Contents

Preface XVII List of Contributors XXI

 From Milligrams to Tons: The Importance of Synthesis and Process Research in the Development of New Drugs 1 Martin Karpf
 Introduction 1 V

- The Synthetic Development of the Monoamine Oxidase-B Inhibitor Lazabemide[™] 6
- The Synthetic Development of the Lipase Inhibitor Tetrahydrolipstatin (Xenical[™]) 6
- 1.4 The Synthetic Development of the HIV Protease Inhibitor Saquinavir (Invirase[™]) 13
- The Synthetic Development of the Influenza Neuraminidase Inhibitor Oseltamivir Phosphate (Tamiflu[™]) 16
- 1.5.1 Introduction 16
- 1.5.2 The Development of the Current Technical Synthesis of Oseltamivir Phosphate *18*
- 1.5.3 The Search for Alternative Routes to Oseltamivir Phosphate 23
- 1.5.3.1The Development of Azide-Free Transformations of the Key Epoxide
Intermediate to Oseltamivir Phosphate23
- 1.5.3.2 The Development of Alternative Syntheses for Oseltamivir Phosphate 27 References 36
- 2 Design of Dynamic Salt Catalysts Based on Acid-Base Combination Chemistry 39

Kazuaki Ishihara

- 2.1 Introduction 39
- 2.2 Dehydrative Condensation Catalysts 41

VI Contents

2.2.1	Esterification Catalysts 41
2.2.2	Dehydrative Cyclocondensation Catalysts 43
2.3	Asymmetric Mannich-Type Catalysts 50
	References 56
3	Asymmetric Oxidation with Hydrogen Peroxide, an Effective and Versatile Oxidant 59
	Tsutomu Katsuki
3.1	Introduction 59
3.2	Asymmetric Epoxidation 60
3.2.1	Asymmetric Epoxidation with Synthetic Enzymes or Organocatalysts 60
3.2.2	Metal-Catalyzed Asymmetric Epoxidation of Unfunctionalized Olefins 62
3.2.3 3.3	Metal-Catalyzed Asymmetric Epoxidation of Allylic Alcohols 67 Asymmetric Oxidation of Sulfides 67
3.3.1	Metal–Salen-Catalyzed Oxidation 68
3.3.2	Metal–Schiff Base-Catalyzed Oxidation 68
3.3.3	Metal–ONNO–Tetradentate Ligand-Catalyzed Oxidation (Including
5.5.5	$cis-\beta$ Metal-Salen-Catalyzed Oxidation) 69
3.3.4	Miscellaneous 72
3.4	Conclusion 73
	References 74
4	Development of Palladium Catalysts for Chemoselective
	Hydrogenation 77
	Hironao Sajiki and Yasunari Monguchi
4.1	Catalyst Poisons and Chemoselective Heterogeneous Catalysts 77
4.1.1	Background 77
4.1.2	Chemoselective Inhibition of the Hydrogenolysis for <i>O</i> -Benzyl Protective Groups by the Addition of a Nitrogen-Containing Base 77
4.1.3	Pd/C(en) Complex as a Heterogeneous Chemoselective Hydrogenation Catalyst 81
4.1.4	Pd/C (Ph ₂ S) Complex as a Heterogeneous Chemoselective Hydrogenation Catalyst 85
4.2	Catalyst Supports and Chemoselective Heterogeneous Catalysts 90
4.2.1	Pd/Fib as a Silk-Fibroin-Supported Chemoselective Hydrogenation
1.2.1	Catalyst 90
4.2.2	Pd-PEI as a Partial Hydrogenation Catalyst of Alkynes
	to Alkenes 93
4.3	Summary 96
	Acknowledgment 97
	References 97

