

Table of Contents

1	Introduction	
	T. F. Jamison and G. Koch	
1	Introduction	1
2	Flow Chemistry System Design and Automation	
	C. W. Coley, J. Imbrogno, Y. Mo, D. A. Thomas, and K. F. Jensen	
2	Flow Chemistry System Design and Automation	3
2.1	Components of a Flow-Chemistry Platform	3
2.2	Reaction Engineering Principles in Flow Chemistry	4
2.2.1	Reactor Flow Profiles and Residence Times	4
2.2.2	Dispersion	6
2.2.3	Multiphase Flows	7
2.2.4	Mixing	7
2.2.5	Heat Transfer	9
2.3	Fluid Handling	11
2.3.1	Liquid Handling	11
2.3.1.1	HPLC Pumps	12
2.3.1.2	Syringe Pumps	13
2.3.1.3	Diaphragm Pumps	13
2.3.1.4	Peristaltic Pumps	13
2.3.1.5	Gear Pumps	13
2.3.2	Gas Supply	14
2.3.3	System Pressurization	14
2.3.4	Pressure-Relief Valves	14
2.4	Reactor Designs	15
2.4.1	Reactors for Single-Phase Liquid Reactions	15
2.4.2	Reactors for Liquid–Liquid and Gas–Liquid Reactions	17
2.4.3	Heterogeneous Systems: Packed-Bed and Trickle-Bed Reactors	19
2.4.4	Photochemical Reactors	21
2.4.5	Electrochemical Reactors	23
2.4.6	Commercial Reactors	25
2.5	Solid Handling	26

2.6	Separations	29
2.6.1	Liquid–Liquid Extraction Coupled with Continuous Phase Separation	29
2.6.2	Multi-Stage Extraction Methods	30
2.6.3	Polymer-Membrane-Based Phase Separation	31
2.6.4	Enhanced Separation Using Dual Membrane Wettability	32
2.7	Analytics	33
2.8	Integrated Systems	34
2.8.1	Modular Continuous End-to-End Production	35
2.8.2	Kilogram-Scale Continuous-Flow cGMP Production	37
2.8.3	Iterative Continuous-Flow Synthesis	37
2.9	Automation, Screening, Optimization, Feedback	39
2.9.1	Screening	39
2.9.1.1	Screening with Off-Line Analysis	39
2.9.1.2	Screening with On-Line Analysis	40
2.9.2	Feedback in Flow	41
2.9.2.1	Determination of Reaction Kinetics	41
2.9.2.2	Self-Optimization of Reaction Conditions (Continuous Variables)	42
2.9.2.3	Self-Optimization of Reaction Conditions (Discrete Variables)	43
2.9.3	Remote Operation	43
2.10	Outlook	44

3 Separation and Purification in the Continuous Synthesis of Fine Chemicals and Pharmaceuticals

M. O’Mahony, S. Ferguson, T. Stelzer, and A. Myerson

3	Separation and Purification in the Continuous Synthesis of Fine Chemicals and Pharmaceuticals	51
3.1	Continuous Homogeneous Liquid-Phase Separations	51
3.1.1	Nanofiltration	52
3.1.2	Organic Solvent Nanofiltration	53
3.1.2.1	Mode of Operation: Concentration, Solvent Swap, Purification	54
3.1.2.2	Homogeneous Purification via Organic Solvent Nanofiltration	57
3.1.2.3	Catalyst Recycle via Organic Solvent Nanofiltration	60
3.1.2.4	Procedures for the Application of Organic Solvent Nanofiltration	60
3.2	Continuous Heterogeneous Liquid–Liquid Phase Separations	63
3.2.1	Continuous Liquid–Liquid Extraction	63
3.2.2	Surface-Tension-Based Liquid–Liquid Extraction	65
3.2.3	Microextractors and Membrane Extractors: Design and Operation	66

