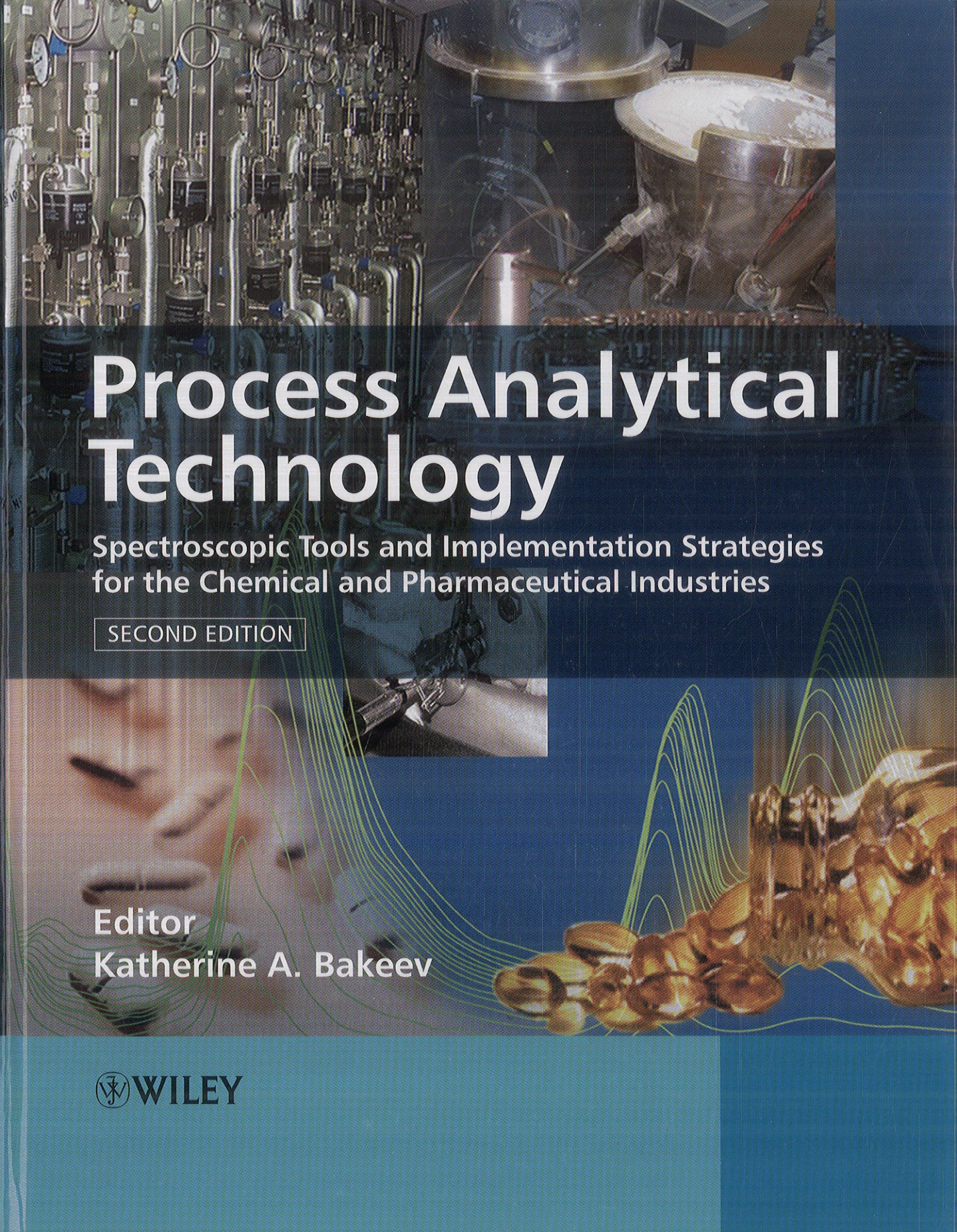




Process Analytical Technology

Spectroscopic Tools and Implementation Strategies
for the Chemical and Pharmaceutical Industries