Contents VII

5	Silicon-Based Carbon–Carbon Bond Formation by Transition Metal Catalysis 101
	Yoshiaki Nakao and Tamejiro Hiyama
5.1	Introduction 101
5.2	Cross-Coupling Reactions 102
5.2.1	Brief Assessment of Early Stage Protocols 102
5.2.2	Cross-Coupling Reactions Using Tetraorganosilanes through Intramolecular Activation 103
5.2.3	Cross-Coupling Reactions Using Organosilanolates 106
5.2.4	Other Tetraorganosilicon Compounds for Cross-Coupling Chemistry 108
5.2.5	New Types of Electrophiles for Silicon-Based Cross-Coupling 111
5.3	Carbonyl Addition Reaction 114
5.3.1	Rhodium-Catalyzed Reactions 114
5.3.2	Nickel-Catalyzed Reactions 115
5.3.3	Palladium-Catalyzed Reactions 117
5.3.4	Copper-Catalyzed Reactions 120
5.3.5	Silver-Catalyzed Reactions 121
5.4	Recent Developments in Catalytic Preparation of Organosilanes 121
	References 123
6	Direct Reductive Amination with Amine Boranes 127
	Karl Matos and Elizabeth R. Burkhardt
6.1	Introduction 127
6.2	Types of Amine Boranes 128
6.2.1	Alkylamine Boranes 128
6.2.2	Aromatic Amine Boranes 129
6.2.2.1	Pyridine borane 130
6.2.2.2	2-Picoline borane 131
6.2.2.3	5-Ethyl-2-methylpyridine borane 131
6.3	Comparison to Sodium Triacetoxyborohydride (STAB) 134
6.4	Primary Amine Synthesis 135
6.5	Stereoselective Reductive Amination 137
6.6	Reaction Solvents 138
6.7	Reaction Workup 138
6.8	Conclusion 141

References 141

Industrial Synthesis of Perfluorinated Building Blocks by Liquid-Phase 7 **Direct Fluorination** 145

Takashi Okazoe

- 7.1 Introduction 145
- 7.2 History of Direct Fluorination 146
- Synthetic Methods Using Perfluorinated Acyl Fluorides for Industrially 7.3 Important Perfluorinated Monomers 149

7.3.1	Direct Application of Liquid-Phase Fluorination 149
7.3.2	The PERFECT Method 150
7.4	Synthesis of Perfluorinated Building Blocks by the PERFECT
	Method 152
7.4.1	Perfluorinated Acyl Fluorides 152
7.4.2	Synthesis of Perfluorinated Ketones by the PERFECT
	Method 154
7.5	Conclusion 156
	References 157
8	Cross-Linked Enzyme Aggregates as Industrial Biocatalysts 159
0	Cross-Linked Enzyme Aggregates as Industrial Biocatalysts 159 Roger A. Sheldon
8.1	Introduction 159
8.2	Cross-Linked Enzyme Aggregates 160
8.2.1	Cross-Linking Agents 160
8.2.2	Protocols for CLEA Preparation 161
8.2.3	Advantages of CLEAs 163
8.2.4	Multi-CLEAs and Combi-CLEAs 164
8.3	CLEAs from Hydrolases 164
8.3.1	Lipase and Esterase CLEAs 165
8.3.2	Protease CLEAs 168
8.3.3	Amidase CLEAs 170
8.3.4	Nitrilases 171
8.3.5	Glycosidases 172
8.4	Oxidoreductases 172
8.4.1	Oxidases 172
8.4.2	Peroxidases 173
8.5	Lyases 174
8.5.1	Nitrile Hydratases 174
8.5.2	C–C Bond Forming Lyases 174
8.6	Combi-CLEAs and Cascade Processes 175
8.7	Reactor Design 176
8.7.1	Membrane Slurry Reactor 177
8.7.2	CLEAs in Microchannel Reactors 177
8.8	Conclusions and Prospects 178
	References 178
9	Application of Whole-Cell Biocatalysts in the Manufacture of Fine
	Chemicals 183
	Michael Schwarm
9.1	Introduction: Early Applications of Biocatalysis for Amino Acid
	Manufacture at Evonik Degussa 183
9.2	Hydantoinase Biocatalysts 187
9.3	Amino Acid Dehydrogenase Biocatalysts 191
9.4	Alcohol Dehydrogenase Biocatalysts 195