3.3	Continuous Crystallization and Crystallizers in Flow	69
3.3.1	Crystallization	69
3.3.1.1	Solubility and Supersaturation	69
3.3.1.2	Nucleation and Crystal Growth	71
3.3.1.3	Breakage and Agglomeration	73
3.3.1.4	Polymorphism and Solvates	74
3.3.2	Types of Continuous Crystallizers	74
3.3.2.1	Tubular Designs for Continuous-Flow Crystallization	76
3.3.3	Novel Developments in Small-Scale Continuous-Flow Crystallization	78
3.3.3.1	Falling-Film Crystallizers	78
3.3.3.2	Microfluidic Crystallization	78
3.3.4	Basic Crystallization Process Design	78
3.3.5	MSMPR Crystallizers in End-to-End Continuous-Flow Manufacturing	82
3.3.5.1	Crystallization in a Compact, On-Demand, Continuous-Flow Manufacturing Platform	83
3.3.6	Industrial Examples of Integrated Flow Synthesis and Continuous Crystallization	83
3.4	Continuous Filtration, Washing, and Drying (FWD) Systems	84
3.4.1	Filtration, Washing, and Drying: Design and Control	85
3.4.1.1	Solid–Liquid Separation by Filtration	85
3.4.1.2	Centrifugal Filtration	87
3.4.1.3	Cake Washing	87
3.4.1.4	Continuous Drying	88
3.4.2	Modeling Filtration Rates	91
3.4.2.1	Improving Filtration Performance	92
3.4.3	Continuous Filtration, Washing, and Drying Technologies for Pharmaceuticals and Fine Chemicals	92
3.4.3.1	Rotary Disc Filter	94
3.4.3.2	Alternating Batch Filtration	95
3.4.3.3	Dynamic Cross-Flow Filtration	95
3.4.3.4	Continuous Carousel Filtration	96
3.4.3.5	Novel-Scale Continuous Filtration, Washing, and Drying Systems	97
3.5	Conclusions	98

4	Flow Photochemistry in Organic Synthesis	
	R. Telmesani, A. C. Sun, A. B. Beeler, and C. R. J. Stephenson	
<hr/>		
4	Flow Photochemistry in Organic Synthesis	103
4.1	Ultraviolet Flow Photochemical Reactions	104
4.1.1	Photocycloadditions	105
4.1.2	Photochemical Rearrangements	116
4.1.3	Reactions of Singlet Oxygen	119
4.1.4	Halogenation	120
4.1.5	Photochemical Generation of Unstable Intermediates	122
4.1.6	Photochemical Activation of Catalysts	124
4.2	Visible-Light Photoredox Catalysis	126
4.2.1	Background and Seminal Studies	127
4.2.2	Perfluoroalkylation	128
4.2.3	Fluorination	132
4.2.4	Dual Photoredox/Transition-Metal Catalysis	133
4.2.5	Synthesis of Natural Products	137
4.2.6	Novel Reactor Design: Merging Luminescent Solar Concentrators and Electrocatalysis with Flow Photochemistry	139
4.3	Conclusions	143
<hr/>		
5	Electrosynthesis in Continuous Flow	
	A. A. Folgueiras-Amador and T. Wirth	
<hr/>		
5	Electrosynthesis in Continuous Flow	147
5.1	Fundamental Aspects of Flow Electrochemistry	147
5.1.1	Principles of Preparative Flow Electrosynthesis	148
5.2	Organic Synthesis with Electrochemical Flow Reactors	148
5.2.1	Divided Cells	148
5.2.1.1	Cation Flow Method for Combinatorial Organic Syntheses	149
5.2.1.2	Electrochemical Dehalogenation	151
5.2.2	Undivided Cells	153
5.2.2.1	Anodic Oxidations	153
5.2.2.1.1	Supporting-Electrolyte-Free Anodic Oxidations	153
5.2.2.1.1.1	Synthesis of Diaryliodonium Salts	153
5.2.2.1.2	Methoxylation of Organic Compounds without a Supporting Electrolyte	155
5.2.2.1.3	Di- and Trifluoromethylation of Electron-Deficient Alkenes	156

