information relating to a drug product is contained in the general monograph relating to the dosage form concerned (see "Monographs on Dosage Forms").

This normally gives a definition of the dosage form e.g. tablets, together with notes as to its production and, where applicable, the test procedures, storage conditions and labelling requirements relevant to that type of product, with cross references to appropriate methods of testing e.g. Uniformity of Dosage Units (*2.9.40*).

The EDQM is also responsible for"**Pharmeuropa**", a quarterly publication which contains "Draft Monographs and General Texts for Comment" together with the latest news on "International Harmonisation".

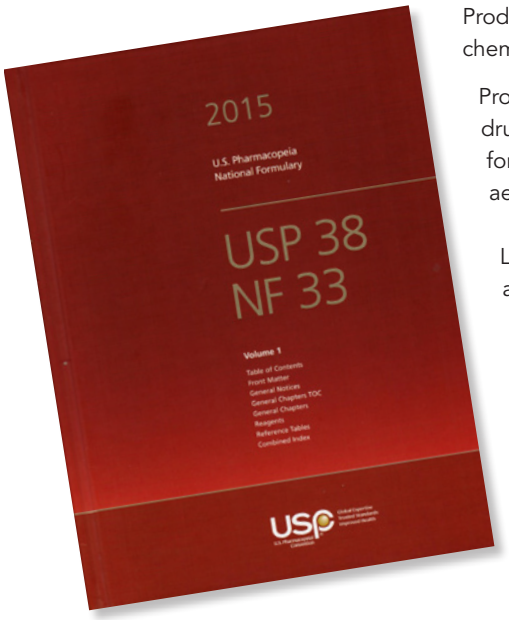
b) United States Pharmacopeia

Hitherto, the **United States Pharmacopeia (USP)** has adopted a similar approach to Ph.Eur. with details of the test procedures to be employed together with all of the other relevant information in product specific monographs with cross references to the appropriate methods of testing e.g. Uniformity of Dosage Units <905>.

A separate chapter, Pharmaceutical Dosage Forms <1151>, gives a general description and definition of the more common dosage forms together with the general principles in their compounding and manufacturing.

However, in USP 38 the Pharmacopeia has introduced a series of new chapters, <1> through to <5>, entitled **General Requirements for Tests and Assays**, which provide general information and the critical quality attributes applicable to the various dosage forms based on their **route of administration** (see Table on Page 11).

The five chapters concerned detail the test procedures relevant to each dosage form, divided between those relating to product **quality** and those to product **performance**, with cross references to the methods of testing as appropriate.



Product **quality** tests assess physical, chemical and microbial attributes.

Product **performance** tests assess drug release from the dosage form concerned or, in the case of aerosols, particle size distribution.

Like Ph.Eur., USP also produces a bi-monthly publication entitled "Pharmacopeial Forum", which contains discussion documents relating to new and/or amended chapters and monographs.

◀ Current USP

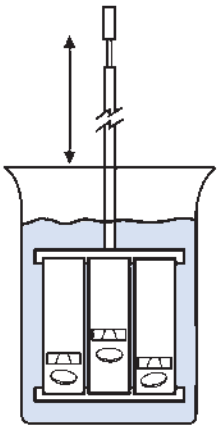
Pharmacopeial Forum ▶

NEW USP 38 CHAPTERS <1> TO <5>

ROUTE OF ADMINSTRATION	Site of Release	Typical Dose Forms	Product Tests for QUALITY	Product Tests for PERFORMANCE
Injections & Implanted Drug Products (Parentals) Chapter <1>	Body tissues and fluids	Injections, particles, liposomes, implants, stents	<1>	<1001> Under development
Oral Drug Products Chapter <2>	Oral	Tablets and Capsules, Liquids	<2>	<701> <711>
Topical and Transdermal Drug Products Chapter <3>	Skin	Semisolids, Transdermal Patches	<3>	<724> <1724>
Mucosal Drug Products Chapter <4>	Ear, eye, nose, throat, urether, vagina, rectum	Various see <4>	<4> Under development	<1004> Under development
Inhalation and Nasal Drug Products Chapter <5>	Lung, nasal cavity	Aerosols, sprays, powders	<5>	<601>, <602> <603>, <604> <1601>, <1602>

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 test 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 positioned 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

** Ph.Eur. 2.9.1 and USP <701>*

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.

PHARMACOPOEIAL 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 offers 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 robust **all metal** construction. The motor drive employed operates 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

"Quick-Release" Basket Assembly

Disintegration Tester DTG 2000 IS

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
- "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

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.

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

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

Basket fitted with Special Cover

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 covered 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	✓

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:

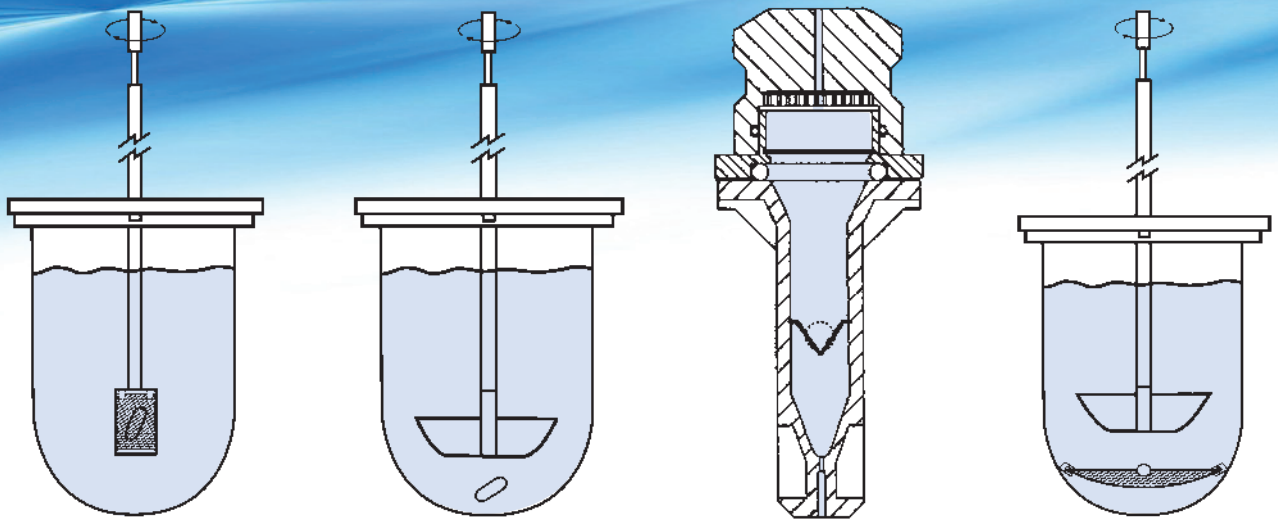
- Optimisation of therapeutic effectiveness during development and stability assessment
- Routine assessment of production quality to ensure uniformity between production lots
- Prediction of *in vivo* availability i.e. bioavailability (where applicable)
- Assessment of **bioequivalence** (production 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 usually 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.



Apparatus 1 - Basket | Apparatus 2 - Paddle | Apparatus 4 - Flow Through Cell | Apparatus 5 - Paddle over Disc

THE ROLE OF THE REGULATOR

The **Quality by Design (QbD)** approach adopted by the EMA, FDA and the Japanese MWHL 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.

Work is currently under way on ICH Q12, which will link with ICH Q8-Q11 guidelines to provide a framework to facilitate the management of the entire "Pharmaceutical Product Lifecycle".

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**.

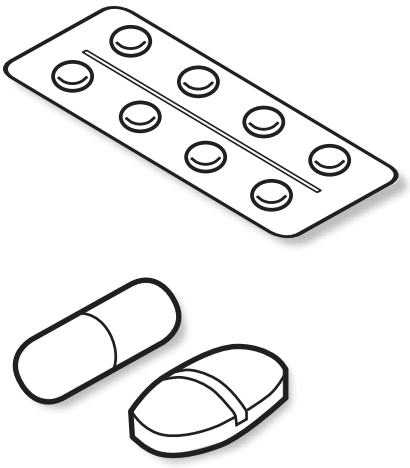
This annex gives examples of many of the essential concepts employed in QbD, including **Critical Quality Attributes (CQAs)**, Design Space and Control Strategy, and its implementation through **Process Analytical Technology (PAT)** tools.

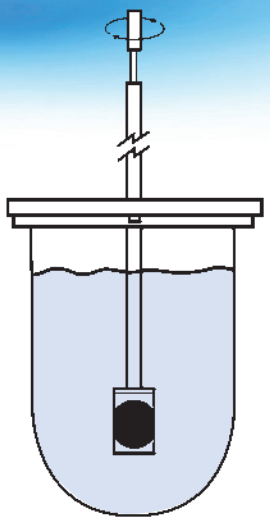
Dissolution or, perhaps more correctly, **Drug Release** is an essential Critical Quality Attribute (CQA) in the development, manufacture and QC of virtually all medicines available today.

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

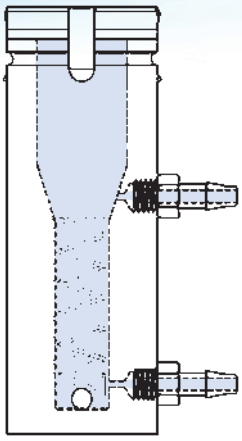
- SUPAC-IR Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation, January 1995
- Dissolution Testing of Immediate Release Solid Oral Dosage Forms, January 1997
- SUPAC-MR 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
- Extended Release Oral Dosage Forms: Development, Evaluation and Application of *In Vitro/In Vivo* Correlations, September 1997
- The use of Mechanical Calibration of Dissolution Apparatus 1 and 2 - Good Manufacturing Practice (CGMP), January 2010
- Q4B Evaluation & Recommendation of Pharmacopeial Texts for Use in the ICH Regions Annex 7 (R2) Dissolution Test General Chapter, June 2011

A similar function to the FDA is provided in the European Union (EU) by the **European Medicines Agency (EMA)** in the form of the **Committee for Medicinal Products for Human Use (CHMP)**, with guidances based principally on ICH recommendations.