9.5	Summary 203
	Acknowledgments 204
	References 204
10	Process Development of Amrubicin Hydrochloride, an Anthracycline
10	Anticancer Drug 207
	Kazuhiko Takahashi and Mitsuharu Hanada
10.1	Introduction 207
10.1	Original Synthetic Route for Amrubicin 208
10.2	Amrubicin Bulk Production Synthetic Method 210
10.3	Safe Synthetic Method of 9-Aminoketone 211
10.3.1	Stereoselective Introduction of 7-Hydroxy Group 213
10.3.3	Polymorphism Study of Amrubicin Hydrochloride 215
10.3.4	Stability of Amrubicin Hydrochloride with Reference to Moisture 216
10.3.4.1	Amrubicin Hydrochloride Moisture Adsorption 217
10.3.4.2	Stability in Various Water Contents 217
10.3.4.3	Establishment of Drying Method 217
10.4	Conclusion 219
	References 219
11	Process Development of HIV Integrase Inhibitor S-1360 221
	Toshiro Konoike and Sumio Shimizu
11.1	Introduction 221
11.2	Discovery of Integrase Inhibitor S-1360 221
11.2.1	Discovery Route of S-1360 222
11.3	Synthesis of Two Starting Materials for S-1360 225
11.3.1	Two One-Step Syntheses of Benzylfuryl Methyl Ketone 2225
11.3.1.1	Friedel–Crafts Alkylation by Anhydrous ZnCl ₂ in
	Dichloromethane 226
11.3.1.2	Friedel–Crafts Alkylation Using Aqueous ZnCl ₂ 226
11.3.2	Two Synthetic Methods to Triazole Ester 3 228
11.3.2.1	Ring Construction Method 228
11.3.2.2	Ring Modification Method 228
11.4	Process Chemistry of S-1360 and Scale-Up of THP Route 229
11.4.1	Protection of Triazole 3 by the Tetrahydropyranyl (THP) Group and
	Claisen Condensation 229
11.4.2	Deprotection of the THP Group and Purification of API Deprotection of the THP Group 230
11.4.2.1	Purification of API 231
11.4.2.2	Quality Assurance and Productivity 232
11.5	Process Development of S-1360 and Commercial Route by
	Methoxyisopropyl (MIP) Protection 233
11.5.1	MIP Route 234

11.5.2 Further Improvement of Productivity 235

X Contents

11.6	Summary and Outlook 235 Acknowledgments 237 References 237
12	An Efficient Synthesis of the Protein Kinase C β Inhibitor JTT-010 239 Takashi Inaba
12.1	Introduction 239
12.2	Synthetic Strategies 240
12.3	Key Intermediate Synthesis 240
12.3.1	Optical Resolution 240
12.3.2	Enzymatic Chiral Induction 242
12.3.3	C–H Bond Activation by a Chiral Catalyst 243
12.3.4	Formal $[3 + 2]$ Cycloaddition Using Chiral Cyclopropane 244
12.4	Replacement of the Hydroxyl Group of 1 with an Amino Group 250
12.5	Construction of JTT-010 251
12.5.1	Stepwise Maleimide Construction 251
12.5.2	Convergent Coupling Reaction to JTT-010 251
12.6	Conclusion 253
	References 254
13	Process Development of Oral Carbapenem Tebipenem Pivoxil, TBPM-PI 257
	Takao Abe and Masataka Kitamura
13.1	Introduction 257
13.2	Discovery of TBPM-PI 257
13.3	Synthetic Process of Side Chain on the C2-Position of TBPM, TAT 260
13.3.1	Original Synthetic Process of TAT Starting from Benzhydrylamine 260
13.3.2	Practical Synthetic Process of TAT from Benzylamine 261
13.3.3	Industrial Synthetic Process of TAT: Back to Classic
	Bunte's Salt 263
13.4	Synthetic Process of TBPM-PI from 4-Nitrobenzyl (1R,5R,6S)-2-
	diphenylphosphoryloxy-6-[(R)-1-hydroxyethyl]-
	1-methyl-1-carbapen-2-em-3-carboxylate, MAP 265
13.4.1	Synthesis of PNB Ester of TBPM, L-188 265
13.4.2	Synthesis of TBPM-4H ₂ O 266
13.4.3	Prodrug Esterification: Synthesis of TBPM Hexetil,
	LJC11,143 267
13.4.4	Synthesis of TBPM-PI 269
13.5	Summary and Outlook 270
	Acknowledgments 271
	References 271