5.2.2.1.2	Anodic Oxidations Using a Supporting Electrolyte	158
5.2.2.1.2.1	Phenol–Arene C–C Cross Coupling	158
5.2.2.1.2.2	Parallel Laminar Flow for Anodic Substitution Reactions in a Microflow Reactor	160
5.2.2.1.2.3	Methoxylation of N-Formylpyrrolidine as a Test Reaction To Compare Different Electrochemical Flow Cells	161
5.2.2.1.2.4	Benzylic Methoxylation/Oxidation	163
5.2.2.1.2.5	In Situ Electrogeneration of <i>ortho</i> -Benzquinone and Subsequent Reaction with Benzenethiols	165
5.2.2.1.2.6	Synthesis of Drug Metabolites on Preparative Scale	166
5.2.2.1.2.7	Electrochemical α -Methoxylation of N-Protected Cyclic Amines and Nazlinine Synthesis	169
5.2.2.1.2.8	N-Heterocyclic Carbene Mediated Synthesis of Esters From Aldehydes via Anodic Oxidation	171
5.2.2.1.2.9	N-Heterocyclic Carbene Mediated Synthesis of Amides from Aldehydes via Anodic Oxidation	173
5.2.2.2	Cathodic Reductions	175
5.2.2.2.1	Supporting-Electrolyte-Free Cathodic Reductions	175
5.2.2.2.1.1	Cathodic Coupling of Activated Alkenes with Benzyl Bromide Derivatives	175
5.2.2.2.2	Cathodic Reductions Using a Supporting Electrolyte	177
5.2.2.3	Paired Electrolysis	177
5.2.2.3.1	Synthesis of Copper–N-Heterocyclic Carbene Complexes	177
5.2.2.3.2	Paired Electrosynthesis of Toluene and Acetophenone	180
5.2.2.3.3	Paired Electrosynthesis of Sorbitol and Gluconic Acid from Glucose	181
5.2.2.3.4	Paired Electrolysis: Oxidation of Silyl-Substituted Carbamates and Reduction of Cinnamyl Chlorides and Acetates	183
5.2.2.4	Indirect Electrolysis: Use of Mediators	185
5.2.2.4.1	2,2,6,6-Tetramethylpiperidin-1-oxyl Mediated Oxidation of Primary and Secondary Alcohols	185

6 Hazardous Reagents in Continuous-Flow Chemistry

R. W. Hicklin, A. E. Strom, E. D. Styduhar, and T. F. Jamison

6	Hazardous Reagents in Continuous-Flow Chemistry	191
6.1	Nitrogen Reagents	192
6.1.1	Nitration Reagents	192
6.1.2	Diazo Reagents	193
6.1.2.1	Diazomethane	193
6.1.2.2	Other Diazoalkane Reagents	195
6.1.2.3	Diazonium Reagents	197

6.1.3	Azide Reagents	199
6.2	Organometallic Reagents	200
6.2.1	Organolithium Reagents	200
6.2.2	Organomagnesium Reagents	203
6.2.3	Organozinc Reagents	205
6.2.4	Organoaluminum Reagents	206
6.3	Oxidants	207
6.3.1	Oxygen	208
6.3.2	Ozone	209
6.3.3	Organic Peroxides	210
6.3.4	Miscellaneous Oxidants	212
6.4	Halogenating Reagents	213
6.4.1	Fluorinating Reagents	213
6.4.2	Chlorinating Reagents	214
6.4.3	Brominating Reagents	215
6.5	Toxic Low-Molecular-Weight Reagents	216
6.5.1	Phosgene	216
6.5.2	Cyanide	218
6.5.3	Carbon Monoxide	219

7**Very Fast Reactions and Extreme Conditions**

H. Kim and J. Yoshida

7	Very Fast Reactions and Extreme Conditions	223
7.1	Swern–Moffatt Oxidation	223
7.2	Diisobutylaluminum Hydride Reduction	225
7.3	Organolithium Reactions	228
7.4	Organomagnesium Reactions	236
7.5	Friedel–Crafts Alkylation	238
7.6	Reactions at High Temperature and High Pressure	240

8**Gaseous Reagents in Continuous-Flow Synthesis**

M. O'Brien and A. Polyzos

8	Gaseous Reagents in Continuous-Flow Synthesis	243
8.1	Approaches to Gas–Liquid Mixing in Flow	244
8.2	Membrane-Based Systems	255
8.3	Conclusions	269