SECOND EDITION

Editor
Katherine A. Bakeev

 WILEY

Contents

<i>Preface to the Second Edition</i>	<i>xvii</i>
<i>List of Contributors</i>	<i>xix</i>
<i>List of Abbreviations</i>	<i>xxi</i>
1 Overview of Process Analysis and PAT	1
Jason E. Dickens	
1.1 Introduction	1
1.1.1 Historical perspective	3
1.1.2 Business drivers	4
1.2 Execution of Process Analysis Projects	5
1.2.1 Wisdoms	5
1.2.2 Team structure	6
1.2.3 Project life cycle	6
1.2.4 Project scoping	9
1.2.5 Common challenges and pitfalls	10
1.3 Process Instrumentation	12
1.3.1 Process instrumentation types	12
1.3.2 Novel process instrumentation	12
1.4 Conclusions	13
1.5 Glossary of Acronyms and Terms	14
References	14
2 Implementation of Process Analytical Technologies	17
Robert Guenard and Gert Thurau	
2.1 Introduction to Implementation of Process Analytical Technologies (PAT) in the Industrial Setting	17
2.1.1 Definition of process analytics	18
2.1.2 Differences between process analyzers and laboratory analysis	19
2.1.3 General industrial drivers for PA	19
2.1.4 Types of applications (R&D versus manufacturing)	20
2.1.5 Organizational considerations	20
2.2 Generalized Process Analytics Work Process	23
2.2.1 Project identification and definition	24
2.2.2 Analytical application development	26

2.2.3	Design, specify and procure	26
2.2.4	Implementation in production	28
2.2.5	Routine operation	29
2.2.6	Continuous improvement	30
2.3	Considerations for PAT Implementation in the Pharmaceutical Industry	30
2.3.1	Introduction	30
2.3.2	Business model	30
2.3.3	Technical differences	31
2.3.4	Regulatory Aspects of Process Analytics in the Pharmaceutical Industry – the Concept of Quality by Design	33
2.4	Conclusions	36
	References	36
3	Process Sampling: Theory of Sampling – the Missing Link in Process Analytical Technologies (PAT)	37
	Kim H. Esbensen and Peter Paasch-Mortensen	
3.1	Introduction	37
3.2	Theory of Sampling – Introduction	39
3.2.1	Heterogeneity	41
3.2.2	Constitutional heterogeneity	41
3.2.3	Distributional heterogeneity	42
3.2.4	Structurally correct sampling	45
3.2.5	Incorrect sampling error	45
3.2.6	Increment delimitation error	45
3.2.7	Increment extraction error	46
3.2.8	Increment preparation error	46
3.2.9	Increment weighing error	47
3.2.10	Total sampling error	48
3.2.11	Global estimation error	48
3.3	Mass Reduction as a Specific Sampling Procedure	48
3.4	Fundamental Sampling Principle	51
3.5	Sampling – a Very Practical Issue	51
3.5.1	Sampling unit operations	52
3.5.2	Understanding process sampling: 0-D versus 1-D LOTS	52
3.5.3	Grab sampling – 0-D and 1-D	54
3.5.4	Correct process sampling: increment delimitation/extraction	56
3.5.5	PAT versus correct process sampling – what is required?	58
3.6	Reactors and Vessels – Identical Process Sampling Issues	60
3.6.1	Correct process sampling with existing process technology	62
3.6.2	Upward flux – representative colocated PAT sampling	62
3.6.3	Upstream colocated PAT sampler	64
3.7	Heterogeneity Characterization of 1-D lots: Variography	66
3.7.1	Process sampling modes	67
3.7.2	The experimental variogram	67
3.7.3	Sampling plan simulation and estimation of TSE	71
3.7.4	TSE estimation for 0-D lots – batch sampling	72
3.7.5	Corporate QC benefits of variographic analysis	73