Contents XI

14	Some Progress in Organic Synthesis of Pharmaceuticals
	in China 273
1 / 1	Delong Liu and Wanbin Zhang
14.1	Introduction 273
14.2	Industrial Synthesis of Chinese Herbal Medicines 274
14.2.1	Industrial Synthesis of Berberine 274
14.2.2	Industrial Synthesis of D,L-Tetrahydropalmatine (THP) 277
14.3	New Agents Derived from Chinese Herbal Medicines 281
14.3.1	Bifendate and Bicyclol 281
14.3.1.1	Bifendate 281
14.3.1.2	Bicyclol 284
14.3.2	Qinghaosu 285
14.3.2.1	Synthesis 285
14.3.2.2	Fixed-Dose Riamet/Coartem 287
14.4	Process Chemistry for L-Ascorbic Acid and Biotin 291
14.4.1	Two Steps Fermentation Method for the Preparation of L-Ascorbic Acid (Vitamin C) 291
14.4.2	Total Synthesis of Biotin (Vitamin B7) 294
14.5	Conclusion and Perspectives 298
	Abbreviations 299
	References 299
15	The Use of Continuous Processing to Make AZD 4407
15	The Use of Continuous Processing to Make AZD 4407 Intermediates 303
15	-
15 15.1	Intermediates 303
	Intermediates 303 Andrew S. Wells
15.1	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303
15.1 15.2	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304
15.1 15.2 15.3	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305
15.1 15.2 15.3	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to Prepare
15.1 15.2 15.3 15.4	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305
15.1 15.2 15.3 15.4	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308
15.1 15.2 15.3 15.4 15.5 15.5.1	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Preparation of Synthons Used in the Microreactor Study308
15.1 15.2 15.3 15.4 15.5 15.5.1 15.5.1.1	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Disulfide Synthesis309
15.1 15.2 15.3 15.4 15.5 15.5.1 15.5.1.1 15.5.1.2	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Preparation of Synthons Used in the Microreactor Study308Disulfide Synthesis308(S)-2-Methyl Tetrahydropyran-4-one309Thiophene Synthon310
15.1 15.2 15.3 15.4 15.5 15.5.1 15.5.1.1 15.5.1.2 15.5.1.3	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Preparation of Synthons Used in the Microreactor Study308Disulfide Synthesis308(S)-2-Methyl Tetrahydropyran-4-one309Thiophene Synthon310n-Hexyl Lithium Versus n-Butyl Lithium310
15.1 15.2 15.3 15.4 15.5 15.5.1 15.5.1.1 15.5.1.2 15.5.1.3 15.5.2	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Preparation of Synthons Used in the Microreactor Study308Disulfide Synthesis308(S)-2-Methyl Tetrahydropyran-4-one309Thiophene Synthon310n-Hexyl Lithium Versus n-Butyl Lithium310Batch Reactions: Lithiation Reaction and Disulfide Linking311
15.1 15.2 15.3 15.4 15.5 15.5.1 15.5.1.1 15.5.1.2 15.5.1.3 15.5.2 15.5.3	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Preparation of Synthons Used in the Microreactor Study308Disulfide Synthesis308(S)-2-Methyl Tetrahydropyran-4-one309Thiophene Synthon310n-Hexyl Lithium Versus n-Butyl Lithium310
15.1 15.2 15.3 15.4 15.5 15.5.1 15.5.1.1 15.5.1.2 15.5.1.3 15.5.2 15.5.3 15.5.4	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Preparation of Synthons Used in the Microreactor Study308Disulfide Synthesis308(S)-2-Methyl Tetrahydropyran-4-one309Thiophene Synthon310n-Hexyl Lithium Versus n-Butyl Lithium310Batch Reactions: Lithiation Reaction and Disulfide Linking311Microreactor Description311
15.1 15.2 15.3 15.4 15.5 15.5.1 15.5.1.1 15.5.1.2 15.5.1.3 15.5.2 15.5.3 15.5.4 15.5.5	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Preparation of Synthons Used in the Microreactor Study308Disulfide Synthesis308(S)-2-Methyl Tetrahydropyran-4-one309Thiophene Synthon310n-Hexyl Lithium Versus n-Butyl Lithium310Batch Reactions: Lithiation Reaction and Disulfide Linking311Microreactor Description311Lithiation Reaction in Flow Mode312Coupling Reaction with Disulfide in Flow Mode313
15.1 15.2 15.3 15.4 15.5 15.5.1 15.5.1.1 15.5.1.2 15.5.1.3 15.5.2 15.5.3 15.5.4 15.5.5 15.5.6	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Preparation of Synthons Used in the Microreactor Study308Disulfide Synthesis308(S)-2-Methyl Tetrahydropyran-4-one309Thiophene Synthon310 <i>n</i> -Hexyl Lithium Versus <i>n</i> -Butyl Lithium310Batch Reactions: Lithiation Reaction and Disulfide Linking311Microreactor Description311Lithiation Reaction in Flow Mode312Coupling Reaction with Disulfide in Flow Mode313
15.1 15.2 15.3 15.4 15.5 15.5.1 15.5.1.1 15.5.1.3 15.5.2 15.5.3 15.5.4 15.5.5 15.5.6 15.5.7	Intermediates303Andrew S. WellsGreen Chemistry and the Drive for Sustainability303Advantages of Chemistry in Continuous-Flow Reactors304Introduction to AZD 4407305Comparison of the Synthetic Routes Used to PrepareAZD 4407305Conversion of Batch to a Flow Process308Preparation of Synthons Used in the Microreactor Study308Disulfide Synthesis308(S)-2-Methyl Tetrahydropyran-4-one309Thiophene Synthon310 <i>n</i> -Hexyl Lithium Versus <i>n</i> -Butyl Lithium310Batch Reactions: Lithiation Reaction and Disulfide Linking311Microreactor Description311Lithiation Reaction in Flow Mode313Linking the Lithiation and Reaction with Disulfide in Flow Mode313