9	Immobilized Reagents and Multistep Processes	
	S. V. Ley, D. L. Browne, and M. O'Brien	
<hr/>		
9	Immobilized Reagents and Multistep Processes	273
9.1	Multistep Configuration	275
9.1.1	Some Preliminary Considerations	276
9.1.2	The Dispersion Problem	277
9.1.3	Use of Monolithic Supports	279
9.1.4	Toward More Complexity	281
9.1.5	Solvent Evaporation and Switching	286
9.1.6	Integrated Synthesis and Screening	287
9.1.7	Multiple Enzyme Cascades	288
9.2	Use of Polymer-Supported Reagents/Scavengers in Multistep Syntheses of Biologically Active Molecules	289
9.2.1	Synthesis of Boscalid	289
9.2.2	Synthesis of Efavirenz	290
9.2.3	Synthesis of Nevirapine	292
9.2.4	Synthesis of Sacubitril	293
9.2.5	Synthesis of Imatinib	296
9.3	Use of Polymer-Supported Reagents/Scavengers in Multistep Syntheses of Natural Products	298
9.3.1	Synthesis of Oxomaritidine	298
9.3.2	Synthesis of Grossamide	299
9.3.3	Synthesis of (+)-Dumetorine	300
9.3.4	Synthesis of Perhydrohistrionicotoxin	303
9.3.5	Synthesis of O-Methyl Siphonazole	305
9.3.6	Synthesis of Spirodienol A	306
9.4	Conclusions and Future Outlook	310
<hr/>		
10	Intermolecular Transition-Metal-Catalyzed C–C Coupling Reactions in Continuous Flow	
	C. Bottecchia and T. Noël	
<hr/>		
10	Intermolecular Transition-Metal-Catalyzed C–C Coupling Reactions in Continuous Flow	313
10.1	Cross-Coupling Reactions in Flow	314
10.1.1	Suzuki–Miyaura Reactions	314
10.1.2	Negishi Coupling	321
10.1.3	Mizoroki–Heck Alkenylation Reactions	324

10.1.4	Palladium-Catalyzed Carbonylative Reactions	327
10.2	C—H Functionalization in Flow	329
10.2.1	C—H Activation	330
10.2.1.1	Cross-Dehydrogenative Coupling	330
10.2.1.2	Palladium-Catalyzed C(sp ³)—H Activation	334
10.2.1.3	Manganese-Catalyzed C—H Activation	335
10.2.1.4	<i>meta</i> -Selective C—H Arylation of Anilines in a Copper Tube Flow Reactor	337
10.2.2	Dual Catalysis in Flow	339
10.3	Conclusions	344
 <hr/>		
11	Immobilized Catalysts for Asymmetric Reactions	
	S. Itsuno and M. S. Ullah	
<hr/>		
11	Immobilized Catalysts for Asymmetric Reactions	347
11.1	Polymer-Immobilized Chiral Organocatalysts	347
11.1.1	Polymer-Immobilized Cinchona Alkaloid Catalysts	347
11.1.2	Polymer-Immobilized Amino Acid Derived Organocatalysts	357
11.1.2.1	Polymer-Immobilized Proline-Based Catalysts	357
11.1.2.2	Polymer-Immobilized Threonine Derivatives	359
11.1.3	Polymer-Immobilized Peptidic Organocatalysts	361
11.1.4	Polymer-Immobilized Chiral Imidazolidinone Catalysts	364
11.1.5	Polymer-Immobilized Chiral Pyrrolidine Catalysts	366
11.1.6	Polymer-Immobilized Chiral Vicinal Diamine Catalysts	367
11.1.7	Polymer-Immobilized Chiral Phosphoric Acid Catalysts	368
11.1.8	Polymer-Immobilized Chiral Benzotetramisole Analogues as Catalysts	370
11.2	Polymer-Immobilized PyBOX Calcium Catalysts	370
11.3	Polymer-Immobilized Chiral Lewis Acid Catalysts	371
11.4	Polymer-Immobilized <i>N</i> -Tosyl-1,2-diphenylethylenediamine Ligands and Their Application to Transition-Metal Catalysis	372
11.5	Polymer-Immobilized Chiral Gold-Based Complexes	377

