Agilent

Intrinsic Dissolution Apparatus

Operator's Manual

Notices

Manual Part Number

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CAUTION

A **CAUTION** notice denotes a hazard. It calls attention to an operating procedure, practice, or the like that, if not correctly performed or adhered to, could result in damage to the product or loss of important data. Do not proceed beyond a **CAUTION** notice until the indicated conditions are fully understood and met.

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Content

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1 Introduction

The measurement of intrinsic dissolution rates is an increasingly important tool in the pharmaceutical research and development laboratory. It allows the characterization of both the crystallized forms and polymorphs of pure drugs and drug formulations by exposing a constant surface area to the dissolution medium. When measuring intrinsic dissolution rates, the parameters which control the rate of dissolution, such as surface area exposed to the medium, temperature, stirring rate, and pH, are kept constant.

Additional information is available in the USP General Chapters, Intrinsic Dissolution <1087>.

This product is warranted to be free from manufacturing defects at the time of delivery. Please report any problems upon receipt of merchandise to an Agilent Customer Care Center. Contact information can be found at www.agilent.com under your country using the Contact Us link.

History of the Intrinsic Dissolution Apparatus

The base of the die has three threaded holes for the attachment of a polished steel plate which provides a mirror-smooth base for the compaction of the drug substance under study. To determine a material's intrinsic dissolution rate, a measured amount of the material is placed into the 0.8 cm diameter cavity of the die. The punch is inserted into the die cavity on top of the test material. The material is compressed using a benchtop tablet press (a hole in the head of the punch allows insertion of a metal bar to facilitate removal after the test). A pellet of the compressed material, called a compact, is formed in the cavity with a single face of defined area (0.5 cm^2) exposed on the bottom of the die. The bottom of the die cavity is threaded so that at least 50% of the compact can dissolve without falling out. The top of the die has a threaded shoulder which allows it to be attached to a holder. The holder is mounted on a laboratory stirring device, and the entire die with the compact still embedded is immersed in the dissolution medium (often contained in a 400 mL water-jacketed beaker) and rotated by the stirring device. Samples are taken and assayed at periodic intervals, enabling the calculation of the dissolution rate per centimeter squared.

High pressure is required to form the compact. The Agilent design uses hardened steel, which stands up to high pressure, and all surfaces in contact with the drug substance are polished for even compression. The bottom of the die contains three threaded holes, enabling the surface plate to be screwed onto the die to prevent slippage during pressing.

Due to the weight of the intrinsic device, the Intrinsic Dissolution Apparatus is designed for use with a dissolution apparatus with a secure shaft mounting system such as a chuck and collet. The dissolution apparatus offers more precise speed and water bath temperature control than a benchtop stirrer and water-jacketed beaker. Also, multiple tests can be run simultaneously.

Figure 1. Secure the Shaft

NOTE The punch is made from hardened steel. Both the punch and the surface plate should be oiled when not in use. See Chapter 5, **"Maintenance"** on page 27. All other parts on the intrinsic dissolution device are fabricated from type 316 stainless steel.

2 Setup

Unpacking Your Intrinsic Dissolution Apparatus

1. Carefully remove the apparatus from its shipping carton. The items are heavy; hold them firmly to prevent them from dropping.
2. Be sure to remove all parts before discarding or storing the packaging.
3. Place the items on a clean, dry, level section of the bench top or table.

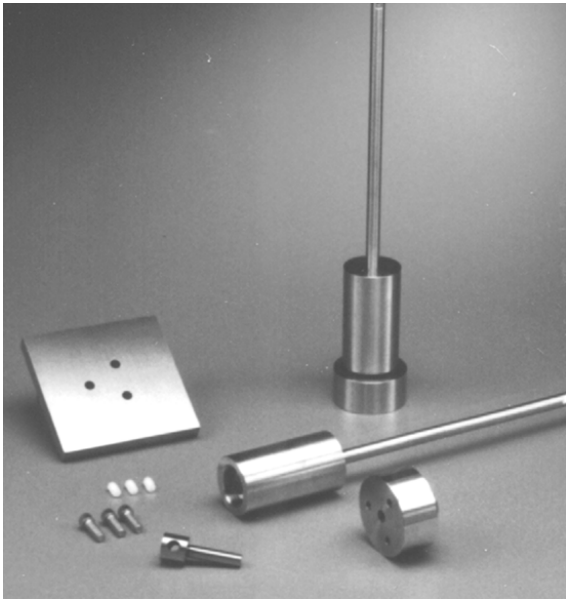

Figure 2. Intrinsic Dissolution Apparatus Items

Also included:

- (3) stainless steel bolts
- (3) nylon screws
- (1) handle bar / punch removal tool

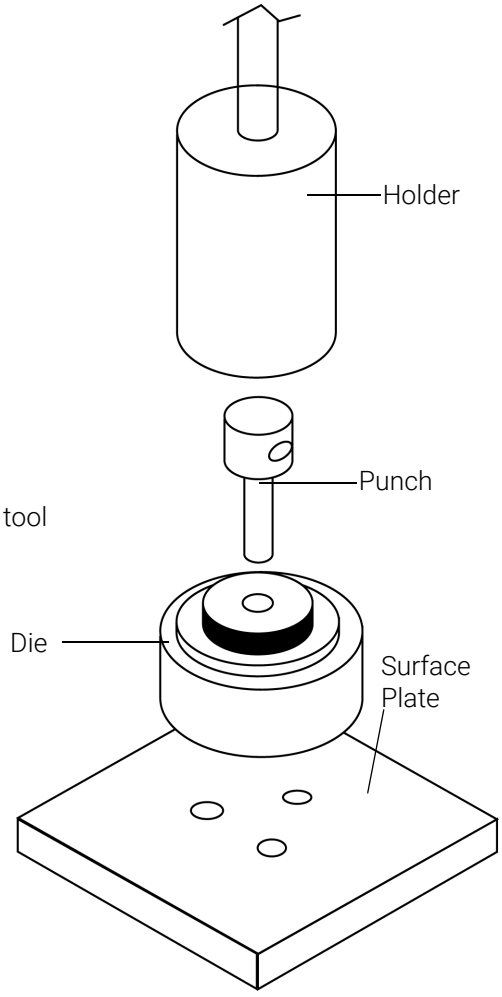

Figure 3. Assembly of the Intrinsic Apparatus

NOTE

The punch and surface plate are made from hardened steel. Both the punch and the surface plate should be oiled when not in use. See Chapter 4, "Maintenance" on page 27. All other parts on the intrinsic dissolution apparatus are fabricated from type 316 stainless steel.

Assembling the Intrinsic Apparatus

1. Ensure all traces of oil are removed from the punch and surface plate.
2. Place the surface plate on a flat surface so that the recessed holes are on the bottom.

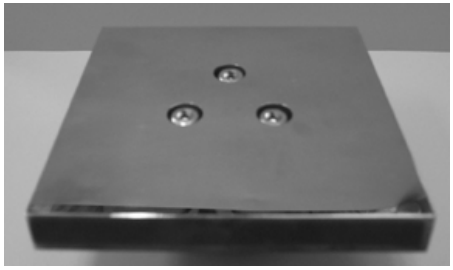

Figure 4. Upside Down View of Surface Plate with Recessed Screws

3. Place the die on top of the surface plate aligning the three holes in the die with the three holes in the surface plate.
4. Pick up the assembly holding the two pieces in the appropriate alignment. Turn the assembly over and use the fastening screws to secure the pieces together.
5. Use an Allen key to tighten the fastening screws. Turn the assembly over again and place it on a laboratory table. Because the holes on the bottom of the surface plate are recessed, the surface plate sits flat when the screws are tightened.
6. Place the washer on the die.
7. Accurately weigh out the test compound.
8. Carefully transfer the test compound into the cavity of the die.

