

Contents

1	Introduction	1
	<i>Alex Langford, Satoshi Ohtake, David Lechuga-Ballesteros, and Ken-ichi Izutsu</i>	
	Acknowledgement	5
	References	6
2	A Concise History of Drying	9
	<i>Sakamon Devahastin and Maturada Jinorose</i>	
2.1	Introduction	9
2.2	History of Drying of Pharmaceutical Products	11
2.3	History of Selected Drying Technologies	13
2.3.1	Freeze Drying	13
2.3.2	Spray Drying	15
2.3.3	Fluidized-Bed Drying	16
2.3.4	Supercritical Drying	16
2.4	Concluding Remarks	18
	Acknowledgments	18
	References	18
	Part I Drug Product Development	23
3	Importance of Drying in Small Molecule Drug Product Development	25
	<i>Paroma Chakravarty and Karthik Nagapudi</i>	
3.1	Introduction	25
3.2	Drying Materials and Dryer Types	33
3.3	Directly Heated (Convective) Dryers	36
3.3.1	Tray Drying	36
3.3.1.1	Description	36
3.3.1.2	Utility	36
3.3.1.3	Drawbacks and Challenges	37
3.3.2	Fluidized-Bed Drying	39
3.3.2.1	Description	39

3.3.2.2	Determination of End Point of Drying	41
3.3.2.3	Advantages, Utility, and Drawbacks	42
3.3.3	Spray Drying	43
3.3.3.1	Description	43
3.3.3.2	Role in Formulation Development	44
3.4	Indirectly Heated (Conductive) Dryers	56
3.4.1	Rotary Drying	56
3.4.1.1	Description	56
3.4.1.2	Advantages and Drawbacks	57
3.4.2	Freeze Drying	57
3.4.2.1	Description	57
3.4.2.2	Advantages and Drawbacks	58
3.4.2.3	Role in Small Molecule Formulation Development	58
3.5	Emerging Drying Technologies	62
3.5.1	Supercritical Fluid (SCF) Drying	62
3.5.1.1	Description	62
3.5.1.2	Advantages and Drawbacks	62
3.5.1.3	Pharmaceutical Applications	63
3.5.2	Microwave Drying	67
3.5.2.1	Pharmaceutical Applications	68
3.6	Summary	74
	References	74
4	Drying for Stabilization of Protein Formulations	91
	<i>Jacqueline Horn, Hanns-Christian Mahler, and Wolfgang Friess</i>	
4.1	Protein Stability	91
4.1.1	Physical Instability of Proteins	92
4.1.2	Chemical Instability of Proteins	92
4.1.2.1	Disulfide Bond Formation	92
4.1.2.2	Deamidation	93
4.1.2.3	Oxidation	94
4.1.2.4	Glycation	94
4.1.3	Analysis of Protein Stability	94
4.1.3.1	Particle Analysis in Protein Formulations	95
4.1.3.2	Other Purity Tests for Proteins	95
4.1.3.3	Analysis of Higher-Order Structure	96
4.2	Protein Stability in the Dried State	96
4.2.1	Theoretical Considerations	96
4.2.1.1	Water Replacement Hypothesis	96
4.2.1.2	Glass Dynamics Hypothesis and Vitrification	97
4.2.2	Analysis of the Dried State	97
4.2.2.1	Investigation of Endo- and Exothermic Processes: Glass Transition and Crystallization	97
4.2.2.2	Sample Morphology: Crystalline or Amorphous Matrix?	98
4.2.2.3	Residual Moisture	98
4.2.3	Excipients Used to Stabilize Proteins in the Dried State	99
4.2.3.1	Sugars	99

4.2.3.2	Polyols	100
4.2.3.3	Polymers	101
4.2.3.4	Amino Acids	102
4.2.3.5	Additional Excipients: Metal Ions/HP- β -CD/Surfactants/Buffers	102
4.3	How Does the Process Influence Protein Stability?	103
4.3.1	Process of Freeze Drying	103
4.3.1.1	Freezing	103
4.3.1.2	Drying	105
4.3.1.3	Typical Defects in Lyophilized Products Beyond Protein Stability	106
4.3.2	Process of Spray Drying	106
4.3.2.1	Protein Stability During Droplet Formation	106
4.3.2.2	Protein Stability During the Drying Phase	107
4.4	Summary	107
	References	107

5	Vaccines and Microorganisms	121
	<i>Akhilesh Bhambhani and Valentyn Antochshuk</i>	
5.1	Introduction	121
5.2	Vaccine Drug Product Development	122
5.2.1	Early Development to Phase I	122
5.2.1.1	Developability	122
5.2.1.2	Pre-formulation	124
5.2.1.3	Formulation Development	127
5.2.2	Late-Stage Development (Phase II and Beyond)	129
5.2.2.1	Scale-Up Considerations and Case Studies	130
5.3	Spray Drying: An Alternate to Lyophilization	132
5.4	Summary and Path Forward	133
	References	134

