
NOTICE: This document contains references to Varian. Please note that Varian, Inc. is now part of Agilent Technologies. For more information, go to www.agilent.com/chem.



Intrinsic Dissolution Apparatus Operator's Manual

**P/N 70-9022
November 2010
Revision D**

Limitation of Liability

The information in this document is subject to change without notice. Varian, Inc. makes no warranty of any kind with regard to this material, including, but not limited to, the implied warranties or merchantability and fitness for a particular purpose. Varian, Inc. shall not be liable for errors contained herein or for incidental consequential damages in connection with the furnishing, performance, or use of this material.

All rights are reserved. Reproduction, adaptation, or translation without prior written permission is prohibited, except as allowed under copyright laws.

First Edition (November 2010)
Intrinsic Dissolution Apparatus Operator's Manual
Part Number 70-9022 Revision D
Printed in the United States of America

The following terms are trademarks of Varian, Inc.:

- Benchsaver™
- BIO-DIS III®
- Enhancer Cell®
- Full Flow Filters™
- Peak Vessel™
- Practical Solutions®
- QA and QAI™
- TruCenter™
- VanKel®
- VK®

All other trademarks are the property of their respective owners.

Varian, Inc.
13000 Weston Parkway
Cary, North Carolina 27513-2250
800.229.1108
919.677.1108
Fax: 919.677.1138
www.varianinc.com



VARIAN

Copyright (c) 1999 - 2010 by Varian, Inc.

Table of Contents

Chapter 1	<i>Introduction</i>	7
	History of the Intrinsic Dissolution Apparatus	8
Chapter 2	<i>Setup</i>	11
	Unpacking Your Intrinsic Dissolution Apparatus	11
	Assembling the Intrinsic Apparatus	14
Chapter 3	<i>Operation</i>	19
	Sample Preparation and Compaction Procedure	19
	Suggested Equipment	19
	Suggested Materials	20
	Preparation of the Compact	20
	General Test Procedure	21
	Sampling and Analysis	22

Table of Contents

Calculation and Interpretation 22

Chapter 4 ***Data Analysis Spreadsheet 25***

Chapter 5 ***Maintenance 27***

Cleaning 27

Index 29

Tell Us How We Are Doing 31

List of Figures

FIGURE 1. Intrinsic Dissolution Apparatus	9
FIGURE 2. Intrinsic Dissolution Apparatus Items	12
FIGURE 3. Assembly of the Intrinsic Apparatus	13
FIGURE 4. Upside Down View of Surface Plate with Recessed Screws	14
FIGURE 5. Center Opening of Die	15
FIGURE 6. Inserting the Punch in the Intrinsic Apparatus	15
FIGURE 7. Tighten Slotted Nylon Screws	16
FIGURE 8. Holder Attached to the Die	16

List of Figures

FIGURE 9. Intrinsic Apparatus Attached to the Dissolution
Tester **17**

FIGURE 10. Experimental Data Plot **23**

Chapter 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 Dissolution Systems Customer Service at 800.229.1108 (inside the US) or 919.677.1108 (outside the US).

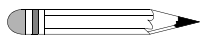
History of the Intrinsic Dissolution Apparatus

The evolution of pharmaceutical testing techniques led to the development of what has become known as the Wood Apparatus for intrinsic dissolution testing by Dr. John Wood in 1963. The original Wood Apparatus consists of a punch and a die fabricated of type 316 stainless steel. 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 cm²) 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.

In our design, the walls of the die cavity are grooved for holding the compressed drug substance within the die cavity during the test. The ends of the cavity are perfectly squared off and the surface area exposed remains constant as the compact dissolves. High pressures are sometimes required to form the compact and the type 316 stainless steel originally used could deform. The Varian 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 tester 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.

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.

FIGURE 1. Intrinsic Dissolution Apparatus



This page was intentionally left blank, except for this message.

