# Table of Contents

## CHAPTER 1 OVERALL CONSIDERATIONS
- Why Dissolution Testing? 2
- Disintegration Tests 2
- Early Dissolution Test Development 5
- Development of Dissolution Testing Standards 6
- Calibrators 8
- Methods of Dissolution Testing 8
- Rotating Basket Method 9
- Paddle Method 9
- Flow-Through Methods 9
- Reciprocating Cylinder Apparatus 10
- Transdermal Dissolution Testing 10
- Classification of Dissolution Techniques 10
- Agitation Methods 11
- Defining an Apparatus 12
- Use of Dissolution Test Data 12

## CHAPTER 2 THEORETICAL CONCEPTS
- Definition of the Dissolution Rate 13
- Surface Area 16
- Surface Area and Flow Dynamics 18
- Input and Output Variables 20
- Bioequivalence and Dissolution Characteristics 21
- Summary of Useful Theoretical Concepts 23

## CHAPTER 3 DISSOLUTION METHODS FOR SOLID DOSAGE FORMS
- Basic Methods — The Rotating Basket (USP/NF Apparatus 1) 28
- Allowable Variations in Apparatus 1 (Basket) 30
- Gold Plating 30
- Basket Mesh 30
- Use of Basket for Nonofficial Tests 31
- Suppositories 31
- Microencapsulated Particles 32
- Basic Methods — The Paddle (USP/NF Apparatus 2) 32
- Allowable Variations in the Paddle Method 34
Table of Contents

Floating Dosage Units 34
Problems with Sinkers 34
Compendial Constraints Common to Apparatus 1 and 2 35
Geometry and Alignment 35
Stirring Rate (rpm) 35
Eccentricity (Wobble) 37
Vertical Position of the Paddle or Basket 37
Flask 37
Sampling Point 38
Media 38
Acceptance Criteria 39
Alternative Methods — Modified Disintegration Apparatus 42
Alternative Methods — Reciprocating Cylinder
   (USP/NF Proposed Apparatus 3) 42
Alternative Methods — Flow-Through
   (USP/NF Proposed Apparatus 4) 45
Flow-Through Variables 49
Advantages 50
Disadvantages 51
Summary of the Proposed Apparatus 4,
   the Flow-Through Cell 51
Other Alternative Methods 51
Summary 52

CHAPTER 4 DISSOLUTION TESTING OF TRANSDERMAL DELIVERY SYSTEMS 53
   Overview 53
   Rate-Limiting Processes 54
   In Vitro Techniques for Transdermal and
      Percutaneous Absorption Studies 54
   Transdermal Dosage Devices 54
   Paddle over Disk 55
   Rotating Cylinder Apparatus 56
   Reciprocating Disk 58
   Percutaneous Absorption 59
   Side-by-Side Cell 59
   The Franz Cell 60
   The Flow-Through Cell Design 61
   Problems Unique to Transdermal Testing 63
   Variables in Percutaneous Absorption Testing 63
   Automating Percutaneous Absorption Study Systems 64
Table of Contents

Flow-Through Cell Systems 64
Franz and Side-by-Side Cells 64
USP Paddle over Disc 66

CHAPTER 5 CONTROLLING VARIABLES 69
Apparatus 1 & 2 — Eccentricity of Stirring Drive 70
Shaft Straightness 72
Guiding the Shaft 72
Other Stirring Device Variables 73
External Vibration 74
Sources of Vibration 75
Torsional Vibration 76
Geometry of Apparatus 76
Alignment of Stirring Device 77
Centering the Stirring Shaft in Flask 78
Agitation Rate 79
Variables with the Basket (Apparatus 1) 80
Dissolution Media Variables — Dissolved Gas 82
Deaerating Media 83
Influence of Released Gases 85
Media Variables — pH 85
Media Variables — Volume 86
Media Variables — Temperature 86
Media Variables — Sink Conditions 87
Flow Pattern Variables 88
Sorption 90
Checklist for Variables 90

CHAPTER 6 SETTING UP FOR DISSOLUTION TESTING 93
Checklist for Dissolution Protocol 94
Inspecting Paddles and Shafts 98
Checking the Eccentricity of Paddles or Baskets 100
Checking the Speed Control 101
Checking Vibration 102
Centering Flasks to the Stirring Drive 102
Analytical Methods and Filtration 102
Distance of the Paddle or Basket from the Bottom of the Flask 104
Calibration of Equipment 106
Table of Contents

Calibrator Tablets 107
Compendial Calibration Requirements 108
Meeting Calibration Limits 109

CHAPTER 7 SOLVING PRACTICAL PROBLEMS 111
Calibration of Apparatus 111
Intrinsic Dissolution 112
Variations of Compendial Methods 113
Checklist for Method Protocol 114
Selecting Method for New Items 115
Low Solubility Drugs — Inadequate Sink 116
Low Concentrations — Difficult Analysis 116
Problem Dosage Forms 117
Dosage Composition 117
Dosage Size 117
Floating Dosage Forms 118
pH Change during Test 119
Validation 119
Comparison of Various Dissolution Methods 121

CHAPTER 8 AUTOMATION OF DISSOLUTION TESTING 125
Advantages from Automation 127
Unit Operations in Dissolution 128
Automation of Setup 129
Automation of Dissolution Process 131
Automating Sampling 133
Classification of Automated Sampling Systems 134
Hidden Problems of Automated Samplers 138
Automating Analytical Procedures 139
Data Reduction in Automated Dissolution 141
Automating Alternative Dissolution Methods 143
Control of Automated Systems 143
Summary — Systems Analysis of Automation 144

REFERENCES 145

INDEX 157