3.8	Data Quality – New Insight from the TOS	75
3.9	Validation in Chemometrics and PAT	76
3.10	Summary	78
	References	79
4	UV-visible Spectroscopy for On-line Analysis	81
	Marcel A. Liauw, Lewis C. Baylor and Patrick E. O'Rourke	
4.1	Introduction	81
4.2	Theory	82
	4.2.1 Chemical concentration	82
	4.2.2 Color	84
	4.2.3 Film thickness	85
	4.2.4 Turbidity	85
	4.2.5 Plasmons/nanoparticles	85
4.3	Instrumentation	85
4.4	Sample Interface	86
	4.4.1 Cuvette/vial	87
	4.4.2 Flow cells	87
	4.4.3 Insertion probe	87
	4.4.4 Reflectance probe	89
4.5	Implementation	89
	4.5.1 A complete process analyzer	89
	4.5.2 Troubleshooting	89
4.6	Applications	91
	4.6.1 Gas and vapor analysis	92
	4.6.2 Liquid analysis	92
	4.6.3 Solid analysis	96
	4.6.4 Other applications	99
4.7	Detailed Application Notes	100
	4.7.1 Gas and vapor analysis: toluene	100
	4.7.2 Liquid analysis: breakthrough curves	101
	4.7.3 Solids analysis: extruded plastic color	101
	4.7.4 Film thickness determination: polymer	103
4.8	Conclusion	104
	References	104
5	Near-infrared Spectroscopy for Process Analytical Technology: Theory, Technology and Implementation	107
	Michael B. Simpson	
5.1	Introduction	107
5.2	Theory of Near-infrared Spectroscopy	112
5.3	Analyser Technologies in the Near-infrared	114
	5.3.1 Light sources and detectors for near-infrared analyzers	114
	5.3.2 The scanning grating monochromator and polychromator diode-array	119
	5.3.3 The acousto-optic tunable filter (AOTF) analyzer	123
	5.3.4 Fourier transform near-infrared analyzers	127
	5.3.5 Emerging technologies in process NIR analyzers	134

5.4	The Sampling Interface	136
5.4.1	Introduction	136
5.4.2	Problem samples: liquids, slurries and solids	142
5.4.3	The use of fiber optics	145
5.5	Practical Examples of Near-infrared Analytical Applications	147
5.5.1	Refinery hydrocarbon streams	148
5.5.2	Polyols, ethoxylated derivatives, ethylene oxide/propylene oxide polyether polyols	149
5.5.3	Oleochemicals, fatty acids, fatty amines and biodiesel	151
5.6	Conclusion	152
	References	153
6	Infrared Spectroscopy for Process Analytical Applications	157
	John P. Coates	
6.1	Introduction	157
6.2	Practical Aspects of IR Spectroscopy	161
6.3	Instrumentation Design and Technology	163
6.4	Process IR Instrumentation	166
6.4.1	Commercially available IR instruments	167
6.4.2	Important IR component technologies	172
6.4.3	New technologies for IR components and instruments	176
6.4.4	Requirements for process infrared analyzers	178
6.4.5	Sample handling for IR process analyzers	185
6.4.6	Issues for consideration in the implementation of process IR	187
6.5	Applications of Process IR Analyzers	189
6.6	Process IR Analyzers: a Review	191
6.7	Trends and Directions	192
	References	193
7	Raman Spectroscopy	195
	Nancy L. Jestel	
7.1	Attractive Features of Raman Spectroscopy	195
7.1.1	Quantitative information	195
7.1.2	Flexible sample forms and sizes used as accessed without damage	196
7.1.3	Flexible sample interfaces	196
7.1.4	Attractive spectral properties and advantageous selection rules	197
7.1.5	High sampling rate	197
7.1.6	Stable and robust equipment	198
7.2	Potential Issues with Raman Spectroscopy	198
7.2.1	High background signals	198
7.2.2	Stability	198
7.2.3	Too much and still too little sensitivity	199
7.2.4	Personnel experience	199
7.2.5	Cost	200
7.3	Fundamentals of Raman Spectroscopy	200