Part II Common Drying Technologies 137

6	Advances in Freeze Drying of Biologics and Future Challenges and Opportunities	139
	<i>Bakul Bhatnagar and Serguei Tchessalov</i>	
6.1	Introduction	139
6.2	Where Are We Now?	139
6.3	Current State	140
6.3.1	Rational Formulation Design: Keeping It Simple	140
6.3.2	Process Design and Monitoring	143
6.3.2.1	Freezing	143
6.3.2.2	Product Temperature Measurement	145
6.3.2.3	Pressure Rise Test/Manometric Temperature Measurement	146
6.3.2.4	SMART Freeze-Dryer™ Technology	146
6.3.2.5	Application of Pirani Gauge for the Control of Primary Drying	147
6.3.2.6	Application of Mass Spectroscopy for Process Control	148

6.3.2.7	Heat Flux Sensors as PAT Tools	148
6.3.2.8	Pressure Decrease Method	149
6.3.2.9	Tunable Diode Laser Absorption Spectroscopy (TDLAS)	149
6.3.2.10	Emerging Analytical Tools for Process Monitoring and Control	149
6.3.2.11	Modeling of Freeze-Drying Process	150
6.3.3	Tools to Monitor Dried Products	150
6.3.3.1	Structure of the Biologic	150
6.3.3.2	Characterizing Matrix Contributions to Stability	151
6.3.3.3	Looking Beyond the Biologic and the Formulation Matrix	152
6.4	Current Challenges	153
6.4.1	Understanding Protein Degradation in the Frozen State and Dried States	153
6.4.2	Process Inefficiency	154
6.5	Vision for the Future	155
6.5.1	Advances in Container-Closure Systems	155
6.5.2	Dryer Design	156
6.5.2.1	Laboratory-Scale Dryers	156
6.5.2.2	Commercial-Scale Freeze Dryers	157
6.5.3	Redefining Product Appearance/Elegance	160
6.5.4	“Intelligent” Formulation and Process Design	160
6.5.5	How Could Alternate Drying Technologies and Freeze Drying Coexist?	161
6.5.5.1	Alternatives to the Current Batch-Based Vial Drying	161
6.6	Summary	162
	Acknowledgments	162
	Tributes	163
	References	164
7	Spray Drying	179
	<i>Reinhard Vehring, Herm Snyder, and David Lechuga-Ballesteros</i>	
7.1	Background	179
7.1.1	Spray-Drying Fundamentals	180
7.1.2	Feedstock Preparation	180
7.1.3	Spray-Drying Equipment	181
7.1.4	Atomization	183
7.1.4.1	Twin-Fluid or Gas (Air)-Assisted Atomizer	184
7.1.4.2	Pressure or Hydraulic Nozzle	185
7.1.4.3	Rotary Atomizer	186
7.1.5	Drying Chamber	187
7.1.6	Particle Collection	189
7.2	Particle Engineering	189
7.2.1	Particle Formation: Evaporation Stage	191
7.2.2	Particle Formation: Solidification Stage	193
7.2.3	Particle Formation: Solidification Stage for Crystallizing Excipients	194
7.2.4	Particle Formation: Deformation Stage	197
7.2.5	Particle Formation: Equilibration Phase	198

- 7.3 Current Status 200
- 7.4 Future Direction: Aseptic Spray Drying 205
- 7.4.1 Initial System Sterilization of Product Contact Surfaces 207
- 7.4.2 Maintaining a Sterile Environment over the Course of the Spray-Dried Batch 208
- 7.4.3 Aseptic Extraction and Handling the Dried Powder Product from the Dryer System 208
- References 209