XII Contents

16	Sustainable Processes Based on Enzymes Enabling 100% Yield and
	100% ee Concepts 321
	Oliver May
16.1	Introduction 321
16.2	Asymmetric Synthesis 322
16.2.1	C–C Bond Formations 322
16.2.2	Production of Chiral Alcohols by Enzymatic Reduction of Ketones 325
16.2.3	Reduction of Activated C=C Bonds 326
16.2.4	Reductive Amination of α -Keto-Acids for the Production of α -Amino Acids 328
16.2.5	Transamination Reactions 330
16.3	Enzymatic Desymmetrization 332
16.4	Enzymatic Deracemization 335
16.5	Dynamic Kinetic Resolution 337
16.6	Summary and Outlook 338
1010	References 339
17	Development of a Novel Synthetic Method for RNA Oligomers 345
	Tadaaki Ohgi and Junichi Yano
17.1	Introduction 345
17.2	Synthesis of CEM Amidites 349
17.3	Synthesis of RNA Oligomers from CEM Amidites 350
	Acknowledgments 360
	References 360
18	Process Research with Explosive Reactions 363
	Hiromu Kawakubo
18.1	Introduction 363
18.2	Safety Evaluation of an Explosive Chemical Process 363
18.3	Standard Procedures for Risk Assessment 365
18.3.1	CHETAH (Chemical Thermodynamic and Energy Release Evaluation
	Program) Calculation 365
18.3.2	DSC (Differential Scanning Calorimetry) 365
18.3.3	DTA (Differential Thermal Analysis) and TG
	(Thermogravimetry) 367
18.3.4	Impact Sensitivity Test 368
18.3.5	Friction Sensitivity Test 368
18.3.6	Pressure Vessel Test 369
18.3.7	Steel Pipe Test 371
18.4	Safety Evaluation of Nitroacetic Acid Ethyl Ester 371
18.4.1	Various Safety Evaluations of Nitroacetic Acid Ethyl Ester 373
18.4.2	Synthesis of Nitroacetic Acid Ethyl Ester and Its Risk
	Assessment 374

