

Contents

1	Introduction.....	1
1.1	Microscopy and Industrial Microscopy	1
1.2	Pharmaceutical Microscopy	1
1.3	Purpose of the Book	2
1.4	Plan of the Book.....	4
1.5	How Best to Use the Book	5
	References	6
2	Polarized Light Microscopy	7
2.1	Introduction.....	7
2.2	Properties of Light.....	8
2.3	Basic Optics	11
2.4	Crystallography	15
2.5	Optical Crystallography	19
	2.5.1 No Polars, Brightfield	22
	2.5.2 One Polar	28
	2.5.3 Crossed Polars	28
	2.5.4 Summary of Optical Crystallography	37
2.6	Measurement of Refractive Indices.....	37
	2.6.1 Introduction.....	37
	2.6.2 Cubic Crystals and Amorphous Materials: Basic Immersion Technique.....	38
	2.6.3 Uniaxial Crystals	41
	2.6.4 Biaxial Crystal Search Method.....	42
	2.6.5 Biaxial Crystals with Aid of Interference Figures.....	45
	2.6.6 Summary of Refractive Index Measurements.....	46
2.7	Instruments and Köhler Illumination	47
	2.7.1 Objectives	48
	2.7.2 Oculars (Eyepiece).....	49
	2.7.3 Light Source.....	49
	2.7.4 Substage Condenser.....	50
	2.7.5 Microscope Stand and Stage.....	50
	2.7.6 Polarizer and Analyzer	51

2.7.7	Compensators.....	51
2.7.8	Köhler Illumination.....	51
2.8	Stereomicroscopy.....	54
2.9	Photomicrography.....	55
2.10	Summary.....	57
2.11	Exercises.....	57
	A. Sample Preparation and Preparation of Crystals.....	57
	B. Microscope Setup: Köhler Illumination.....	58
	C. Polarized Light.....	59
	D. Interference colors.....	60
	E. Refractive Index: Cubic, Uniaxial, Biaxial, High low.....	61
	F. Optical Crystallography.....	62
	References.....	63
	Internet References.....	64
3	Thermal Microscopy.....	65
3.1	Introduction.....	65
3.2	Instruments and Methods.....	66
3.3	Calibration.....	69
3.4	Test Strategy.....	71
3.5	Observations.....	72
3.5.1	Melting Point.....	72
3.5.2	Solid–Solid Transformations.....	75
3.5.3	Solid–Liquid–Solid Transformations.....	75
3.5.4	Sublimation.....	76
3.5.5	Cooling.....	78
3.5.6	Dehydration and Desolvation.....	78
3.6	Fusion Techniques and Other Applications.....	79
3.7	Summary.....	81
3.8	Exercises.....	81
	A. Sample Preparation and Experimental Setup.....	81
	B. Calibration and Performance Checks.....	82
	C. Effects of Heating Rate.....	82
	D. Phase Transformations.....	83
	E. Fusion.....	83
	References.....	83
	Internet References.....	84
4	Scanning Electron Microscopy and Energy-Dispersive X-Ray Spectrometry.....	85
4.1	Introduction.....	85
4.2	Scanning Electron Microscopy.....	86
4.2.1	Basic Operation of SEM.....	86
4.2.2	Electron Beam–Specimen Interactions.....	89
4.2.3	Backscatter Electron Emission and Detection.....	91

4.2.4	Secondary Electron Emission and Detection	94
4.2.5	SEM Instruments	98
4.3	Sample Preparation and Imaging Strategy for Pharmaceuticals.....	102
4.3.1	Drug Substance	102
4.3.2	Drug Product	107
4.4	Energy Dispersive X-Ray Spectrometry	108
4.4.1	Theory	108
4.4.2	Qualitative Analysis	114
4.4.3	Quantitative Analysis	117
4.4.4	Elemental Mapping	120
4.4.5	EDS with Low-Vacuum SEM	123
4.5	Summary	125
4.6	Exercises	126
	A. Sample Preparation.....	126
	B. Secondary and Backscattered Electron Imaging	127
	C. Low-Vacuum SEM	127
	D. EDS Qualitative Analysis	128
	E. Elemental Mapping	128
	References	129
	Internet References	130
5	Infrared and Raman Microscopy	131
5.1	Introduction.....	131
5.2	Infrared Microscopy.....	132
5.2.1	Theory	132
5.2.2	Instruments.....	134
5.2.3	Sample Preparation and Testing.....	136
5.2.4	Calibration and Performance Checks.....	140
5.3	Raman Microscopy	141
5.3.1	Theory	141
5.3.2	Instruments.....	142
5.3.3	Sample Preparation and Testing.....	144
5.3.4	Calibration and Performance Checks.....	146
5.4	Applications	147
5.4.1	Solid-State Analysis.....	147
5.4.2	Contaminant Analysis	151
5.4.3	Chemical Imaging	152
5.5	Summary	153
5.6	Exercises	154
	A. Basic Operation	154
	B. Operating Parameters	154
	C. Spectral Interpretation	155
	D. Mapping.....	155
	References.....	155
	Internet Resources.....	156