Chapter 2 **Setup**

Unpacking Your Intrinsic Dissolution Apparatus

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

FIGURE 2. Intrinsic Dissolution Apparatus Items

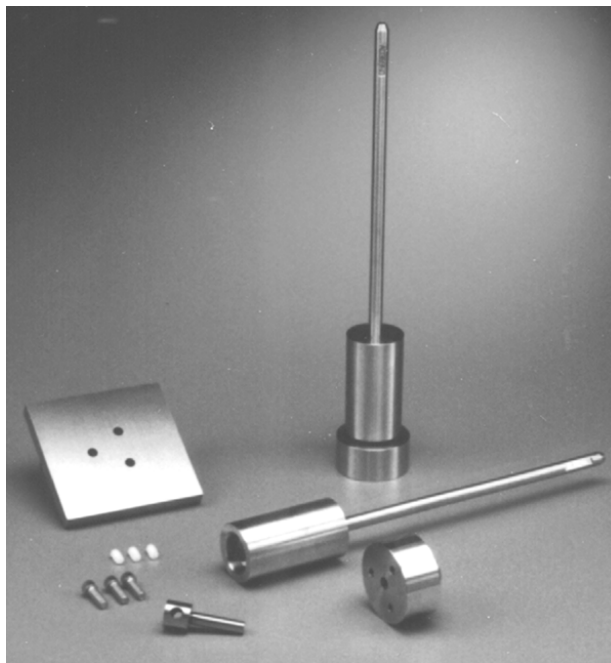
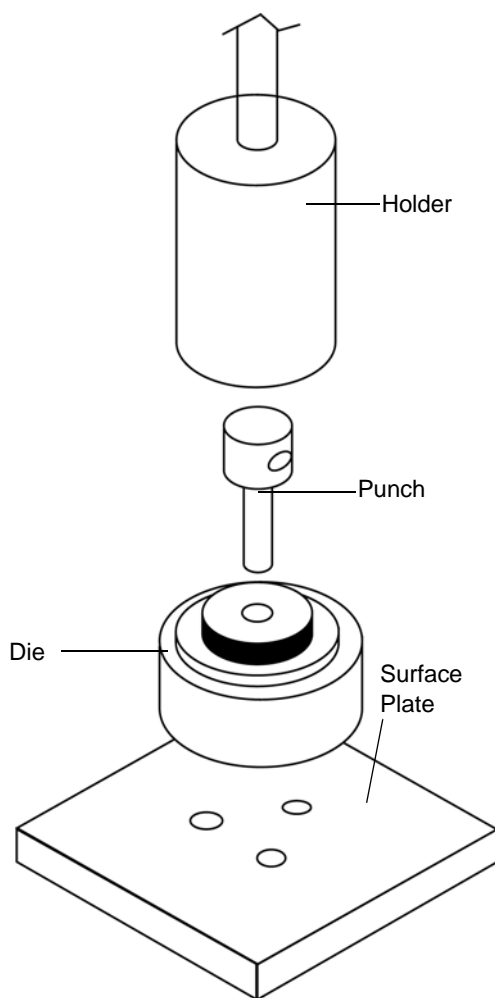
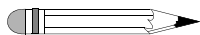


FIGURE 3. Assembly of the Intrinsic Apparatus



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 5, "Maintenance," on page 27. All other parts on the intrinsic dissolution apparatus are fabricated from type 316 stainless steel.

Assembling the Intrinsic Apparatus

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

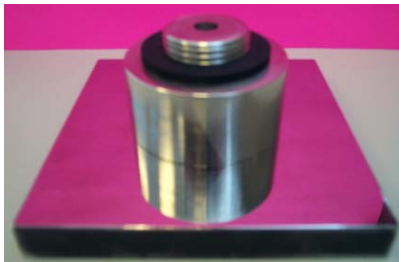
FIGURE 4. Upside Down View of Surface Plate with Recessed Screws



- Step 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.
- Step 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.
- Step 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.
- Step 6. Place the washer on the die.
- Step 7. Accurately weigh out the test compound.

Step 8. Carefully transfer the test compound into the cavity of the die.

FIGURE 5. Center Opening of Die



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

FIGURE 6. Inserting the Punch in the Intrinsic Apparatus



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

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

Step 12. Remove the assembly from the laboratory press.

- Step 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.
- Step 14. Remove the punch and die from the surface plate.
- Step 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