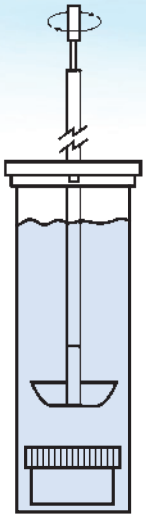




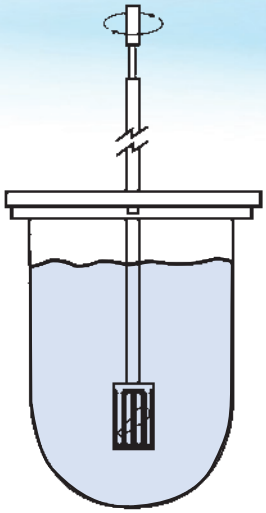
Apparatus 6 - Cylinder



Vertical Diffusion Cell (Franz Cell)



Special Immersion Cell



Special Suppository Basket

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 Pharmacopeia (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> Assessment of Drug Product Performance
<1092> Dissolution Procedure: Development & Validation
<1094> Capsules - Dissolution
<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)** and **Immersion Cell** now included in the US Pharmacopeia and used for testing the *in vitro* release rate of semi-solid dosage forms such as creams, gels and ointments (Semisolid Drug Products - Performance Tests USP Chapter <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 on Page 20).

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 (≥100 rpm may be more suitable for modified release dosage forms).

- Beads (use a finer mesh basket where appropriate)
- Orally disintegrating (orodispersibles)
- Capsules (preferred over Apparatus 2)
- 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 (≥100 rpm may be suitable for modified release forms).

- Capsules
- Liquid Filled Capsules
- Powders
- Tablets (preferred over Apparatus 1)
- Hydrogels
- Orally disintegrating (orodispersibles)
- Suspensions
- * 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 Chapter <1724> - 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
- Implants
- Ointments
- Gels
- Lotions
- 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.

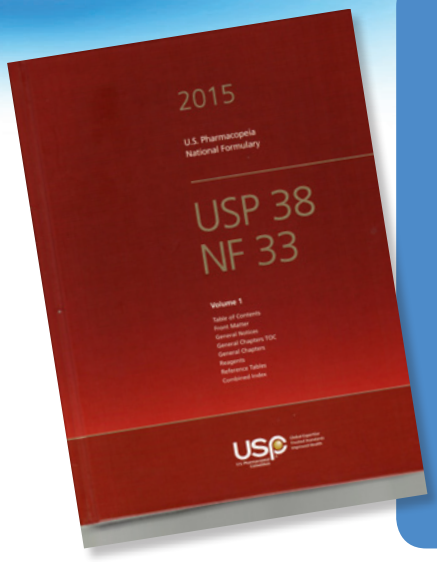
- Creams
- Implants
- Ointments
- Gels
- Lotions
- Microparticulates

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, it 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 those 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 41) 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 extruding 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 precison 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 Copley Dissolution Tester Series DIS-EMC described on Page 30.

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

This alternative approach was endorsed by the Food and Drug Adminstration (FDA) in its 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 *FDA Document No. DPA-LOP.002 "Mechanical Qualification of Dissolution Apparatus 1 and 2"* or *ASTM E 2503-13 "Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus*")* 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 PVT 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 opposite illustrates the differences between the current specifications and the suggested Enhanced Mechanical Calibration specifications from both the FDA* and the USP.

** Note: For all intents and purposes, the ASTM E 2503-13 standard is comparable to that of the FDA (Document No. DPA-LOP.002).*

Comparison between Compendial and Enhanced Mechanical Calibration Specifications

Calibration Parameter	Current Pharmacopoeia	Enhanced USP Specification	Enhanced FDA Specification
Bench Horizontality		≤ 1° from the horizontal	No Specification Given
Vessel Support Horizontality		≤ 0.5° from the horizontal in two orthogonal directions	No Specification Given
Basket Conformance	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"	
Paddle Conformance	Must conform to <711> Free of "Gross Defects"	Must conform to <711> Free of "Gross Defects"	Must conform to <711> Free of "Gross Defects"
Vessel Conformance	Must conform to <711> Free of "Gross Defects"	Must conform to <711> Free of "Gross Defects"	Must conform to <711> Free of "Gross Defects"
Shaft Wobble; Basket	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
Shaft Wobble; Paddle	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
Shaft Verticality	N/A	<0.5° from vertical. Check two positions	<0.5° from vertical. Check two orthogonal positions
Wobble; Basket	≤ 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
Wobble; Paddle		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	
Shaft Centricity; Basket (Vessel Centring)	≤ 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)
Shaft Centricity; Paddle (Vessel Centring)	≤ 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
Vessel Verticality	N/A	± 0.5° from vertical. Check two positions.	≤ 1.0° from vertical. Check two orthogonal positions
Height Check; Basket Depth	25 ± 2.0 mm	25.0 ± 2.0 mm - measure each position	25 ± 2.0 mm
Height Check; Paddle Depth	25 ± 2.0 mm	25.0 ± 2.0 mm - measure each position	25 ± 2.0 mm
Rotational Speed	± 4% from target	± 1 rpm evaluated at 50 and 100 rpm.	± 2 rpm
Temperature	37 ± 0.5°C	37 ± 0.5°C (All vessels to be within 0.4°C of each other when filled with 500 mL of media)	37 ± 0.5°C

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 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 and 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 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.

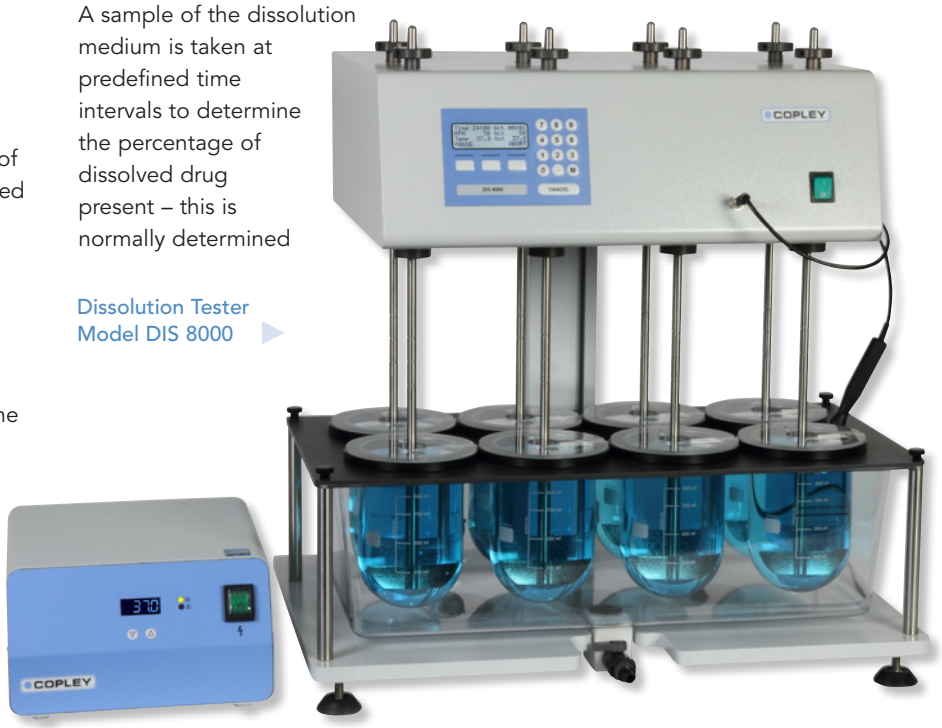
During the test, a motor is used to rotate the drive shaft at the speed (normally 50, 75 or 100 rpm) specified in the Pharmacopoeias.

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

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 actions 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

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 (all metal) "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.

Unfettered access to the critical sampling area above the water bath

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.
- **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.

Interchangeable Baskets/Paddles

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.

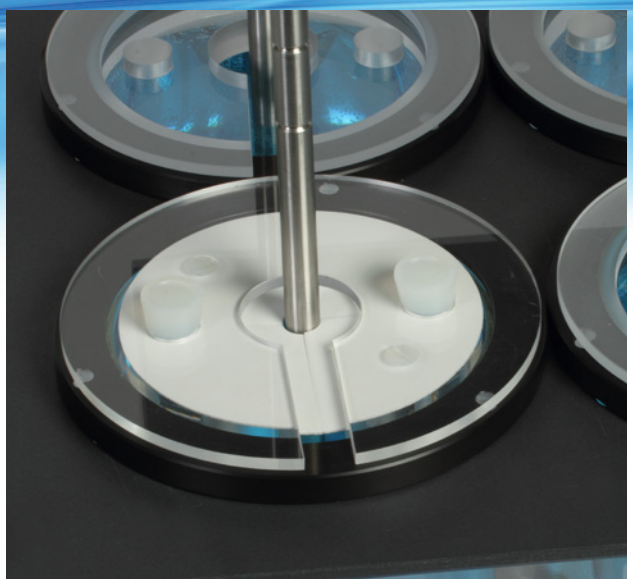
BASKETS, PADDLES AND ROTATING CYLINDERS

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 it allows the baskets/ paddles to be pushed upwards to gain maximum accessibility to the vessels.

"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 required.

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 positioned 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.

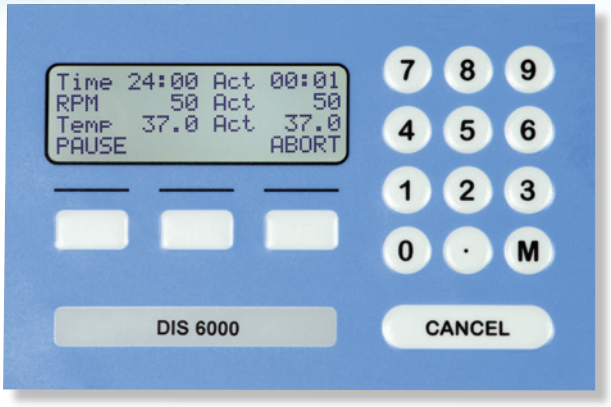
The digital heater/circulator has an accuracy of **+/- 0.1 degrees C** thus ensuring a constant and even distribution of heat throughout the bath. It is fitted with an **adjustable over-temperature cut-out** and alarm indicator, together with a **low-level cut-out** which operates if there is insufficient water available in the bath.

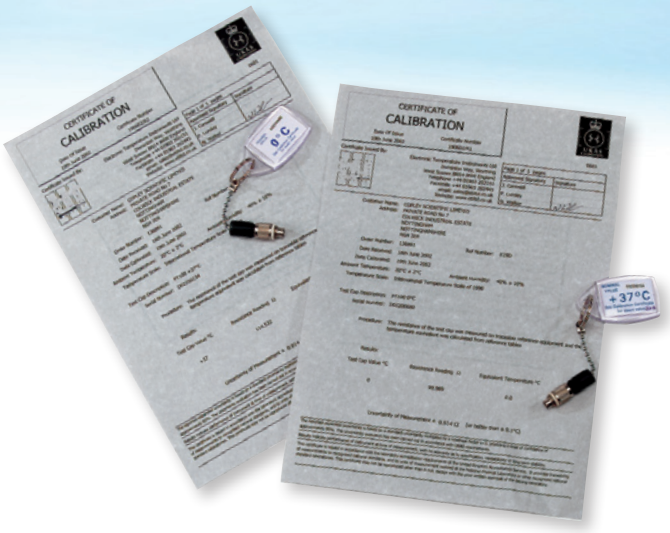
The one piece vacuum formed water bath is constructed in rigid PETG and has been specifically designed to eliminate leaks and to make it easier to clean. A fill line is provided on each bath to indicate the level to which the bath must be filled.