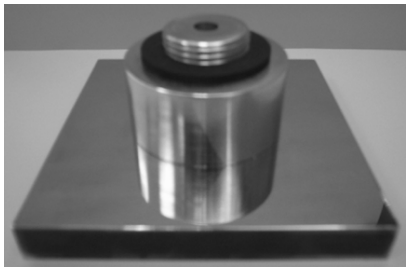

Figure 5. Center Opening of Die

9 Place the punch in the cavity over the test compound.

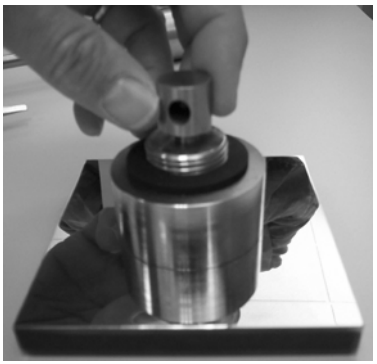

Figure 6. Inserting the Punch in the Intrinsic Apparatus

10 Place the entire assembly in a laboratory press equipped with an accurate pressure gauge.

11 Apply pressure to compress the material. Take care not to overcompress the drug substance.

12 Remove the assembly from the laboratory press.

13 Turn the assembly over and remove the three fastening screws from the surface plate. Be careful not to let the punch and die fall when the fastening screws are removed.

14 Remove the punch and die from the surface plate.

15 Place the slotted nylon screws provided with the apparatus in the holes in the bottom of the die. Use a screwdriver to tighten the screws.

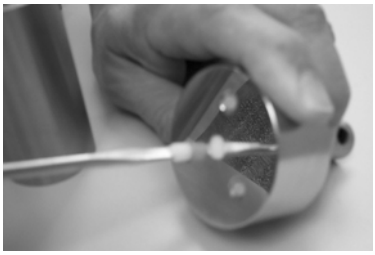

Figure 7. Tighten Slotted Nylon Screws

16 Insert the top of the die, with the punch still in place, into the holder and tighten.

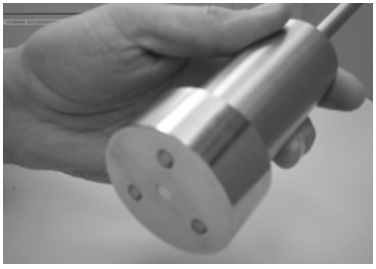

Figure 8. Holder Attached to the Die

17 Remove all loose powder from the surface of the die.

18 Insert the intrinsic assembly into the dissolution apparatus spindle assembly and tighten. Carefully lower the drive unit and adjust the height so that the exposed surface of the compacted pellet is 3.8 cm from the bottom of the vessel.

NOTE The dissolution apparatus should have suitable means of securing the intrinsic device. Due to the weight of the device, a chuck and collet system works best.

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3 Operation

Sample Preparation and Compaction Procedure

NOTE The following procedures are intended for illustration and guidance only. Actual practice depends upon the nature of the material being tested and the equipment used.

Suggested Equipment

- Intrinsic Dissolution Assembly (including punch, die, holder and surface plate)
- Hydraulic bench top press with accurate pressure gauge (Carver Press or E-Z Press)
- Dissolution apparatus with variable speed control
- Actinic (tinted) vessels for light-sensitive compounds
- Sampling device
- Detection device (UV-Vis spectrophotometer or HPLC)

Suggested Materials

- Test compound
- Degassed dissolution medium
- Standard solution prepared with same degassed dissolution medium

Preparation of the Compact

1. Accurately weigh out the compound to be tested on a piece of tared weighing paper.
2. Attach the surface plate to the underside of the die and secure with the three fastening screws provided.
3. Carefully and evenly pour the weighed material into the die cavity.
4. Place the punch into the cavity.
5. Place the intrinsic assembly into a suitable hydraulic press.
6. Compress the material in a hydraulic press for one minute at the minimum compression pressure necessary to form a nondisintegrating compacted pellet or compact.

CAUTION **Use no more than 5,000 pounds of force on the die. Even though it is fabricated of hardened steel, excessive force will jam the punch into the die cavity. Damage caused by excess force is not covered under warranty.**

7. Detach the surface plate and screw the die with punch still in place into the holder.
8. Remove all loose powder from the surface of the die by blowing it with compressed air or nitrogen.