7.4	Raman Instrumentation	203
7.4.1	Safety	203
7.4.2	Laser wavelength selection	204
7.4.3	Laser power and stability	204
7.4.4	Spectrometer	205
7.4.5	Sample interface (probes)	206
7.4.6	Communications	208
7.4.7	Maintenance	209
7.5	Quantitative Raman	209
7.6	Applications	212
7.6.1	Acylation, alkylation, catalytic cracking, and transesterification	213
7.6.2	Bioreactors	213
7.6.3	Blending	214
7.6.4	Calcination	214
7.6.5	Catalysis	215
7.6.6	Chlorination	216
7.6.7	Counterfeit pharmaceuticals	217
7.6.8	Extrusion	218
7.6.9	Forensics	218
7.6.10	Hydrogenation	218
7.6.11	Hydrolysis	219
7.6.12	Medical diagnostics	219
7.6.13	Microwave-assisted organic synthesis	219
7.6.14	Mobile or field uses	220
7.6.15	Natural products	220
7.6.16	Orientation, stress, or strain	221
7.6.17	Ozonolysis	222
7.6.18	Polymerization	222
7.6.19	Polymer curing	224
7.6.20	Polymorphs (crystal forms)	225
7.6.21	Product properties	228
7.6.22	Purification: distillation, filtration, drying	229
7.6.23	Thin films or coatings	229
7.7	Current State of Process Raman Spectroscopy	230
	References	231
8	Near-infrared Chemical Imaging for Product and Process Understanding	245
	E. Neil Lewis, Joseph W. Schoppelrei, Lisa Makein, Linda H. Kidder and Eunah Lee	
8.1	The PAT Initiative	245
8.2	The Role of Near-infrared Chemical Imaging (NIR-CI) in the Pharmaceutical Industry	246
8.2.1	Characterization of solid dosage forms	246
8.2.2	'A picture is worth a thousand words'	247
8.3	Evolution of NIR Imaging Instrumentation	247
8.3.1	Spatially resolved spectroscopy – mapping	247
8.3.2	The infrared focal-plane array	247
8.3.3	Wavelength selection	248

8.3.4	The benefits of NIR spectroscopy	248
8.3.5	NIR imaging instrumentation	249
8.4	Chemical Imaging Principles	251
8.4.1	The hypercube	251
8.4.2	Data analysis	251
8.4.3	Spectral correction	252
8.4.4	Spectral preprocessing	253
8.4.5	Classification	253
8.4.6	Image processing – statistical	255
8.4.7	Image processing – morphology	257
8.5	PAT Applications	257
8.5.1	Content uniformity measurements – ‘self calibrating’	258
8.5.2	Quality assurance – imaging an intact blister pack	260
8.5.3	Contaminant detection	261
8.5.4	Imaging of coatings – advanced design delivery systems	263
8.6	Processing Case Study: Estimating ‘Abundance’ of Sample Components	267
8.6.1	Experimental	268
8.6.2	Spectral correction and preprocessing	268
8.6.3	Analysis	268
8.6.4	Conclusions	273
8.7	Processing Case Study: Determining Blend Homogeneity Through Statistical Analysis	273
8.7.1	Experimental	273
8.7.2	Observing visual contrast in the image	274
8.7.3	Statistical analysis of the image	274
8.7.4	Blend uniformity measurement	276
8.7.5	Conclusions	276
8.8	Final Thoughts	277
	Acknowledgements	278
	References	278
9	Acoustic Chemometric Monitoring of Industrial Production Processes	281
	Maths Halstensen and Kim H. Esbensen	
9.1	What is Acoustic Chemometrics?	281
9.2	How Acoustic Chemometrics Works	282
9.2.1	Acoustic sensors	282
9.2.2	Mounting acoustic sensors (accelerometers)	283
9.2.3	Signal processing	284
9.2.4	Chemometric data analysis	284
9.2.5	Acoustic chemometrics as a PAT tool	284
9.3	Industrial Production Process Monitoring	285
9.3.1	Fluidized bed granulation monitoring	285
9.3.2	Pilot scale studies	286
9.3.3	Monitoring of a start-up sequence of a continuous fluidized bed granulator	291
9.3.4	Process monitoring as an early warning of critical shutdown situations	295
9.3.5	Acoustic chemometrics for fluid flow quantification	296
9.4	Available On-line Acoustic Chemometric Equipment	299