The water bath and the easy to clean teflon-coated 316 stainless steel vessel support plate are supported by 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





Temperature Calibration Certificate

DISSOLUTION TESTER DIS 8000

OPERATION

The control of all models is provided by a membrane keypad linked to a 4 line, 20 character back-lit 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 printout 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 Calibration Tools section on page 39.

AUTOMATION

Manual dissolution testing is extremely time consuming and tedious. For this reason, many users are turning to completely 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)
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 (all metal), 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, with no further adjustments 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 printout)

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 33

DIS 8000 with DissoMate Media Preparation Station

DISSOLUTION TESTER DIS 6000

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

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 printout of time, date, bath identifcation, 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.

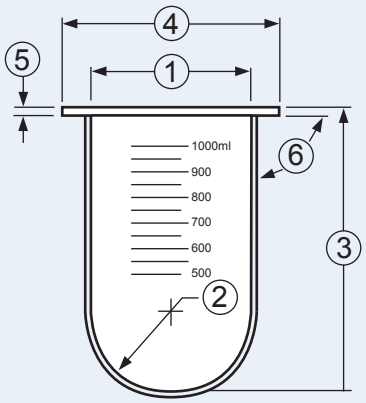
In all other respects, the Dissolution Tester DIS 6000 is similar in construction to the DIS 8000 described on the preceding pages.

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 33

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 for you.

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

The standard versions of the DIS 6000 and DIS 8000 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 percentage 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 11 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 extruding 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 23 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 betters 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 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

Tablet Drop (before)

Tablet Drop (after)

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)

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 (below) 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.

Manual Sampling Cannula

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 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**).
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 32 for probe filters.

Resident Probe wth Luer fitting (left) and with Omnifit fitting (middle) together with a Return Line Insert (right)

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)

SPARE PARTS AND ACCESSORIES

Carrying Rack for 4 Vessels

SUNDRIES

Storage Rack for 8 Baskets or Paddles

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.

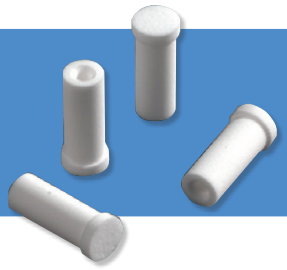
Thus, if the results using the reference standards prove satisfactory, it can be assumed that the physical and mechanical variables of the system are within the specified limits and that any anomalies are due to the dosage form under test.

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

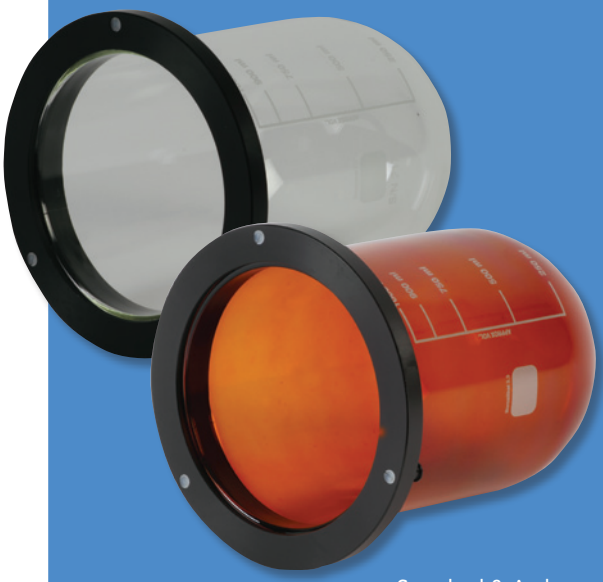
SPARE PARTS AND ACCESSORIES

Dissolution Drive Shaft

316 SS Basket

3 Prong Spring & Basket Holder

316 Stainless Steel & Teflon Coated Paddles



Standard & Amber Coated Vessels

316 SS, Basket & 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 Vessel Cover Cat.No.1353
	CAPSULE SINKERS AND WEIGHTS
1356	Set of 6 316 Stainless Steel Sinkers
1356A	Set of 8 316 Stainless Steel Sinkers
1345	Set of 6 Basket Sinkers (Japanese Pharmacopoeia)
1348	Wire, 316 Stainless Steel (50 ft length)
1357	Set of 6 3-prong Plastic Sinkers
	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**

TRANSDERMAL PATCH TESTING (DRUG RELEASE)

PADDLE OVER DISK
The "Paddle over Disk" technique 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 Pharmacopeia (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

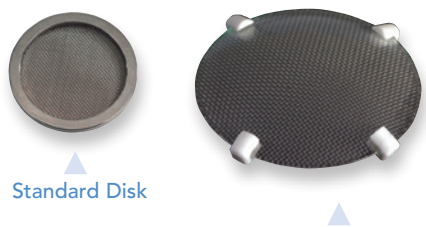
ROTATING CYLINDER
An alternative method for the testing of **transdermal patches,** USP Method 6 (Ph.Eur. Chapter 2.9.4. Method 3), employs the same dissolution equipment as USP Method 1, simply substituting a cylinder stirring element in place of the standard basket (see main photos and left).

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 (Cuprophan 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 Cuprophan 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)
1386	Cylinder Stirring Element including Extension (USP Method 6)
1386B	Height Gauge for Cylinder Stirring Element
1387	Cuprophan Flat Membrane 150 pm (10 Sheets)

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 7 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 normally consists of six or eight 7 mm diameter punch and die set kits together with a hand operated press specifically designed to allow the compression of the material into a compact.

Final Assembly prior to placement in Dissolution Tester

Hand Operated Press

The punch and die set kits can be purchased singularly if required.

The compaction process is relatively simple:

1) Place the die on to the lower punch (compaction plate).

2) Fill the die cavity (the hole in the centre of the die) with sufficient powdered drug to reach the top.

3) Use a flat blade or spatula to level off the powder such that the top of the powder is flush with the top of the die.

4) Now place the upper punch on to the top of the die locating the punch tip over the sample, and using light pressure from the hand, compact the powder mixture into the hole.

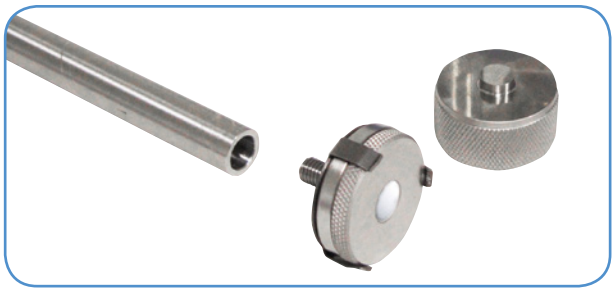
5) Then place the entire assembly into the hand operated press, and with the force transmitted to the top of the punch, apply the appropriate pressure (approx. 2 tons) to compact the powder.

6) Now release the assembly from the press, remove the die containing the compact and locate it into the three pronged spring holder as shown in the photographs below.

7) Finally, 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.

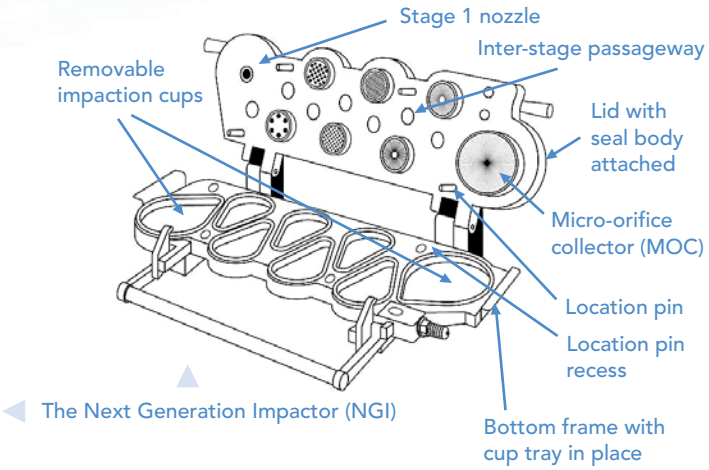
8) Repeat the exercise for the other assemblies (where applicable).

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



Drive Shaft, Intrinsic Dissolution Assembly and Top Punch

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



The Next Generation Impactor (NGI)

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

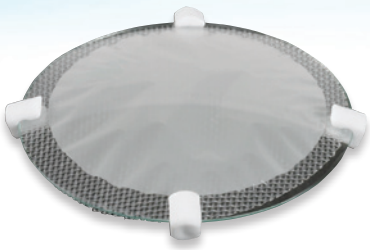
Based on a concept developed by Professor Jason McConville at the College of Pharmacy, University of Texas, the NGI Dissolution Cup and Membrane Holder incorporates a modification of the standard NGI collection cup.

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



Watchglass/PTFE Assembly for use with ACI

The small amount of aqueous fluid and surfactant found in the lung makes 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 (28.3 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 Techologies (August 2011) p. 15-23.*

Cat. No.	Description
6001	NGI Dissolution Cup and Membrane Holder (each)
6002	55 mm Punch (for cutting filters to size)
6003	Watch Glass/PTFE Assembly for use with ACI (each)
6004	Pack of 100 Polycarbonate Filters (0.1 micron x 76 mm diameter)

SPECIAL APPLICATIONS

SMALL VOLUME CONVERSION KITS

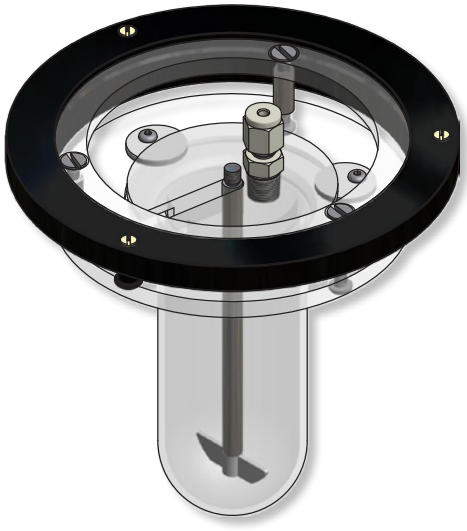
Two conversion kits comprising special low volume vessels of either 100 or 200 mL capacity with appropriate mini-paddles are available for low dose formulations.