6	Specialized Microscopy Techniques	157
6.1	Introduction	157
6.2	Confocal Microscopy	157
6.3	Scanning Probe Microscopy	159
6.4	Transmission Electron Microscopy.....	160
6.5	Differential Interference Contrast and Hoffmann Modulation Contrast.....	162
6.6	Phase Contrast.....	163
6.7	Dispersion Staining	165
6.8	Dark Field and Rheinberg Illumination	167
6.9	Flourescence Microscopy.....	168
6.10	Freeze-Dry Microscopy	170
6.11	Thermal Microscopy in the SEM.....	170
6.12	Summary	171
	References	171
	Internet Reference	172
7	Image Analysis	173
7.1	Introduction.....	173
7.2	General Principles	174
7.3	Sample Preparation	175
7.3.1	Introduction.....	175
7.3.2	Optical Microscopy Sample Preparation	176
7.3.3	SEM Sample Preparation.....	179
7.4	Image Production	181
7.4.1	General Considerations.....	181
7.4.2	Image Production with the Optical Microscope	182
7.4.3	Image Production with the SEM.....	182
7.4.4	Choice of Microscopy: Resolution and Magnification	183
7.5	Image Collection	183
7.6	Image Processing	185
7.7	Segmentation.....	187
7.8	Binary Operations	188
7.8.1	Feature Improvements.....	188
7.8.2	Removal of Unwanted Features and Noise.....	191
7.9	Measurements	193
7.9.1	General Considerations.....	193
7.9.2	Field Measurements	194
7.9.3	Object Measurements.....	194
7.10	Calibration, Performance Checks, and Size Standards	202
7.11	Data Presentation and Statistics	203
7.12	Exercises	207
	A. Sample Preparation.....	208
	B. Image Collection	208
	C. Image Processing.....	208

D. Image Segmentation	209
E. Binary Operations.....	209
F. Measurements.....	209
G. Statistics and Data Presentation.....	210
References	210
Internet References.....	211
8 Polymorphism.....	213
8.1 Introduction.....	213
8.2 Theory	214
8.2.1 Solid-State Forms.....	214
8.2.2 Form Relationships	218
8.3 Solid-State Form Discovery and Selection	222
8.3.1 General Considerations	222
8.3.2 Form Discovery.....	223
8.3.3 Form Selection	226
8.4 Analytical Characterization of Solid-State Forms	227
8.5 Caffeine Polymorphism: A Practical Example	228
8.5.1 Introduction.....	228
8.5.2 Caffeine Properties.....	229
8.5.3 Caffeine Form Discovery – Initial Tests	230
8.5.4 Form Discovery – Polymorph Screening.....	234
8.5.5 Form Stability and Form Relationships	238
8.5.6 Thermodynamic Relationship of Anhydrous Polymorphs	240
8.5.7 Caffeine Hydrate	241
8.5.8 Caffeine Example Summary	242
8.6 Summary	243
References	244
Caffeine Polymorphism	245
Regulatory Guidance	246
Additional General References	246
9 Size and Shape Analysis	247
9.1 Introduction	247
9.2 Qualitative Shape Analysis	248
9.3 Image Analysis Examples.....	250
9.3.1 Image Analysis of Hydrocortisone Cream with Optical Microscopy	250
9.3.2 Image Analysis of Carbon Black with SEM.....	254
9.3.3 Image Analysis of Generic Naproxen Sodium Tablet: Backscatter and EDS	258
9.3.4 Summary of Exercises	264
9.4 Method Development and Error Analysis.....	264
9.4.1 General Considerations	264

9.4.2	Method Development.....	265
9.4.3	Error Analysis and Validation.....	266
9.5	Specifications.....	273
9.6	Automation.....	274
9.7	Summary.....	276
	References.....	276
	Internet Reference.....	276
10	Contaminant Analysis.....	277
10.1	Introduction.....	277
10.2	Robert's Rules for Contaminant Identification.....	279
10.2.1	Rule #1: Think Before You Act.....	279
10.2.2	Rule #2: Get All the Information Before You Start.....	279
10.2.3	Rule #3: Clearly Establish the Goal of the Investigation.....	280
10.2.4	Rule #4: Every Experiment Should Test a Hypothesis....	281
10.2.5	Rule #5: Start Simple and Progress to Complex.....	281
10.2.6	Rule #6: Maintain Clear Distinction Between Fact and Hypothesis.....	283
10.2.7	Rule #7: Verify Conclusions.....	283
10.2.8	Rule #8: Document as You Work.....	284
10.2.9	Rule #9: Have a Clear Exit Strategy.....	285
10.3	Practical Examples.....	286
10.3.1	Introduction and Method of Analysis.....	286
10.3.2	Dust.....	286
10.3.3	Activated Charcoal in Powdered Sugar.....	289
10.3.4	Polymer Tubing in Corn Starch.....	294
10.3.5	Silicone Oil in Water.....	299
10.4	Laboratory Requirements for Contaminant Identification.....	301
10.5	Summary.....	302
	Reference.....	303
	General References.....	303
	Internet References.....	303
11	Conclusion.....	305
11.1	General Summary.....	305
11.2	Training and Education.....	307
11.3	Experts vs. Generalists.....	308
11.4	Conclusion.....	309
	Index.....	311



<http://www.springer.com/978-1-4419-8830-0>

Pharmaceutical Microscopy

Carlton, R.A.

2011, XIV, 321 p., Hardcover

ISBN: 978-1-4419-8830-0