9.5	Discussion	301
9.5.1	Granulator monitoring	301
9.5.2	Process state monitoring	301
9.5.3	Ammonia concentration monitoring	301
9.6	Conclusions	302
	References	302
10	Process NMR Spectroscopy: Technology and On-line Applications	303
	John C. Edwards and Paul J. Giammatteo	
10.1	Introduction	303
10.2	NMR Spectroscopy Overview	305
10.2.1	The NMR phenomenon	305
10.2.2	Time-domain-NMR: utilization of the FID and spin relaxation	309
10.2.3	High-resolution NMR: obtaining a spectrum with resolved chemical shift information	312
10.3	Process NMR Instrumentation	313
10.3.1	Spectrometer and magnet design	313
10.3.2	Sampling and experimental design	316
10.4	Postprocessing Methodologies for NMR Data	317
10.5	Advantages and Limitations of NMR as a Process Analytical Technology	320
10.5.1	Advantages	320
10.5.2	Limitations	321
10.6	On-line and At-line Applications	321
10.6.1	Time-domain NMR	322
10.6.2	High-resolution NMR: chemometric applications	323
10.7	Current Development and Applications	330
10.8	Conclusions	331
	References	332
11	Fluorescent Sensing and Process Analytical Applications	337
	Jason E. Dickens	
11.1	Introduction	337
11.2	Luminescence Fundamentals	338
11.2.1	Luminescence nomenclature	338
11.2.2	Luminescence processes	338
11.2.3	Fluorophore classification	338
11.3	LIF Sensing Fundamentals	341
11.3.1	LIF sensing classification	341
11.3.2	Luminescence spectroscopy	342
11.3.3	LIF signal response function	343
11.4	LIF Sensing Instrumentation	343
11.4.1	LIF photometric instrument specification	345
11.4.2	LIF Instrument selection	347
11.5	Luminescent Detection Risks	347
11.6	Process Analytical Technology Applications	348
11.6.1	Petrochemical, chemical and nuclear field applications	349
11.6.2	Pharmaceutical PAT applications	349

11.7	Conclusions	350
	References	351
12	Chemometrics in Process Analytical Technology (PAT)	353
	Charles E. Miller	
12.1	Introduction	353
	12.1.1 What is chemometrics?	353
	12.1.2 Some history	354
	12.1.3 Some philosophy	355
	12.1.4 Chemometrics in analytical chemistry?	355
	12.1.5 Chemometrics in process analytical chemistry?	356
12.2	Foundations of Chemometrics	356
	12.2.1 Notation	356
	12.2.2 Some basic statistics	358
	12.2.3 Linear regression	359
	12.2.4 Multiple linear regression	361
	12.2.5 Principal components analysis (PCA)	362
	12.2.6 Design of experiments (DOE)	366
12.3	Chemometric Methods in PAT	368
	12.3.1 Data preprocessing	369
	12.3.2 Quantitative model building	377
	12.3.3 Qualitative model building	389
	12.3.4 Exploratory analysis	397
12.4	Overfitting and Model Validation	407
	12.4.1 Overfitting and underfitting	407
	12.4.2 Test set validation	408
	12.4.3 Cross validation	410
12.5	Outliers	413
	12.5.1 Introduction to outliers	413
	12.5.2 Outlier detection and remediation	413
12.6	Calibration Strategies in PAT	416
	12.6.1 The 'calibration strategy space'	417
	12.6.2 Strategies for direct versus inverse modeling methods	418
	12.6.3 Hybrid strategies	419
12.7	Sample and Variable Selection in Chemometrics	420
	12.7.1 Sample selection	420
	12.7.2 Variable selection	421
12.8	Troubleshooting/Improving an Existing Method	425
	12.8.1 Method assessment	425
	12.8.2 Model improvement strategies	425
12.9	Calibration Transfer and Instrument Standardization	426
	12.9.1 Slope/intercept adjustment	428
	12.9.2 Piecewise direct standardization (PDS)	428
	12.9.3 Generalized least squares (GLS) weighting	429
	12.9.4 Shenk–Westerhaus method	429
	12.9.5 Other transfer/standardization methods	429