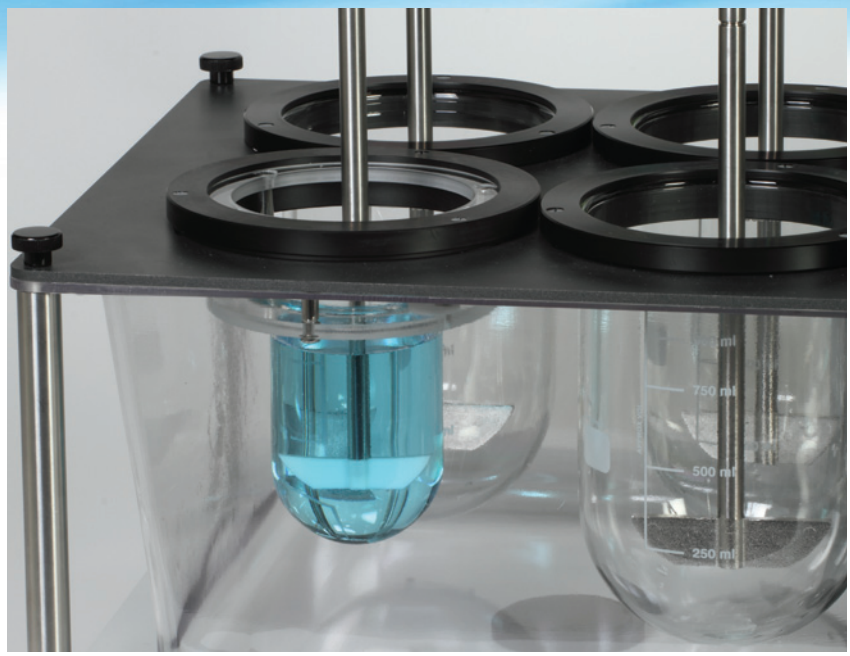
Some dosage forms, with small quantities (or extended release) of drug, require much lower concentrations than are usual in the standard 1000 mL vessel.

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 71 for further details).

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.

Special Coarse Mesh Basket

BASKET FOR THE DISSOLUTION OF SUPPOSITORIES

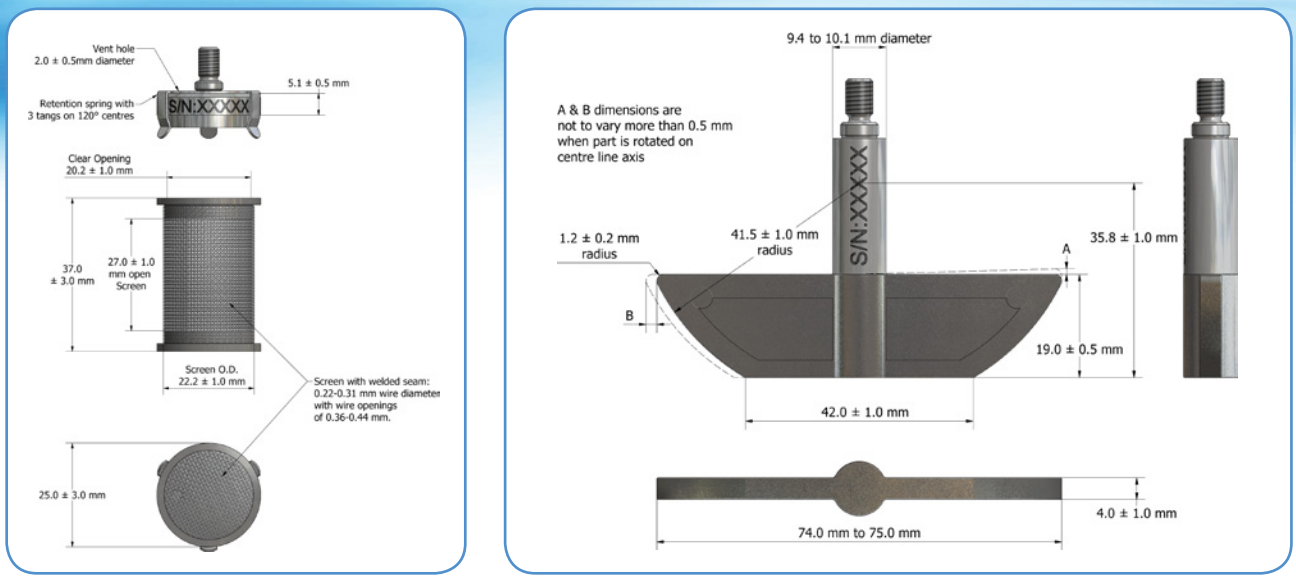
Oil based suppositories give unacceptable and unreproducible results utilising the standard 40 mesh stainless steel dissolution basket, since the suppository base has a tendency to block the filter mesh.

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



Dissolution Basket and Paddle Specifications (ICH Harmonised Tripartite Guideline Q4B Annex 7 (R2))

CALIBRATION TOOLS

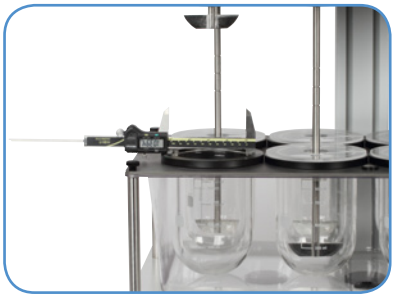
Whether employing the conventional approach to qualification specified in USP Chapter <711> - using a combination of less rigid mechanical checks supported by the traditional Performance Verification Test (PVT) with prednisone - or the more recent FDA approach based on a more rigid series of mechanical checks alone, it is essential that your dissolution tester is checked on a regular basis to ensure that it conforms with the relevant criteria.

FDA's current good manufacturing practice (CGMP) regulations require that "laboratory apparatus be calibrated at suitable intervals in accordance with an established written programme of scheduled procedures (21 CFR 211.160(b)(4) and 211.68)".

Copley Scientific provides a complete range of calibration and qualification tools to ensure that your equipment complies with the appropriate guidance including:

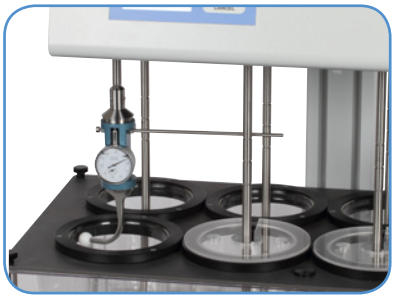
- Speed, Temperature & Vibration
- Horizontal & Vertical Levelling
- Basket, Paddle & Vessel Conformance
- Basket & Paddle Height
- Basket, Paddle & Shaft Wobble
- Vessel Verticality and Centring
- Shaft Verticality

Calibration Kit (see details overleaf)



Basket, Paddle & Vessel Conformance

Basket/Paddle Wobble



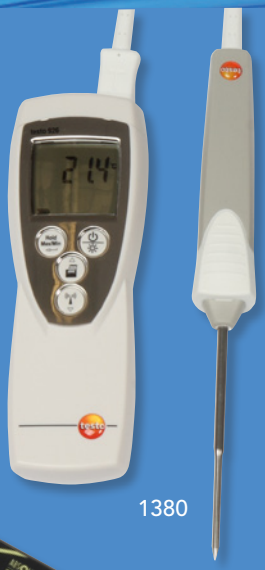
Vessel Centricity

Horizontal & Vertical Levelling

Shaft Rotational Speed (Tachometer)

CALIBRATION TOOLS

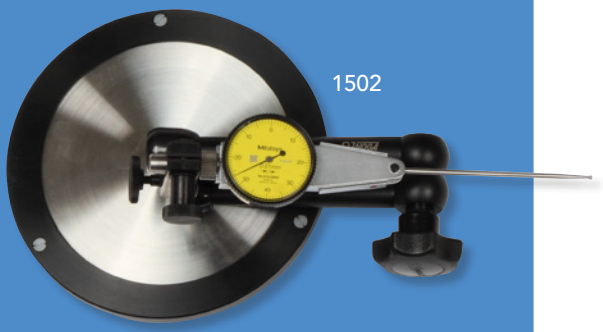
1378



1380

1381

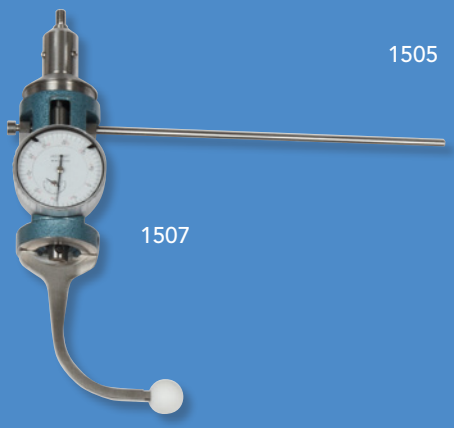
1501



1502

1503

1505



1507

Cat. No.	Description
1378	Height Checker
1380	Temperature Checker (Digital Thermometer)
1381	Speed Checker (Tachometer)
1501	Digital Caliper Model 500
1502	Wobble Checker
1503	Level Checker (Spirit Level)
1505	Stopwatch
1507	Centricity Checker
1508	Calibration Tool Kit complete (includes above tools)
1509	Verification Rig for Wobble & Centricity Checkers*
1320	Vibration Meter*

* Not included in the standard Calibration Tool Kit

Note: All items UKAS calibrated as appropriate.

1508

1509* (shown with 1507)

1320*

Note: Chapter <1092>, USP 38, 1st Supp., now specifically recommends a dissolved oxygen level of > 6 ppm.

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 nine variables and 36 two-factor variables studied, three variables stood out as being statistically significant as far as mean percentage 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.

