Contents

Preface				Example 3-3 Losartan 57			
1.	1. Introduction to Crystallization Issues			Example 3-4 Example 3-5 Example 3-6			61
100	1.1 Crystal Properties and Polymorphism (Chapters 2 and 3) 2		m		mple 3-0	HCl Salt of a Drug Candidate 62 Second HCl Salt of	9
	1.2	Nucleation and Growth Kinetics (Chapter 4) 3			mple 3-8	Drug Candidate Prednisolone	66
	1.3	Critical Issues (Chapter 5) 3		DAG	impie 5 0	t-Butylacetate 70	0
	1.4	Mixing and Crystallization		Exa	mple 3-9		
		(Chapter 6) 4		3.4		Direction 76	
	1.5	Crystallization Process Options					
	1.6	(Chapters 7–10) 4 Special Applications (Chapter 11)	9	4. Kin	etics		77
	1.6 Special Applications (Chapter 11)1.7 Regulatory Issues 10		9	4.1	Supersat	uration and Rate	
2.	Properties		13	4.2	Nucleati	on 79	
	2.1	Solubility 13		4.3	Crystal (Growth 87	
	2.2	Supersaturation, Metastable Zone,		4.4		e/Seed Aging and	
		and Induction Time 21				Ripening 98	
	2.3	Oil, Amorphous, and Crystalline States 25		4.5		d Product: Size Distri phology 99	bution
	2.4	Polymorphism 29					
	2.5	Solvate 32		5. Crit	tical Issue	es in Crystallization	
	2.6			Pra	ctice		101
	27	and Solid Mixture 34		5.1	Introduc	tion 101	
	2.7	Inclusion and Occlusion 37		5.2	Nucleati	on 101	
	2.8	Adsorption, Hygroscopicity, and Deliquescence 39		5.3	Growth	104	
	2.9			5.4	Oiling C	out, Agglomeration/	
	2.10				Aggrega		
		Surface Area 44		5.5	Seeding		
				5.6		Generation of	
3	Poly	morphism	49	6.7	Supersat		
				5.7	Summar	y of Critical Issues	116
	3.1	Phase Rule 49					
	3.2	Phase Transition 50		6. Mixing and Crystallization 117			
	3.3 Evan			6.1	Introduc	tion 117	
		nple 3-1 Indomethacin 53 nple 3-2 Sulindac 55		6.2		Considerations 11	8
	AJACH.	ipic 5 2 Sumidae 55			the state of the s		

	6.3 Mixing Effects on Nucleation 119	9	Example 9-2 Rejection of Isomeric				
	6.4 Mixing Effects on Crystal		Impurities of Final Bulk				
	Growth 123		Active Product 185				
	6.5 Mixing Scale-up 126		Example 9-3 Crystallization of a				
	6.6 Crystallization Equipment 127		Pharmaceutical Product				
	Example 6-1 135		with Poor Nucleation				
	Example 6.1		and Growth				
			Characteristics 188				
7.	Cooling Crystallization 1.	37	Example 9-4 Impact of Solvent and				
	7.1 Batch Operation 137		Supersaturation on				
	7.2 Continuous Operations 143		Particle Size and				
	7.3 Process Design—Examples 147		Crystal Form 192				
	Example 7-1 Intermediate in a Multistep						
	Synthesis 147						
	Example 7-2 Pure Crystallization		Example 9-5 Crystallization of				
	of an API 150		an API Using				
	Example 7-3 Crystallization Using		Impinging Jets 197				
	the Heel from the		Example 9-6 Crystallization of a				
	Previous Batch as		Pharmaceutical Product				
			Candidate Using an				
	Seed 154		Impinging Jet with				
	Example 7-4 Resolution of Ibuprofen		Recycle 204				
	Via Stereospecific						
	Crystallization 155		10. Reactive Crystallization 207				
	Example 7-5 Crystallization of						
	Pure Bulk with		10.1 Introduction 207				
	Polymorphism 160		10.2 Control of Particle Size 209				
	Example 7-6 Continuous Separation		10.3 Key Issues in Organic Reactive				
	of Stereoisomers 161		Crystallization 210				
			10.4 Scale-up 218				
8.	Evaporative Crystallization 1	67	Example 10-1 Reactive Crystallization				
_		_	of an API 218				
	8.1 Introduction 167		Example 10-2 Reactive Crystallization				
	8.2 Solubility Diagrams 167		of an Intermediate 223				
	8.3 Factors Affecting Nucleation and		Example 10-3 Reactive Crystallization				
	Growth 170		of a Sodium Salt of an				
	8.4 Scale-up 171		API 225				
	8.5 Equipment 171		Example 10-4 Reactive Crystallization				
	Example 8-1 Crystallization of a		of an API 228				
	Pharmaceutical		10.5 Creation of Fine Particles—In-Line				
	Intermediate Salt 175		Reactive Crystallization 231				
	Example 8-2 Crystallization of the						
	Sodium Salt of a Drug		11. Special Applications 23				
	Candidate 177		Tr. opecial replacations				
			11.1 Introduction 235				
0	Anticolyant Constallization	70	11.2 Crystallization with Supercritical				
9.	Antisolvent Crystallization 1	79	Fluids 236				
	9.1 Semibatch Operation 179		11.3 Ultrasound in Crystallization 237				
	Example 9-1 Crystallization of an		11.4 Computational Fluid Dynamics in				
	Intermediate 184		Crystallization 238				

Example 11-1	Sterile Crystallization of	Example 11-5 Freeze Crystallization o	The same of the sa	
	Imipenem 238	Imipenem 255		
Example 11-2	Enhanced Selectivity of a	Example 11-6 Continuous Separation	of	
	Consecutive-Competitive	Stereoisomers 259		
	Reaction by Crystallization	11.5 Strategic Considerations for		
	of the Desired Product	Development of a New Crystalliz	ation	
	During the Reaction 243	Process 272		
Example 11-3	Applying Solubility to			
1.7	Improve Reaction	References	279	
	Selectivity 246			
Example 11-4	Melt Crystallization of Dimethyl Sulfoxide 251	Index		