General Test Procedure

1. Raise the drive unit to its highest position.
2. Loosen the chuck on one of the spindle assemblies by turning it counterclockwise. Carefully insert the end of the 3/8-inch holder shaft into the spindle assembly. Because the shaft is held very firmly, it could be necessary to use moderate force.
3. Adjust the height so the exposed surface of the compact will be 3.8 cm from the bottom of the vessel when the drive unit is lowered. Tighten the chuck to hold it in place.
4. Repeat the procedure for the remaining intrinsic assemblies. Leave the drive unit in the up position.
5. Set the spindle speed for the desired rate of dissolution. Speeds of 50 - 100 RPM are typical.
6. Lower the intrinsic apparatus into the vessel containing the medium at 37 °C, as determined by the Arrhenius equation, until the assembly is at the proper depth.

NOTE When lowering the assembly into the media, ensure there are no air bubbles on the exposed surface of the compact. If air bubbles appear, tap the shaft gently to dislodge them, taking care not to damage the compact.

7. Start the spindle rotation at time zero.
8. Pull samples at the appropriate time intervals.
9. Upon completion of the test, remove the assembly from the medium and follow the cleaning instructions in Chapter 5, "Maintenance" on page 27.

Sampling and Analysis

Take samples at preset time intervals over the predetermined length of the test. The total test length will vary with the nature of the material. In all cases, samples should be taken until a minimum of ten percent of the test material has gone into solution. Prepare a standard curve and assay samples using a suitable means of detection.

Calculation and Interpretation

An integrated form of the modified Noyes and Whitney equation is used for calculation. As long as sink conditions are maintained, the concentration gradient can be considered a constant. More detailed information can be found in *Dissolution, Bioavailablity, and Bioequivalance* by Hamed M. Abdou.

The data for the cumulative amount dissolved at each timepoint should be corrected for sampling losses. To calculate the intrinsic dissolution rate, plot the cumulative amount of sample dissolved per unit area of the compact against time until 10% is dissolved. The cumulative amount dissolved per unit area is given by the cumulative amount dissolved at each timepoint divided by the surface area exposed (0.5 cm^2). Linear regression should then be performed on data points up to and including the timepoint beyond which 10% is dissolved. The intrinsic dissolution rate of the test material (in $mg/min/cm^2$) at the selected stirring speed is given by the slope of the regression line.

The figure on the next page shows an experimental data plot and the calculated regression line:

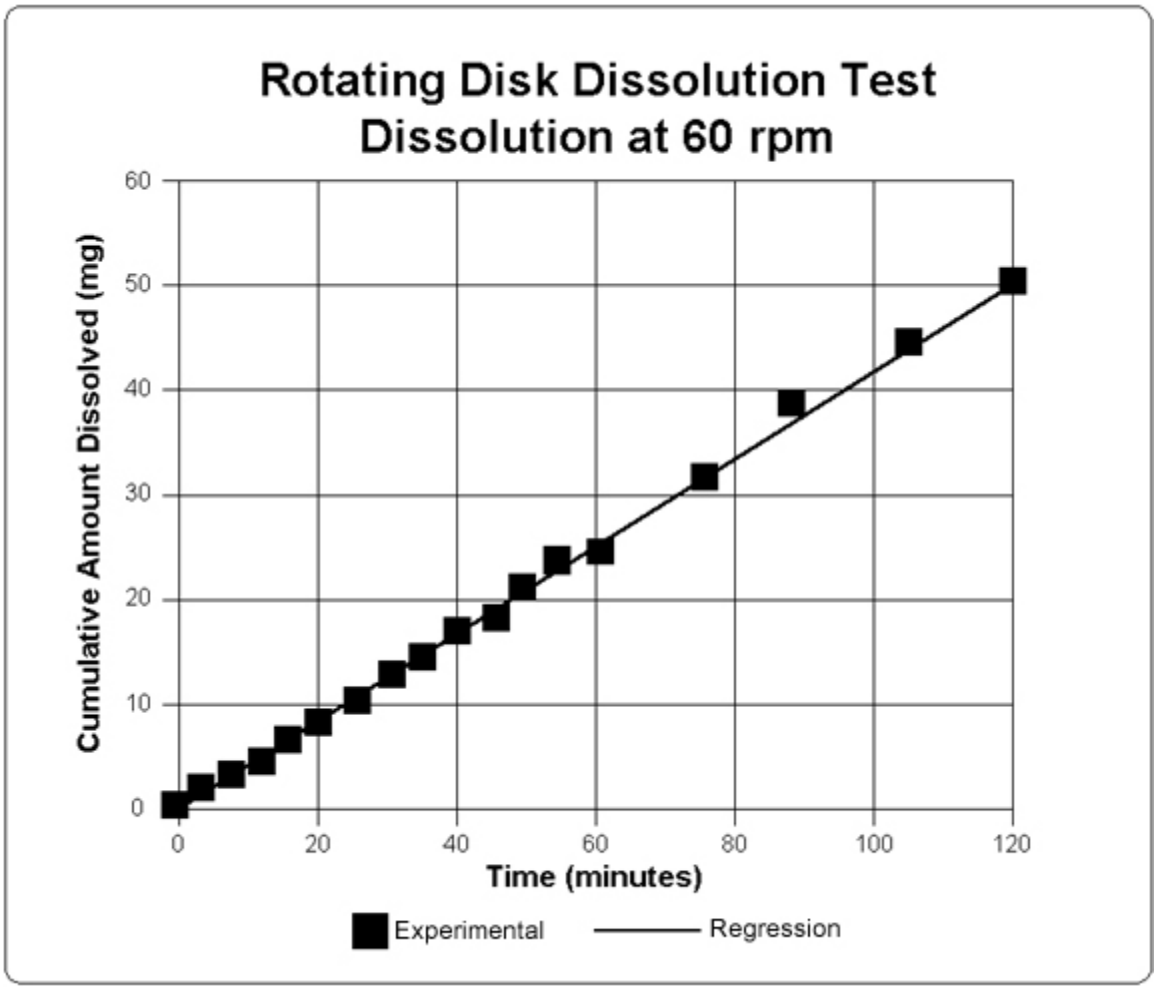

Figure 9. Experimental Data Plot

Data Analysis

A typical data analysis spreadsheet is displayed on the following page. The corrected cumulative amount dissolved equals sampling correction plus the uncorrected cumulative amount dissolved. Linear regression on data from 0 to 50 minutes gives an intrinsic dissolution rate of 0.4096 mg/min/cm².

Sample time (min)	Sample con. (µg/mL)	Sample volume (mL)	Dilution ratio	Sampling correction	Cumulative amt. dissolved	
					Uncorrected (mg)	Corrected (mg)
0	0.141	3	1	0	0.021	0.021
1	3.528	3	1	0.011	0.529	0.53
2	6.351	3	1	0.019	0.953	0.964
3	10.162	3	1	0.03	1.524	1.535
4	13.831	3	1	0.041	2.075	2.135
5	16.372	3	1	0.049	2.456	2.558
7	22.017	3	1	0.066	3.303	3.454
9	27.804	3	1	0.083	4.171	4.388
11	33.449	3	1	0.1	5.017	5.318
13	38.671	3	1	0.116	5.801	6.202
15	43.47	3	1	0.13	6.521	6.921
20	56.031	3	1	0.168	8.405	9.052
25	67.887	3	1	0.204	10.183	10.998
30	79.883	3	1	0.24	11.982	13.002
35	90.892	3	1	0.273	13.634	14.893
40	102.042	3	1	0.306	15.306	16.838
45	112.768	3	1	0.338	16.915	18.447
50	123.071	3	11	0.369	18.461	20.637
55	12.843	3	11	0.141	21.192	23.737
60	13.267	3	11	0.146	28.877	24.577
75	17.501	3	11	0.193	35.63	31.709
90	21.594	3	11	0.238	41.452	38.655
106	25.122	3	11	0.276	47.041	44.714
120	28.51	3	11	0.314	47.041	50.579

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4 Maintenance

Preventive Maintenance

Cleaning

After each use, it is necessary to clean the Intrinsic Dissolution Apparatus. Complete the following steps:

1. Remove the punch with the aid of the included handle bar / punch removal tool.
2. Thoroughly rinse the die, punch, holder, and surface plate with water.
3. Dry completely.
4. Apply a light coating of light machine oil to the punch and surface plate to prevent rust and corrosion.

CAUTION **Take careful steps to clean and lubricate your Intrinsic Dissolution Apparatus or the punch and surface plate will rust and become severely pitted.**

In This Book

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