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 Pharmacopeias 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, equilibriate 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

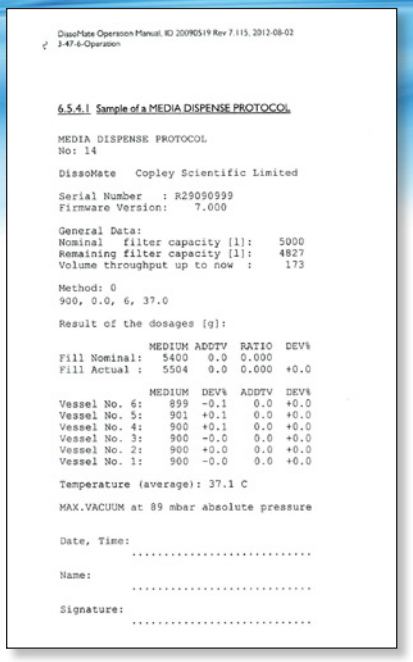
In addition to conformity to the compendial and regulatory requirements, there are a number of user requirements which must be taken into account:

- 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	✓

Dissomate with Dissolution Tester

Dispense Nozzle



DissoMate Protocol Printout

DissoMate Operation Manual, ID 20090519 Rev 7.115, 2012-08-02
3-47-6-Operation

6.5.4.1 Sample of a MEDIA DISPENSE PROTOCOL

```
MEDIA DISPENSE PROTOCOL
No: 14

DissoMate   Copley Scientific Limited

Serial Number    : R29090999
Firmware Version:     7.000

General Data:
Nominal   filter capacity [l]:    5000
Remaining filter capacity [l]:    4827
Volume throughput up to now  :     173

Method: 0
900, 0.0, 6, 37.0

Result of the dosages [g]:

             MEDIUM ADDTV  RATIO  DEV%
Fill Nominal:   5400   0.0 0.000
Fill Actual :   5504   0.0 0.000  +0.0

             MEDIUM  DEV%  ADDTV  DEV%
Vessel No. 6:    899  -0.1    0.0  +0.0
Vessel No. 5:    901  +0.1    0.0  +0.0
Vessel No. 4:    900  +0.1    0.0  +0.0
Vessel No. 3:    900  -0.0    0.0  +0.0
Vessel No. 2:    900  +0.0    0.0  +0.0
Vessel No. 1:    900  -0.0    0.0  +0.0

Temperature (average): 37.1 C

MAX.VACUUM at 89 mbar absolute pressure

Date, Time:
          ..........................

Name:
          ..........................

Signature:
          ..........................
```

MEDIA PREPARATION - THE DISSOMATE

The DissoMate Media Preparation Station Model X8 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 the 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.

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

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 of the X8* 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 reaeration 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%).

***New:** A second and larger unit, the X15, which allows for 15 litres of fresh medium sufficient to serve two baths is now available as an option.

DissoMate with Disintegration Tester

MEDIA PREPARATION - THE DISSOMATE

It typically takes 15 minutes from start to prepare eight 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 giving details of 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 x 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 Model X8
1514	DissoMate Model X15
1323	Printer (including cable)
1324	Validation Logbook
1510	Manual Validation Tools
1515	Automated 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 six 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 comprise 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 eight 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.

With this technique, medium from each individual test vessel is circulated continuously through each of a series of flow cells (nominally six to eight) 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 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 six, seven or eight 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 six to eight 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 six or eight dissolution vessels at predetermined time intervals and deposit them in test tubes or HPLC vials for subsequent analysis (see No.1. on Page 44).

The system employs a series of six or eight 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 two 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

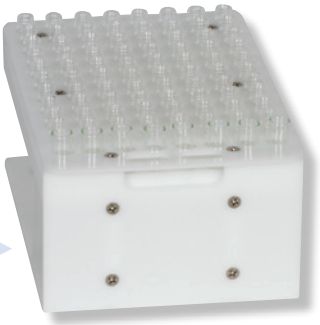
2. METHOD MENU
The Method Menu is activated by pressing the SET UP button.

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 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 eight 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.

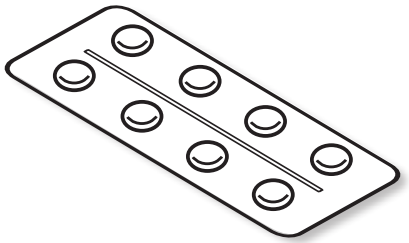
3.8 System Menu
Allows you to set up your system parameters in order to meet your own individual needs. The DissoFract measures 30 x 58 x 35 cm (w x d x h) and weighs 23 kg.

DissoFract Sampling System

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)
1513	Pack (of 50) 45 Micron Filters for special probes
1328	HPLC Vial Rack (spare)
1511	Test Tube Rack (spare)
1330	Printer (including USB cable)
1319	Validation Logbook
1512	Validation Tools

Friability

INTRODUCTION



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

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 test apparatus comprises a motor capable of rotating a 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.

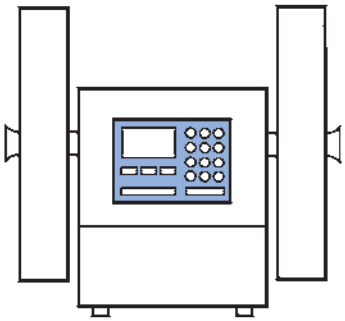
Abrasion drums for carrying out tests into the attrition of tablets caused by the product rubbing together during transit are also available on request.

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 51 and 52 is a relatively 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)



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, with either one (Model FR 1000) or two (Model FR 2000) test drums.

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)

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

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 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.

OPERATION

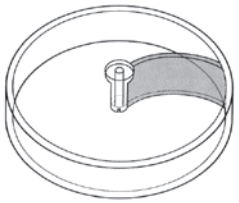
Considerable attention was paid to the design of the FR and FRV series to ensure that the number of actions necessary to perform a test are kept to a minimum. Consequently, once the method (number of revolutions or time) has been selected and the test duration set, it is only necessary to press the START 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) x 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
1410	Qualification Tools
1407	Abrasion Drum (Optional extra)
1408	Friability Drum (Spare)
1409	Device for angling friability tester at 10 degrees

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 for both research and development and quality control applications.

Following review, the instrument has now been included in the 8th 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 42 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.

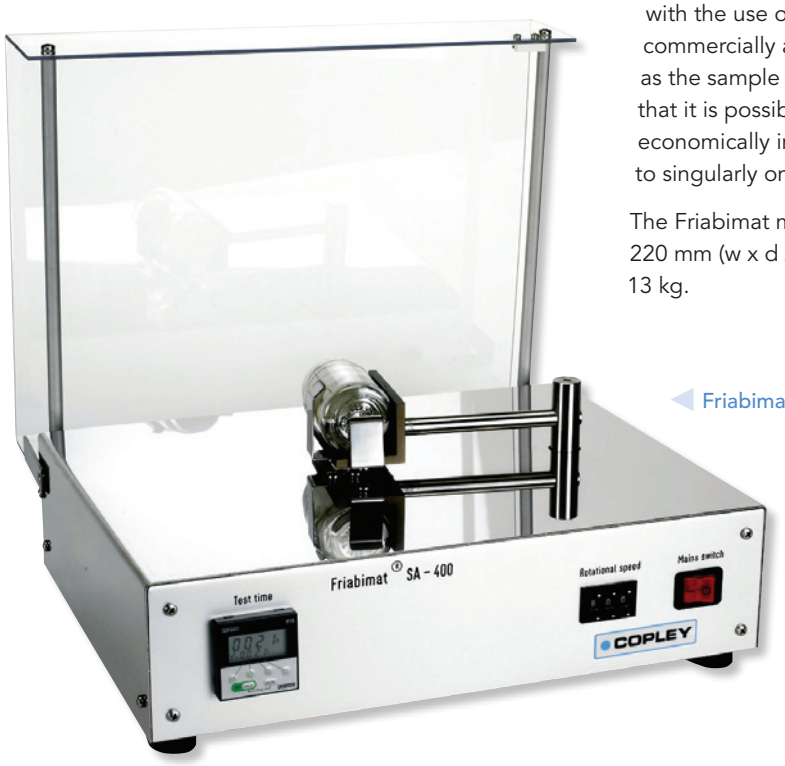
The abrasive action is generated by the horizontal shaking movement of the oscillating arm, which causes the samples to rub against and collide with each other and/or the internal surfaces of the sample container.

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.

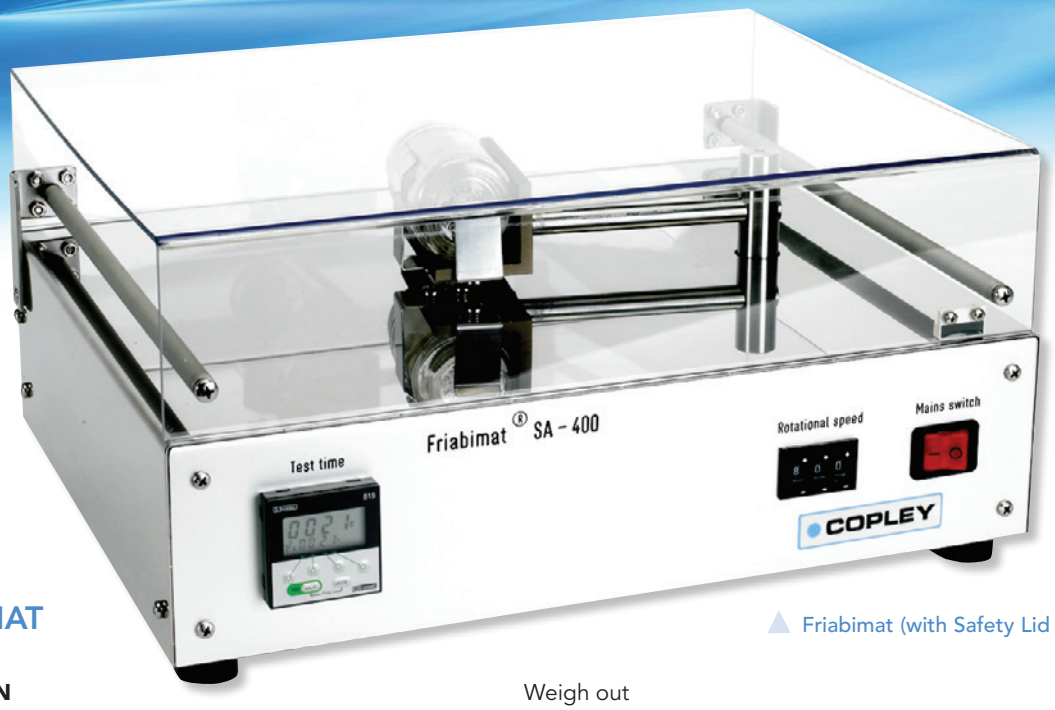
This enables the user to optimise the test conditions applicable to each formulation and reproduce it at will.

Average test times are between two and four 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 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.

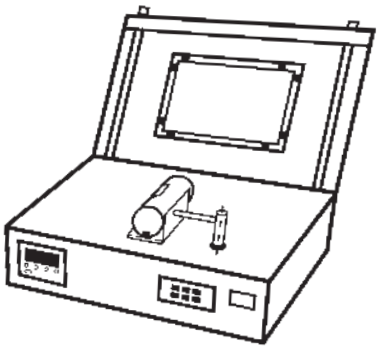
Note: The Friabimat is fitted with a **safety interlock** which automatically pauses operation if the safety cover is opened during a test. The test can be re-started once again by simply closing the lid.

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) x 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)

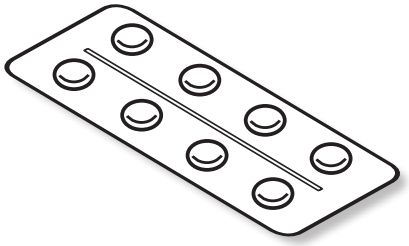


Oscillating Container

Cat. No.	Description
1450	Friabimat Model SA-400 including 1 Glass Container
1451	Oscillation Frequency Verification Chart
1452	Pack of 100 Spare Glass Containers
1453	IQ/OQ/PQ Documentation Pack
1455	Qualification Tools
1454	355 Micron Sieve

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 printout 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 Pharmacopeia (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 kg 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 printout 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. If **diameter** measurements are required, ensure that this option is selected prior to operation.