12	Pushing the Limits of Solid-Phase Peptide Synthesis with Continuous Flow	
	A. J. Mijalis, A. Steinauer, A. Schepartz, and B. L. Pentelute	
<hr/>		
12	Pushing the Limits of Solid-Phase Peptide Synthesis with Continuous Flow	381
12.1	Continuous-Flow Solid-Phase Peptide Synthesis: Historical Context	382
12.2	Difficult Sequences: A Chemical Justification for Activation and Aminoacylation in Flow	386
12.3	Improving Atom Economy of Peptide Synthesis with Flow Amino Acid Activation	392
12.4	Monitoring Fmoc Removal in Flow Solid-Phase Peptide Synthesis	393
12.5	Side Reactions of Resin-Bound Peptides at Elevated Temperature	395
12.6	Engineering Advancements	396
12.7	Sample Protocol for Flow Solid-Phase Peptide Synthesis	396
12.8	Conclusions	397
<hr/>		
13	The Controlled Synthesis of Carbohydrates	
	S. Moon, K. Gilmore, and P. H. Seeberger	
<hr/>		
13	The Controlled Synthesis of Carbohydrates	399
13.1	Formation of the Glycosidic Bond	402
13.2	Functional-Group Manipulation	413
13.3	Multistep Synthesis (Glycosylation and/or Protection/Deprotection)	419
13.4	Conclusions	426
<hr/>		
14	Continuous-Flow Syntheses of Active Pharmaceutical Ingredients	
	R. L. Beingessner, A. R. Longstreet, T. A. McTeague, L. P. Kelly, H. Seo, T. H. Tran, A. C. Wicker, and T. F. Jamison	
<hr/>		
14	Continuous-Flow Syntheses of Active Pharmaceutical Ingredients	429
14.1	Efavirenz	429
14.2	Imatinib	433
14.3	(–)-Oseltamivir	441
14.4	Ibuprofen	444
14.5	Rolipram and Other GABA Derivatives	448
14.6	Methylphenidate Hydrochloride	455
14.7	Rufinamide	457

15	Flow Chemistry in the Pharmaceutical Industry	
<hr/>		
15.1	Flow Chemistry in the Pharmaceutical Industry: Part 1	
	A. G. O'Brien	
<hr/>		
15.1	Flow Chemistry in the Pharmaceutical Industry: Part 1	463
15.1.1	Process Selection	464
15.1.1.1	Safety	464
15.1.1.2	Economic Factors	464
15.1.1.3	Reaction Kinetics	464
15.1.1.4	Engineering Factors	465
15.1.2	Process Development	467
15.1.2.1	Preliminary Condition Screening	467
15.1.2.2	Approaches to Optimization and Experimental Design	469
15.1.2.3	Reaction Monitoring in Flow	471
15.1.2.4	Combination of Unit Operations: "Multistep" Processes	471
15.1.3	Scaleup	472
15.1.4	Commercialization	473
15.1.5	Conclusions	474
<hr/>		
15.2	Flow Chemistry in the Pharmaceutical Industry: Part 2	
	S. A. May and M. S. Kerr	
<hr/>		
15.2	Flow Chemistry in the Pharmaceutical Industry: Part 2	477
15.2.1	Speed to Early Phase Delivery	477
15.2.1.1	Reactions in Thermal Plug-Flow Reactors	477
15.2.1.2	Intermittent Stirred-Tank Reactors	480
15.2.2	Hybrid Batch/Flow Processes at Manufacturing Scale	481
15.2.2.1	Development of a Grignard Reaction Based Flow Process for the Synthesis of a Benzyl Alcohol	481
15.2.2.2	High-Pressure Homogeneous Reductive Amination	484
15.2.2.3	Thermal Deprotection in Manufacturing	486
15.2.3	Small-Volume Continuous Facility	488
15.2.3.1	Flow Synthesis of Tasisulam	488
15.2.4	Conclusions	492

15.3	Flow Chemistry in the Pharmaceutical Industry: Part 3	
	S. M. Opalka, W. F. Kiesman, and D.-I. A. Kwok	
<hr/>		
15.3	Flow Chemistry in the Pharmaceutical Industry: Part 3	495
15.3.1	Reaction of Interest: Lithiation/Formylation of an Aryl Halide	496
15.3.1.1	Lithiation/Formylation in a Plate Microreactor	499
15.3.1.2	Lithiation/Formylation in a Plug-Flow Reactor	500
15.3.1.3	Lithiation/Formylation in a Spinning-Disk Reactor	502
15.3.2	Learnings and Flow Development Outlook	504
<hr/>		
	Keyword Index	509
	Author Index	531
	Abbreviations	551