- 18.5 Development of an Efficient Method for the Synthesis of Nitrobenzene
 Derivatives 376
 References 380
- 19 Scientific Strategy for Optical Resolution by Salt Crystallization: New Methodologies for Controlling Crystal Shape, Crystallization, and Chirality of Diastereomeric Salt 381

Rumiko Sakurai and Kenichi Sakai

- 19.1 Introduction 381
- 19.2 Control of Crystal Shape: Crystal Habit Modification 382
- 19.2.1 Significance of Crystal Shape in Industrial-Scale Production 382
- 19.2.2 Effective Additive for Controlling Crystal Shape 384
- 19.2.3 Mechanism of Crystal Habit Modification 385
- 19.3 Control of Crystallization: Concept of Space Filler 387
- 19.3.1 Evaluation of Molecular Size 387
- 19.3.2 Concept of Space Filler 388
- 19.3.3 Resolution of MMT 388
- 19.3.4 Crystal Structures of the Salts 390
- 19.4 Control of Chirality: Dielectrically Controlled Optical Resolution (DCR) 391
- 19.4.1 DCR 391
- 19.4.1.1 DCR in Resolution of (RS)-ACL with (S)-TPA 391
- 19.4.1.2 DCR in Resolution of (RS)-PTE with (S)-MA 394
- 19.5 Conclusion and Prospect 397 References 397

20 Development of New Drug and Crystal Polymorphs 401

Mitsuhisa Yamano

- 20.1 Introduction 401
- 20.2 Scope of Crystal Polymorphs 402
- 20.3 Late-Appearing Polymorphs 402
- 20.4 Late-Appearing Polymorphs as a Process Research Issue 403
- 20.5 Drug Substance Form Selection 404
- 20.6 Polymorph Screening 405
- 20.7 Thermodynamically Stable Polymorphs 406
- 20.7.1 One-Component System 406
- 20.7.2 Multicomponent System 406
- 20.8 Polymorph Control 409
- 20.8.1 Nucleation and Seeding 411
- 20.8.2 Ostwald's Stage Rule 411
- 20.8.3 Unintentional Seeding 416
- 20.9 Primary Nucleation 416
- 20.10 Summary 417