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 Pharmacopeia**, 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).** Diameter, if selected, is reported in **mm.**

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 instruct 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.

** If **diameter** measurements are required, ensure that the diameter measurement option is set to "On every test" at this point.*

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

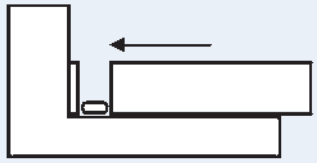
Testing of the next sample can be initiated in two ways depending on the set-up mode: (a) by pressing the <Test> key or (b) by lowering the guard.

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 six samples are tested respectively.

At the end of the test, to initiate the printout 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 diameter selection, 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 by 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 printout of individual tablet results and diameter printout, 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.

Weight and Thickness Measurment

Calibration Certificate

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 to help 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 and diameter (optional) - simply add a balance and/or a Mitutoyo micrometer for measuring thickness and you have a complete system for measuring the hardness, diameter, 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 and diameter (see section on OPERATION on Page 56).

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 diameter and hardness (f required).

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

Cat. No.	Description
2501	Tablet Hardness Tester Model TBF 1000
2501A	Tablet Hardness Tester Model TBF 1000 (with polished S/S 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
2505	IQ/OQ/PQ Documentation Pack
2506	Pack of 10 Paper Rolls
2511	Re-Calibraton Certificate
2507	Sartorius Balance Model Quintix 224-1 CEU (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 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 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 Chaper <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 Pharmacopeia Chapter <1174>** on **Powder Flow.**

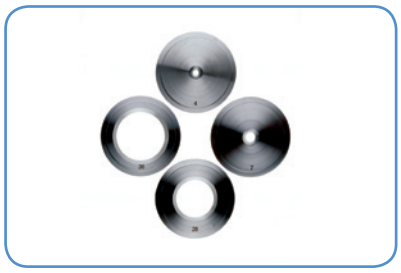
The widespread use of powders in the pharmaceutical industry has led to a proliferation of test methods for measuring powder flow.

The 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 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 suggest 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 six times the diameter of the particles and
c) The diameter of the cylinder is greater than two 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 Attachments

BEP2 with Funnel Attachment

BEP2 with Funnel and Angle of Repose Attachments

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 61).

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 four 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)

Manually Operated Stirrer

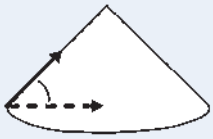
ANGLE OF REPOSE ATTACHMENT

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.

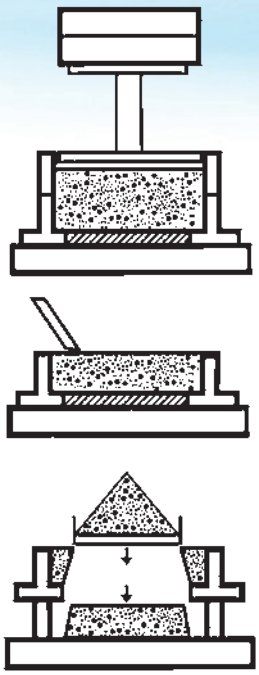
For this particular test, the funnel is normally equipped with a special 10 mm i.d. nozzle mounted 75 mm above the test platform. If necessary, the contents may be stirred to assist in the powder flow (see left).

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 63 indicates the flow properties associated with corresponding Angles of Repose.



BEP2 with Funnel and Shear Cell Attachments

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 kg.

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
1658	IQ/OQ Documentation Pack
1659	Qualification Tools

* Requires the Funnel Attachment (Cat.No.1652) to operate

BULK DENSITY TESTERS

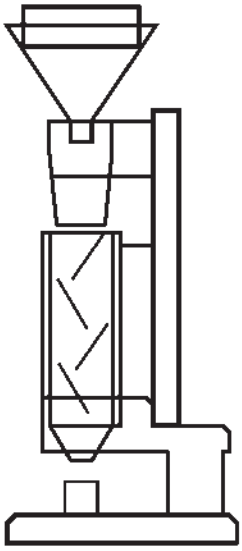
The bulk density of powders can be extremely difficult to measure since the slightest disturbance may result in a change in the results.

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 Page 65).

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 SCOTT VOLUMETER

The **Bulk Density Tester (Scott Volumeter)** is described in **USP Chapter <616> Method 2** and **European Pharmacopoeia Chapter 2.9.34** 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.

18-mesh and 10-mesh screen filter inserts

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^3)
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 has been designed to measure the tapped density of powders, granules and similar products in accordance with **Methods 1 and 2** of **USP Chapter <616>** and **European Pharmacopoeia Chapter 2.9.34**

This technique is particularly useful in powder flowability studies and also in determining the amount of settlement during transit in order 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 the specified distance of 3 +/- 0.2 mm 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 (one or two). 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 x 250 mL Cylinder)
1602	Tapped Density Tester JV 2000 (2 x 250 mL Cylinders)
1603	IQ/OQ/PQ Documentation Pack
1616	Qualification Tools
1604	250 mL Measuring Cylinder (spare)
1605	100 mL Measuring Cylinder (option)
1605A	Special Platform for use with 100 mL Cylinder (option)
1606	Acoustic Cabinet

Semisolids

INTRODUCTION

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

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.

VDC Test System
Model HDT 1

The cell comprises two parts: (a) the donor chamber containing the sample to be tested and (b) the receptor chamber 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 (mcg/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.

Vertical Diffusion Cell Test System Model HDT 1000 (without cells, with "open" cell tops and with "occluded" cell tops

VERTICAL DIFFUSION CELL TEST SYSTEM MODEL HDT 1000

The **HDT 1000 Vertical Diffusion Cell Test System** has been specifically designed to accommodate **10 diffusion cells.**

It comprises a heated aluminium block capable of 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 (ambient +5 to 150 degrees C) and stirrer speed (400 to 2000 rpm) are set, controlled and displayed from a single control panel on the front of the unit.

The HDT 1000 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 80 x 325 x 145 mm (w x d x h) - a footprint less than an A4 sheet of paper.

A second, low cost test system (the **HDT 1)** is available to accommodate a **single diffusion cell.**

CELLS

All of the cells employed in the Vertical Diffusion Cell Systems feature a unique clamping system to replace the conventional clamps used on more traditional cells and to simplify cell preparation and sample collection.

Two sizes of cell are available corresponding to the cells described as Models "B" and "C" in Chapter <1724> of the current USP.

The **Type "B" cell** has a surface diameter of ~11 mm, a surface area of ~1.00 cm^2 and a receptor medium volume of ~7 mL. The **Type "C"** Cell has a 15 mm orifice, a surface area of ~1.77 cm^2 and a volume of ~11 mL.

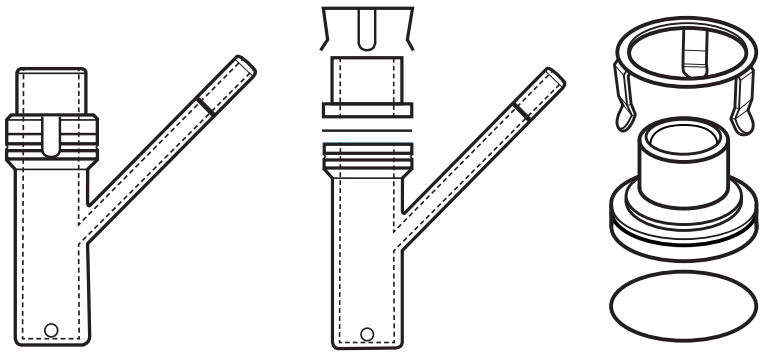
Both cells are manufactured from inert borosilicate glass and are fitted with a side sampling arm to facilitate filling, sample withdrawal and media replacement.

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.

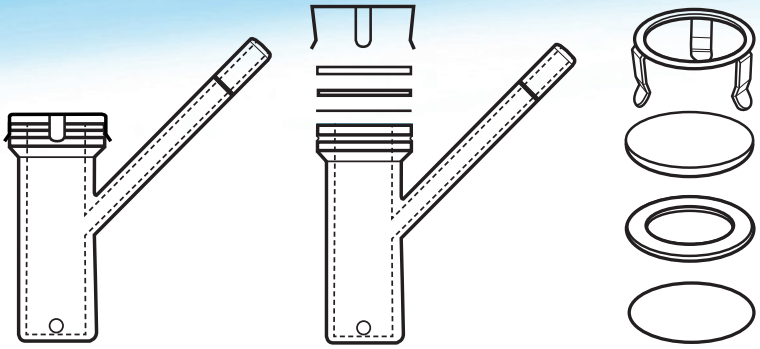
All of the cells are supplied complete with individual cell tops for **both "closed or occluded"** operation (as per USP Model "A") and **"open"**operation (as per USP Models "B" and "C") respectively.

The sample is separated from the receptor media by a synthetic, inert and highly permeable support membrane.

In the case of the "closed/occluded" cell top, the sample is constrained within the cavity of the PTFE sample chamber sandwiched between the membrane and a glass disk (see Page 68).



Cell Type C with "**Open**" Cell Top together with exploded Cell and Sample Holder



Cell Type "C" with **"Closed"** Cell Top together with exploded Cell and Sample Holder

Filling the cell

VERTICAL DIFFUSION (FRANZ) CELLS

Cell Preparation and Sampling - General Test Procedures

It is important to determine the exact volume of each cell prior to testing. This should be done with the magnetic stirrer bead in position.

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).

If possible, allow the membrane to equilibrate with the medium, in situ, for at least 30 minutes prior to application of the dosage form concerned.

Ensure that the receptor medium used to bathe the membrane is degassed prior to use in order to avoid air bubbles collecting underneath the membrane and impairing the diffusion process.

During the test itself, the temperature of the receptor medium should be maintained at that commensurate with the site of treatment, normally 32 +/- 1° C for skin or 37 +/- 1° C for vaginal preparations.

The stirring rate, normally 600 rpm +/- 10%, should be sufficient to maintain adequate mixing during the test.

Samples should be taken from each cell within +/- 2 minutes of the predetermined time intervals required by the test protocol.

"Open" Model

The design of the "open" cell top is illustrated in the schematic on Page 67. The **cell top** comprises three parts - the cell top, the membrane and the three pronged spring clip which serves to clip the cell top and membrane to the main body of the cell.