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

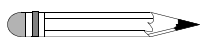
FIGURE 8. Holder Attached to the Die



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

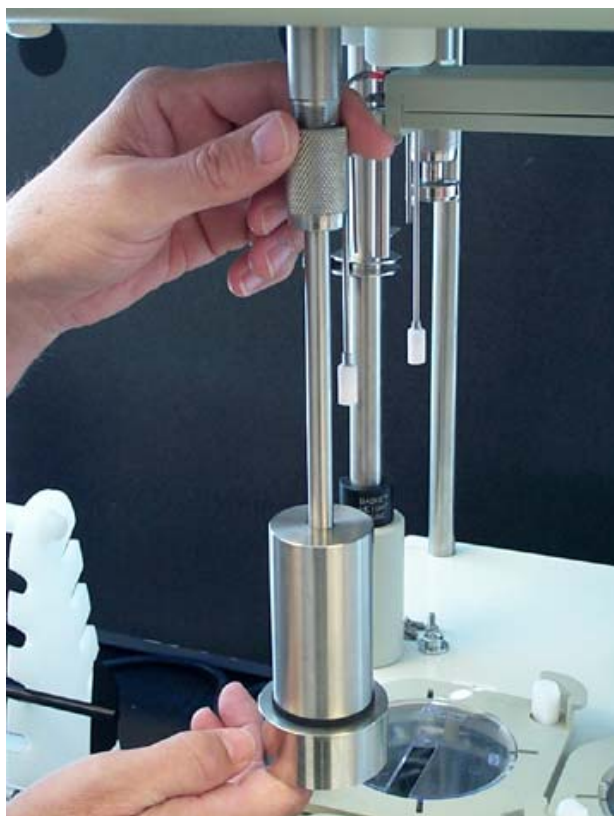
- Step 18. Insert the intrinsic assembly into the dissolution apparatus spindle assembly and tighten. Carefully lower the drive unit and adjust the height so that the exposed surface of the compacted pellet is 3.8 cm from the bottom of the vessel. See Figure 9, "Intrinsic Apparatus Attached to the Dissolution Tester," below.

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.

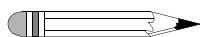
FIGURE 9. Intrinsic Apparatus Attached to the Dissolution Tester



This page was intentionally left blank, except for this message.

Chapter 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 tester with variable speed control
- Actinic (tinted) vessels for light-sensitive compounds
- Sampling device (syringe with cannula or VK 8000)
- 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

- Step 1. Accurately weigh out the compound to be tested on a piece of tared weighing paper.
- Step 2. Attach the surface plate to the underside of the die and secure with the three fastening screws provided.
- Step 3. Carefully and evenly pour the weighed material into the die cavity.
- Step 4. Place the punch into the cavity.
- Step 5. Place the intrinsic assembly into a suitable hydraulic press.
- Step 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

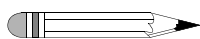
Use no more than 5,000 pounds of force on the die. Even though it is fabricated of hardened steel, excessive force will jam the punch into the die cavity. Damage caused by excess force is not covered under warranty.

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

General Test Procedure

- Step 1. Raise the drive unit to its highest position.
- Step 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.
- Step 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.
- Step 4. Repeat the procedure for the remaining intrinsic assemblies. Leave the drive unit in the up position.
- Step 5. Set the spindle speed for the desired rate of dissolution. Speeds of 50 - 100 RPM are typical.
- Step 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.

- Step 7. Start the spindle rotation at time zero.
- Step 8. Pull samples at the appropriate time intervals.
- Step 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.