12.10	Chemometric Model Deployment Issues in PAT	430
12.10.1	Outliers in prediction	430
12.10.2	Deployment software	432
12.10.3	Data systems, and control system integration	432
12.10.4	Method updating	433
12.11	People Issues	433
12.12	The Final Word	434
	References	434
13	On-line PAT Applications of Spectroscopy in the Pharmaceutical Industry	439
	<i>Brandye Smith-Goettler</i>	
13.1	Background	439
13.2	Reaction Monitoring	441
13.3	Crystallization	442
13.4	API Drying	443
13.5	Nanomilling	444
13.6	Hot-melt Extrusion	445
13.7	Granulation	446
13.7.1	Wet granulation	446
13.7.2	Roller compaction	449
13.8	Powder Blending	450
13.8.1	Lubrication	451
13.8.2	Powder flow	451
13.9	Compression	452
13.10	Coating	452
13.11	Biologics	453
13.11.1	Fermentation	453
13.11.2	Freeze-drying	454
13.12	Cleaning Validation	454
13.13	Conclusions	455
	References	455
14	NIR spectroscopy in Pharmaceutical Analysis: Off-line and At-line PAT Applications	463
	<i>Marcelo Blanco Romá and Manel Alcalá Bernárdez</i>	
14.1	Introduction	463
14.1.1	Operational procedures	464
14.1.2	Instrument qualification	466
14.2	Foundation of Qualitative Method Development	466
14.2.1	Pattern recognition methods	467
14.2.2	Construction of spectral libraries	468
14.2.3	Identification and qualification	470
14.3	Foundation of Quantitative Method Development	471
14.3.1	Selection and preparation of samples	472
14.3.2	Preparation and selection of samples	473
14.3.3	Determination of reference values	474
14.3.4	Acquisition of spectra	474

14.3.5	Construction of the calibration model	475
14.3.6	Model validation	476
14.3.7	Prediction of new samples	476
14.4	Method Validation	476
14.5	Calibration Transfer	476
14.6	Pharmaceutical Applications	478
14.6.1	Identification of raw materials	478
14.6.2	Homogeneity	478
14.6.3	Moisture	480
14.6.4	Determination of physical parameters	481
14.6.5	Determination of chemical composition	483
14.7	Conclusions	485
	References	486
15	Near-infrared Spectroscopy (NIR) as a PAT Tool in the Chemical Industry: Added Value and Implementation Challenges	493
	Ann M. Brearley and Susan J. Foulk	
15.1	Introduction	493
15.2	Successful Process Analyzer Implementation	494
15.2.1	A process for successful process analyzer implementation	494
15.2.2	How NIR process analyzers contribute to business value	497
15.2.3	Issues to consider in setting technical requirements for a process analyzer	498
15.2.4	Capabilities and limitations of NIR	499
15.2.5	General challenges in process analyzer implementation	500
15.2.6	Approaches to calibrating an NIR analyzer on-line	502
15.2.7	Special challenges in NIR monitoring of polymer melts	505
15.3	Example Applications	506
15.3.1	Monitoring monomer conversion during emulsion polymerization	506
15.3.2	Monitoring a diethylbenzene isomer separation process	508
15.3.3	Monitoring the composition of copolymers and polymer blends in an extruder	509
15.3.4	Rapid identification of carpet face fiber	512
15.3.5	Monitoring the composition of spinning solution	514
15.3.6	Monitoring end groups and viscosity in polyester melts	516
15.3.7	In-line monitoring of a copolymerization reaction	518
	References	520
16	Future Trends for PAT for Increased Process Understanding and Growing Applications in Biomanufacturing	521
	Katherine A. Bakeev and Jose C. Menezes	
16.1	Introduction	521
16.2	Regulatory Guidance and its Impact on PAT	522
16.3	Going Beyond Process Analyzers Towards Solutions	524
16.3.1	Design of experiments for risk-based analysis	526
16.3.2	Sample and process fingerprinting with PAT tools	527
16.3.3	Design and Control Spaces	528
16.3.4	Chemometrics and process analysis	528

16.4	Emerging Application Areas of PAT	529
16.4.1	Biofuels	529
16.4.2	Biomanufacturing	530
16.5	New and Emerging Sensor and Control Technologies	531
16.5.1	Terahertz spectroscopy	531
16.5.2	Integrated sensing and processing	532
16.5.3	Dielectric spectroscopy	533
16.5.4	Process chromatography	533
16.5.5	Mass spectrometry	534
16.5.6	Microwave resonance	534
16.5.7	Novel sensors	535
16.5.8	Inferential sensors	536
16.6	Advances in Sampling: NeSSI	537
16.7	Challenges Ahead	537
16.7.1	Continuous process validation	538
16.7.2	Data challenges: data handling and fusion	539
16.7.3	Regulatory challenges	539
16.7.4	Enterprise systems for managing data	539
16.8	Conclusion	540
	References	540
	Index	545