Insert the stirring bar into the bottom of the cell, then place the membrane followed by the cell top on the cell body. The joint between the cell top and body may be sealed with stretched paraffin wax film if required. Secure the assembly using the three pronged clip provided for this purpose.

Fill the receptor chamber with medium as shown, tilting the cell in multiple orientations such that any air bubbles trapped in the cell can escape via the sampling arm. The volume of medium is adjusted to the level marked on the sampling arm. Start the stirrer.

Initiate the test by adding the sample directly to the membrane surface (USP recommends not less than 1.0 mL/cm^2 or 1.0 g/cm^2). The donor chamber may be sealed with occlusive film if required.

Approx. 10 minutes prior to sampling, confirm the volume in the sampling arm and adjust it to the calibration mark as necessary. The sample should be taken from the centre of the mixing chamber using a syringe. Replace the sample volume removed with fresh media.

"Closed or Occluded" Model

The design of this cell top is based on the Vertical Diffusion Cell described in USP Chapter <1724> as Model "A". The cell top is "occluded" to prevent the ingress of air and hence minimise back-diffusion from sampling and also to provide a sample of known volume.

The **cell top** comprises a three part sandwich made up of:

a) Clear view sample support disk
b) PTFE sample chamber ring and
c) 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 is quick and easy. Insert the clear view glass support disk 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. 150 mg or 250 mg according to cell), removing any excess with the aid of a spatula.

Finally, place the membrane over the top of the sample 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.

Cell B - Open Top

Cell C - Open Top

Cell B - Closed Top

Cell C - Closed Top

Taking a sample & replacing media

VERTICAL DIFFUSION (FRANZ) CELLS

With the stirring bar in position, fill the cell body with the specified receptor medium, suitably degassed to remove air bubbles and prewarmed using suitable means to the requisite temperature such that there is a positive meniscus covering the top of the cell.

Now place the assembled sample holder on to the cell body with the membrane down and in contact with the receptor medium.

Check for and remove any air bubbles prior to placing the cell into the HDT 1000 and commencing stirring to initiate the test.

The joint between the cell top and body may be sealed with stretched paraffin wax film if so required.

Approx. 10 minutes prior to sampling, confirm the volume in the sampling arm and adjust it to the calibration mark as necessary. The sample should be taken from the centre of the mixing chamber using a suitable syringe.

It is essential, following sampling, to ensure that the volume of receptor medium, and hence contact between medium and the membrane, is maintained.

Replace the sample volume removed with fresh media such that the level is adjusted to the mark on the sampling arm. Ensure no air bubbles are present.

Membrane Selection
It is up to the user to select the appropriate membrane for his intended purpose. Typical membranes used are Acetate Plus (cellulose acetate), Cellosic, Polycarbonate, Nylon, Supor (polysulfone), Teflon and Tuffryn.

Some vertical diffusion cells are used in *in vitro* permeation studies on transdermal patches in which case excised human, animal skin or synthetic membranes such as the Cotran range (from 3M) can be used.

Copley Scientific offer a choice of three synthetic membranes as follows:

PVDF Membranes
The FDA Guidance for "Non-sterile Semisolid Dosage Forms SUPAC-SS CMC 7" dated May 1997, states any "appropriate inert and commercially available synthetic membrane such as polysulfone, cellulose acetate/nitrate mixed ester, ...of appropriate size to fit the diffusion cell diameter".

The 25 mm o.d. PVDF Membrane Cat. No.7270 is a hydrophilic polymeric membrane with a pore size of 0.45 microns that falls within this category.

Tuffryn Polysulfone Membranes
In 2009, USP published details of a suggested "Performance Verification Test (PVT)" for VDCs ("Stimuli to the Revision Process", USP Pharmacopeial Forum Vol.35(3) [May-June 2009]).

The PVT was based on a proposed USP Hydrocortisone Cream Reference Standard using the Tuffryn membrane concerned. Tuffryn is another relatively inert hydrophilic polymeric membrane having a pore size of 0.45 microns, based on polysulfone.

As at today, there is no PVT currently incorporated into the Pharmacopeia.

Strat-M Membranes
The Strat-M Membrane is a relatively 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.

This construction provides a strong correlation to human skin whilst reducing the high test variability associated with biological models.

Note: Annex 1 of the EMA "Guideline on quality of transdermal patches" effective17/06/2015 suggests the use of the VDC for permeation studies on transdermal patches

Vacuum Deaerating Apparatus Model VDA complete with Vacuum Pump, Differential Pressure Meter and Dissolved Oxygen Meter

Degassing

Air bubbles accumulating on the underside of the membrane concerned are the single largest source of problem in Vertical Diffusion Cell testing.

For this reason, it is essential that the receptor medium used to bathe the membrane is degassed prior to use if air bubbles and hence impaired diffusion is not to take place.

The **Vacuum Deaeration Apparatus Model VDA** is an inexpensive unit that has been specifically designed to obviate this problem.

The VDA itself comprises of:

- A 500 mL pressure bottle containing the receptor medium concerned.
- A waterbath to heat the contents of the bottle up to 45 degrees
- A magnetic stirrer/heater to stir the contents of the bottle whilst heating it and the surrounding water bath.
- A condensate filter to prevent condensate from damaging the vacuum pump concerned.

In addition, the following items are required to provide a full system:

- A vacuum pump to provide the necessary vacuum
- A differential pressure meter to display pressure and to test for leaks
- A dissolved oxygen meter to measure and display dissolved oxygen levels in the media.

USP 38 Chapter <1092> now suggests an oxygen concentration of less than 6 ppm as being effective as a marker for adequate deaeration of dissolution media.

The VDA System guarantees to reduce oxygen levels to below 4 ppm.

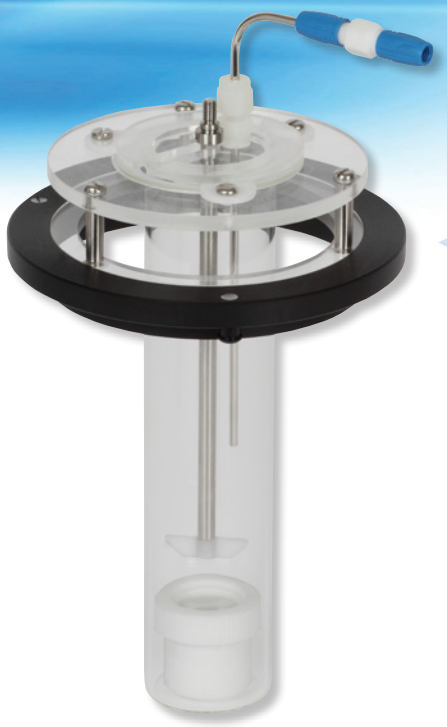
It operates by heating the receptor media up to 45 degrees C under vacuum conditions of -90 kPa differential pressure whilst continuously stirring at speeds in excess of 1000 rpm to produce truly air free receptor media.

Once deaerated, the system can be used to maintain the temperature of the degassed dissolution medium to the required temperature for testing i.e. 32 or 37 degrees C.

20 mL Syringe for filling cells

2 mL Syringe for taking samples

Cat. No.	Description
7290	10 Cell Vertical Diffusion Cell Test System HDT 1000 (excl. Cells)
7276	Single Cell Vertical Diffusion Cell Test System HDT 1 (excl. Cells)
7298	Vertical Diffusion Cell 11.28 mm x 7 mL Type "B" (in Glass)
7299	Vertical Diffusion Cell 15 mm x 11 mL Type "C" (in Glass)
7297	Parafilm Laboratory Film (250' x 2")
7295	Syringe 2 mL complete with luer and sampling tube
7296	Syringe 20 mL complete with luer and media filling tube
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.
7289	Storage Rack for 10 Vertical Diffusion Cells (Type "B" and/or "C")
7277	IQ/OQ/PQ Documentation Pack for HDT 1/1000
7272	Qualifications Tools for HDT 1/1000
7291	Vacuum Deaerating Apparatus Model VDA
7300	IQ/OQ/PQ Documentation Pack for VDA
7903	Low Capacity Vacuum Pump Model LCP5
7293	Differential Pressure Meter
7294	Dissolved Oxygen Meter



Immersion Cell with 200 mL Small Volume Conversion Kit

IMMERSION CELL

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

The **Immersion Cell (USP Model A)** 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 38) in order to avoid the issue of dead space under the cell, were a round bottomed vessel to be used.

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 Pages 41 and 70) 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^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.

Immersion Cell

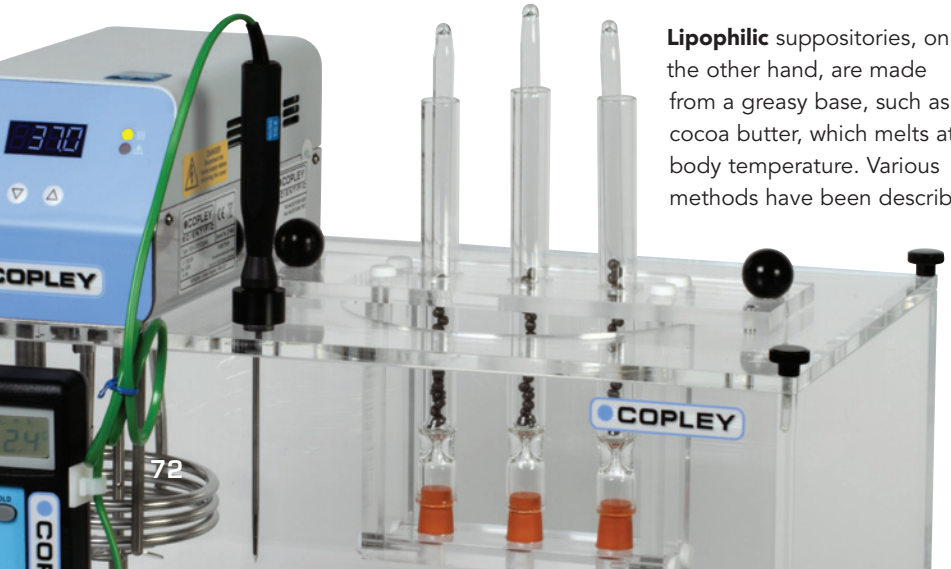
Cat. No.	Description
7280	Immersion Cell
7281	200 mL Small Volume Conversion Kit for Immersion Cell
7270	Pack of 100 PVDF Membranes 25 mm o.d.
7274	Pack of 100 Tuffryn Polysulfone Membranes 25 mm o.d.
7275	Pack of 60 Strat-M Membranes 25 mm o.d.

Suppositories

INTRODUCTION

Vaginal Tablet Tester
Model VTT

Softening Time Attachment



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 38), a paddle method (see Page 19) 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 8th 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 chapters.