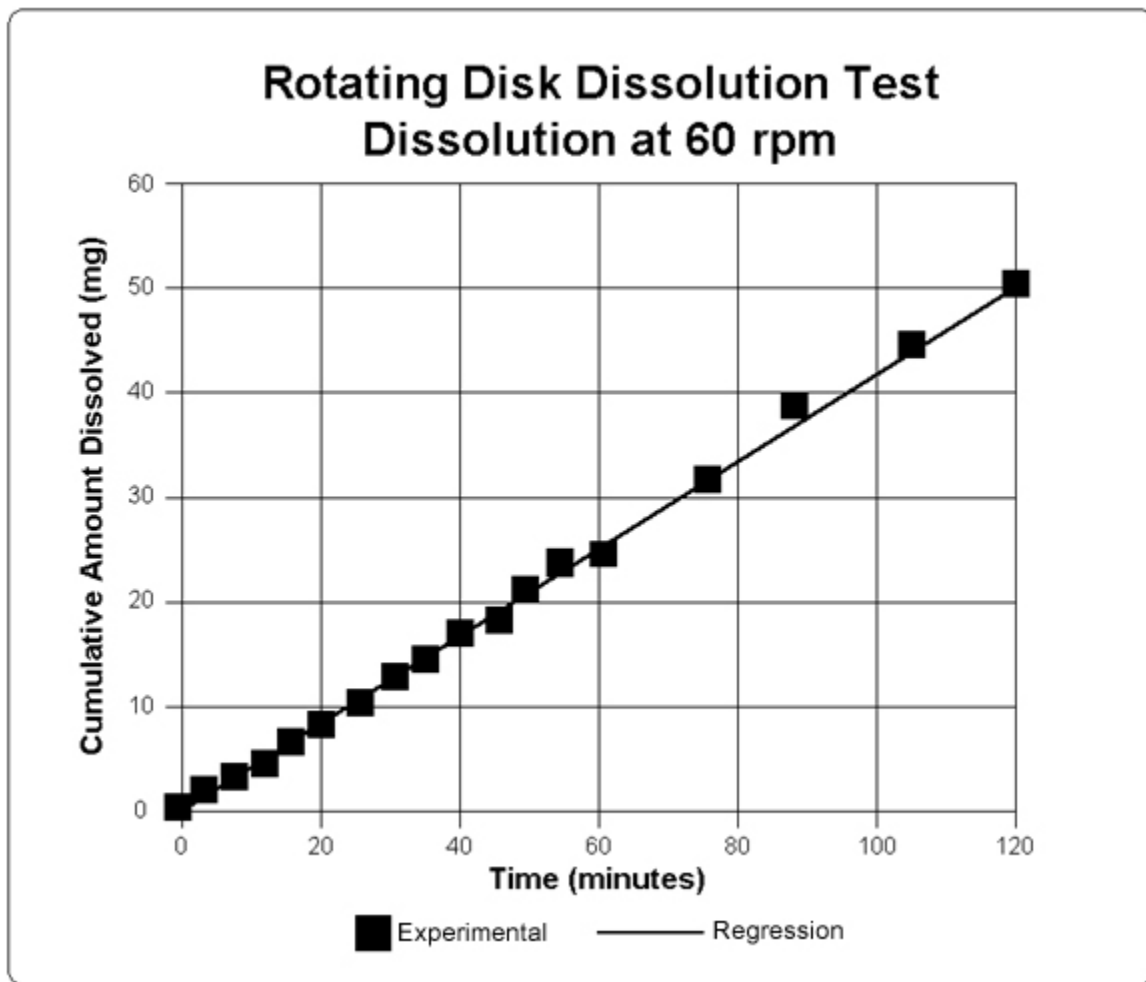
Calculation and Interpretation

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, Bioavailability, and Bioequivalence* 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 cm²). 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/cm²) at the selected stirring speed is given by the slope of the regression line.

The following figure shows an experimental data plot and the calculated regression line:

FIGURE 10. Experimental Data Plot



This page was intentionally left blank, except for this message.

Chapter 4 Data Analysis Spreadsheet

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

Chapter 5 *Maintenance*

Cleaning

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

- Step 1. Thoroughly rinse the die, punch, holder, and surface plate with water.
- Step 2. Dry completely.
- Step 3. 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.

This page was intentionally left blank, except for this message.

Index

a

analysis 22
assembling the intrinsic apparatus 14

c

calculation 22
cleaning instructions 27
compaction procedure 19

d

data analysis spreadsheet 25
dr. john wood 8

e

equipment, suggested 19
experimental data plot 23

g

general test procedure 21

h

history 8

i

interpretation 22
introduction 7

m

maintenance 27
materials, suggested 20

o

operating your intrinsic dissolution
apparatus 19

p

preparation of the compact 20

r

reader comment form 31

s

sample preparation 19
sampling 22
setting up the intrinsic dissolution
apparatus 11

Index

u

unpacking your intrinsic dissolution
apparatus 11

w

wood apparatus, history 8
wood, dr. john 8



Tell Us How We Are Doing

We listen to our customers. We work hard to make our technical documentation user friendly and to make the information in our manuals easy to retrieve and use. We'd like you to tell us the kinds of additional information you'd find helpful in our documentation. Your feedback will be carefully considered when we prepare future editions of this manual.

This manual should contain the following additional information:

The most useful thing about this book is:

This manual would be more helpful if:

My general impressions of this book are:

May we contact you regarding your comments? ____ YES ____ NO (If yes, please write your name, address, and telephone number here.)

Please return this form via mail to: Technical Writing / Dissolution Systems, Varian, Inc., 13000 Weston Parkway, Cary, North Carolina 27513-2250 USA. Optionally, you can return this form via fax at 1.919.677.1550. Always, feel free to telephone us to discuss your comments at 1.800.229.1108.