Acknowledgments 418

References 418

XIV Contents

21	Development of LIPOzymes Based on Biomembrane Process
	Chemistry 421
	Hiroshi Umakoshi, Toshinori Shimanouchi, and Ryoichi Kuboi
21.1	Introduction 421
21.2	From "Process Chemistry" to "Biomembrane Process
	Chemistry'' 422
21.3	Recognition (Separation) Function of Liposomes 425
21.4	LIPOzyme: Liposome with Enzyme-Like Activity? 428
21.4.1	Break-Down Type LIPOzyme 428
21.4.2	Build-Up Type LIPOzyme 431
21.5	Biomembrane Interference 433
21.6	Summary 438
	Acknowledgments 439
	References 439
22	Matching Chemistry with Chemical Engineering for Optimum Design
	and Performance of Pharmaceutical Processing 443
	Amit V. Mahulkar, Parag R. Gogate, and Aniruddha B. Pandit
22.1	Concept of Molecule to Money 443
22.2	Steps Involved in Bringing Molecule to Market 444
22.2.1	Synthesis in Lab 444
22.2.2	Kilo Lab 445
22.2.3	Pilot Plant 446
22.2.4	Full-Scale Plant 447
22.3	Interrelation in Each Step and Concept of Unit Operations 448
22.4	Unit Operations 449
22.4.1	Mixing 449
22.4.1.1	Utility of Mixing 449
22.4.1.2	Types of Equipments 449
22.4.1.3	Selection Criteria 451
22.4.2	Crystallization 452
22.4.2.1	Utility of Crystallization 452
22.4.2.2	Types of Equipments 452
22.4.2.3	Selection Criteria 453
22.4.3	Filtration and Centrifugation 454
22.4.3.1	Utility of Filtration 454
22.4.3.2	Types of Equipments 455
22.4.3.3	Selection Criteria for Filtration 457
22.4.4	Centrifugation 458
22.4.4.1	Utility of Centrifugation 458
22.4.4.2	Types of Equipments 458
22.4.4.3	Selection Criteria 460
22.4.5	Drying 460
22.4.5.1	Utility of Drying 460
22.4.5.2	Types of Equipments 461

22.4.5.3	Selection Criteria 463
22.5	Scale-up Problems 464
22.6	Optimization and Intensification of Unit Operations 464
22.6.1	Step I: Establishing Material and Energy Balance across All the
	Equipments 465
22.6.2	Step II: Preliminary Evaluation of All the Major Equipments 465
22.6.3	Step III: Analysis of All the Operations and Equipments at Relatively
	Intricate Levels 465
22.6.4	Step IV: Mathematical Modeling of Individual Equipment and
	Subsequently the Entire Plant 465
22.7	Summary 466
	References 466
23	The Integration of Safety, Health, and Environmental Considerations
	into Process Development 469
	Wesley White, Vyv Coombe, and Jonathan Moseley
23.1	Introduction 469
23.1.1	The SHE Triggers Model 469
23.1.2	Introduction to AZD4619 473
23.2	Process Safety 474
23.2.1	Assessment of Chemical Reaction Hazards 475
23.2.2	Assessment of Operational Hazards 475
23.2.3	Basis of Safety 475
23.2.4	Process Safety Triggers 476
23.2.4.1	Early Delivery 476
23.2.4.2	Later Process Safety Triggers 476
23.2.4.3	Technology Transfer 477
23.2.5	Application of Process Safety to AZD4619 477
23.2.5.1	General Hazards of Aqueous Diazotization and the Basis of
	Safety 477
23.2.5.2	Additions of Acetone, Water, Hydrochloric Acid, and
	Acrylic Acid 478
23.2.5.3	Addition of Sodium Nitrite 478
23.3	Health 479
23.3.1	Introduction 479
23.3.2	Health Triggers 479
23.3.2.1	Early Delivery 479
23.3.2.2	Synthetic Route Evaluation 480
23.3.2.3	Process Design 480
23.3.2.4	Process Optimization and Understanding 481
23.3.2.5	Technology Transfer 481
23.3.3	Application of Health Triggers to AZD4619 482
23.4	Environment 482
23.4.1	Introduction 482
23.4.2	Environment Triggers 482

23.4.2 Environment Triggers 482

XVI Contents

23.4.2.1	Early Delivery and Synthetic Route Evaluation 482
23.4.2.2	Process Design 484
23.4.2.3	Process Optimization and Understanding 484
23.4.2.4	Technology Transfer 485
23.4.3	Application of Environmental Triggers to AZD4619 485
23.5	The Use of Risk Assessment 486
23.6	Conclusion 487
	Acknowledgments 488
	References 488

Index 489