Digital Timer

Removing the Test Station

Suppository Disintegration Tester Model SDT 1000

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

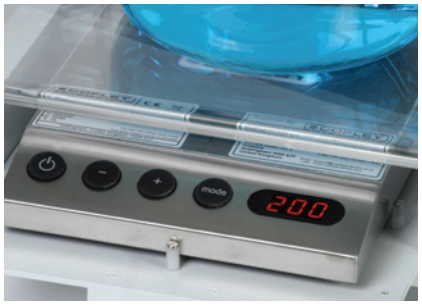
Preheat the test medium to 36-37 degrees C using the combination of the immersion thermostat provided and the slow speed stirrer (optional).

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 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.

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).

A separate unit, the **VTT**, is available for testing **vaginal tablets.** This employs the same sample holder as that in the SDT in conjunction with a low form beaker and heater/stirrer. The sample holder is placed in the beaker which is filled with the test medium (preheated to 36-37 degrees C) such that it just covers the perforations on the upper plate. The tablet to be tested is now placed on the plate and covered with a suitable glass plate to maintain appropriate conditions of humidity. The test is then repeated for two more tablets. All samples should disintegrate within the stated time.



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)
1708	IQ/OQ/PQ Documentation Pack
1707	Qualification Tools
1710	Digital Timer with Audible Alarm (including calibration)
1800	Vaginal Tablet Tester VTT

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).

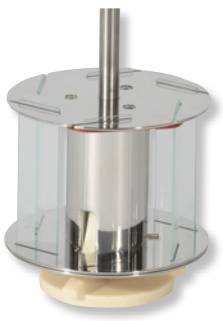
The ability of a detergent product to remove stains or affect colour changes within a fabric is dependent on a number of factors: the fabric under test, the degree and type of soiling or staining, the temperature and sometimes pH and hardness of the water used in the test, the stirrer speed and the wash 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. 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.

The same method can also be applied to the testing of light duty detergents, as used in domestic dish washers, using a suitable accessory.



Dishwasher Slide Accessory

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 (see photo opposite) 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 seven.

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, or paddles which allow pieces of fabric to be attached to them, are also available.

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 equilibriate 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)

Standard Stirrers

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)
6408	Dishwasher Slide Accessory for Tergotometer
6409	Pack of 10 O-Rings (spare)
6410	Pack of 60 Glass Slides (spare)

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, 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 are 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 convenient 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 500

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 and 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 units at a single push of a button with a **resolution of 0.01 mm** or 0.0005". The gauge can be set to zero at any point, thus enabling the display to show a +/- variance.

The gauge can be used in **four modes**, 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.

TABLET THICKNESS TESTERS

Tablet Thickness Tester 700

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 the "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.

TABLET THICKNESS TESTER 547
The **Tablet Thickness Tester Model 547** (see photo opposite) 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 release the thumb lever to close the jaws. Then read off the measured value from the digital display.

Provision is made to measure in either metric or imperial units 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, 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.**

Mini Processor for SPC 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:

(a) the **test methods** used to monitor pharmaceuticals must meet proper standards of accuracy and reliability and

(b) 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 Pharmacopeia (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:

(a) the term **"qualification"** be applied to instrumentation and

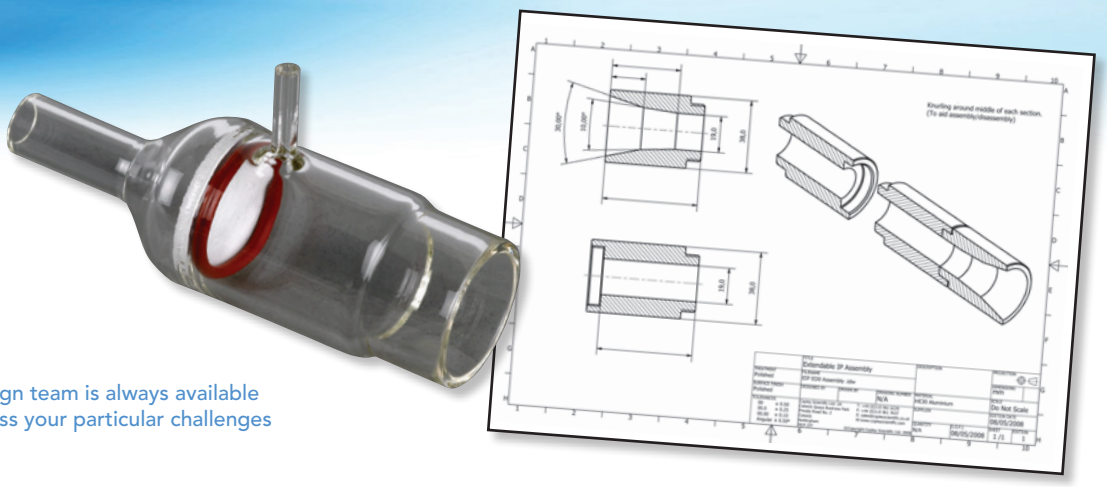
(b) the term **"validation"** to processes and software

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 are suitable for their 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.



Our design team is always available to address your particular challenges

DESIGN, SERVICING AND TRAINING

DESIGN

Our design team has many years' experience working closely with the pharmaceutical industry in helping to develop their ideas for solving particular problems.

Whether you have a longstanding problem, or one that has been created by the introduction of a new process, or an idea for a new product, or even a bespoke design that you need manufacturing, we would be delighted to hear from you.

SERVICING

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

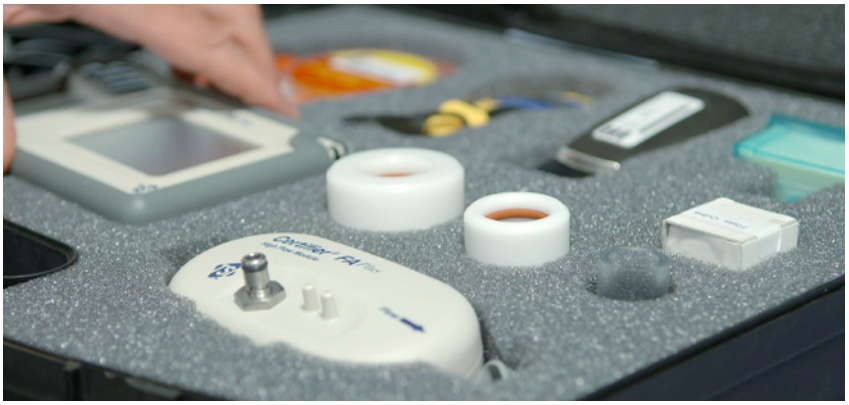
Contracts can be prepared for individual instruments or complete calibration management systems.

The creation of a typical service contract follows a structured format, which starts with determining the scope. This usually involves the customer supplying a detailed asset list of equipment requiring calibration, from which a proposal is made. This is reviewed by the customer and then if acceptable implemented, typically on an annual basis.

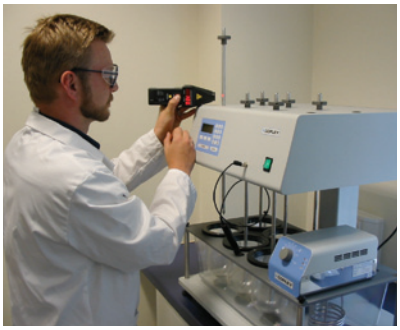
Our skilled engineers and technicians are trained to a high standard on the complete range of Copley Scientific and other related products and fully understand all aspects of calibration and qualification (IQ/OQ/PQ) procedures from performance to document control and storage.

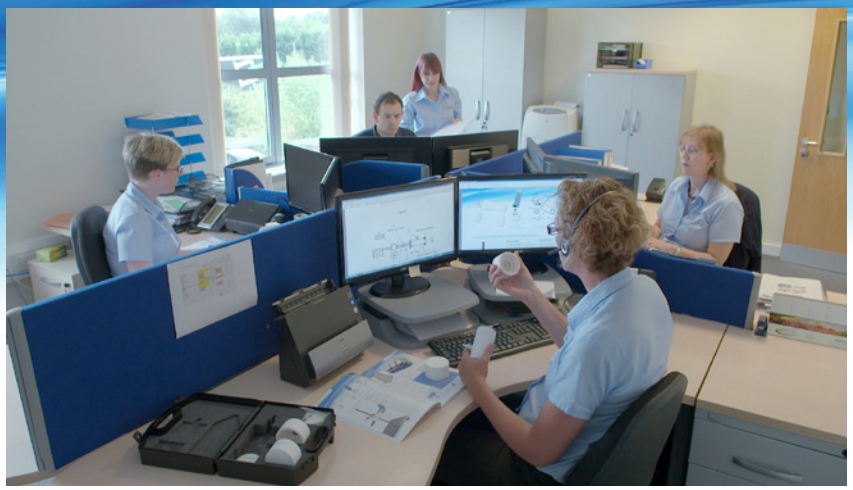
All documentation supplied conforms to GxP standards as required by the international regulatory authorities.

We will be pleased to discuss your individual requirements and quote accordingly.



Copley Scientific offers a range of in-house and on-site service options





TRAINING

As one of the world leaders in the supply of test equipment to the pharmaceutical industry, Copley Scientific offers a range of tailored training packages for both analysts and lab 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).

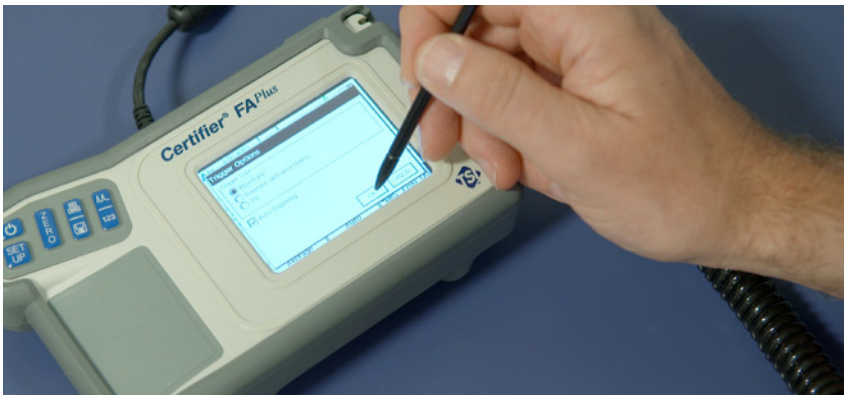
Typical training programs include:

- Presentation on dosage technology, test equipment, regulatory requirements, monographs and methodology, new industry developments, etc.
- 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 courses can be tailored to your specific requirements

- Training of users in operation of the equipment supplied
- Troubleshooting, Questions and Answers

Please feel free to contact us to discuss your requirements. We will be pleased to provide you with a quotation for a training program designed to meet your particular needs.



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