Part III Next Generation Drying Technologies 217

- 8 Spray Freeze Drying 219**
Bernhard Luy and Howard Stamato
 - 8.1 Introduction 219
 - 8.2 Background 220
 - 8.2.1 Shelf Freeze Drying 220
 - 8.2.2 Spray Freeze Drying 221
 - 8.2.2.1 Single Dose vs. Bulk Manufacturing 221
 - 8.2.2.2 Process Considerations 222
 - 8.2.3 Spray-Freeze-Drying Developments 224
 - 8.3 Spray Freezing and Dynamic Freeze Drying 225
 - 8.3.1 Spray Freezing 225
 - 8.3.2 Dynamic Freeze Drying 229
 - 8.3.2.1 Rotary Freeze-Drying Technology 229
 - 8.3.2.2 Process Considerations 230
 - 8.3.3 Industrial Application: Integration of Process Steps to a Process Line 231
 - 8.3.4 Product Innovation Potential 233
 - 8.3.5 Bulkware Innovation Potential: Supply Chain Flexibility 235
 - 8.4 Conclusion 235
 - References 236
- 9 Microwave Drying of Pharmaceuticals 239**
Tim Durance, Reihaneh Noorbakhsh, Gary Sandberg, and Natalia Sáenz-Garza
 - 9.1 Fundamentals of Microwave Heating and Drying 239
 - 9.1.1 Theory of Microwave Heating and Drying 239
 - 9.1.2 Ionic Conduction 240
 - 9.1.3 Dipolar Rotation/Vibration 240
 - 9.1.4 Microwave Application at Low Pressures 241
 - 9.2 Equipment Used for Microwave Freeze Drying 242
 - 9.2.1 Microwave Generators 242
 - 9.2.2 Chambers 242
 - 9.2.3 Vacuum Systems 243
 - 9.2.4 Safety and Microwave Leakage Control 245
 - 9.3 Formulation Characterization 246

9.3.1	Dielectric Properties, Microwave Absorption, and Depth of Penetration	246
9.3.2	Glass Transition Temperature and Collapse	248
9.3.3	Excipients for Microwave Freeze Drying of Pharmaceutical Products	248
9.4	Dehydration Process Using Microwave Freeze Drying	249
9.4.1	Primary Drying	249
9.4.2	Secondary Drying	250
9.4.3	Control of Drying	251
9.5	Advantages and Challenges of Pharmaceutical Microwave Freeze Drying	251
9.5.1	Advantages	251
9.5.2	Challenges	251
9.6	Some of the Published Patents for Application of Microwave Freeze Drying	252
	References	253
10	Foam Drying	257
	<i>Phillip M. Lovalenti and Vu Truong-Le</i>	
10.1	Introduction	257
10.1.1	Challenges in Developing Stable Dosage Forms for Biopharmaceuticals	258
10.1.2	Chapter Overview	258
10.2	Comparison of Drying Methods	258
10.2.1	Brief Description of Established Pharmaceutical Drying Methods	258
10.2.1.1	Freeze Drying	259
10.2.1.2	Spray Drying	259
10.2.1.3	Vacuum Foam Drying	259
10.2.1.4	Other Drying Methods	260
10.2.2	Advantages of Foam Drying over Other Methods	261
10.3	Foam Drying: Historical Perspective	262
10.3.1	Foam Drying in the Food Industry	262
10.3.2	Foam Drying in the Pharmaceutical Industry	263
10.4	The Foam-Drying Process	263
10.4.1	Detailed Thermal Cycle and Equipment Parameters	263
10.4.2	Wet Blend Requirements	265
10.4.3	Variants of the Foam-Drying Process	266
10.4.3.1	Annear	266
10.4.3.2	Roser and Gribbon	266
10.4.3.3	Bronshtein (PFF)	266
10.4.3.4	Truong (FFD)	268
10.4.3.5	Truong (CFD)	268
10.4.3.6	Bronshtein (PBV)	268
10.4.4	Challenges to Commercialization	269
10.4.4.1	Process Stresses	269
10.4.4.2	Scalability and Process Robustness	269
10.4.4.3	Drug Delivery Requirements	270

10.4.4.4	Barriers to Change in the Pharmaceutical Industry	270
10.5	Application of Foam Drying to Biostabilization	270
10.5.1	Formulation Considerations	271
10.5.1.1	Moisture Content	271
10.5.1.2	Buffers and pH	271
10.5.1.3	Glass Formers	271
10.5.1.4	Foaming Agents	272
10.5.1.5	Polymers	272
10.5.1.6	Plasticizers	272
10.5.1.7	Proteins and Amino Acids	272
10.5.2	Examples of Foam-Dried Biopharmaceuticals: Case Studies	273
10.5.2.1	<i>Protein: IgG₁ Monoclonal Antibody</i>	273
10.5.2.2	<i>Viral Vaccine: Influenza</i>	274
10.5.2.3	<i>Bacterial Vaccine: Ty21a</i>	275
10.5.2.4	<i>Human Cells: T Cells</i>	276
10.6	Physiochemical Characterization of the Foam-Dried Product	277
10.6.1	Thermal Analysis and Protein Secondary Structure	277
10.6.2	Specific Surface Area and Surface Composition Analysis	278
10.6.3	Molecular Mobility and Amorphous Structure Analysis	278
10.7	Conclusions and Future Prospects	279
	References	279
11	Effects of Electric and Magnetic Field on Freezing	283
	<i>Arun S. Mujumdar and Meng W. Woo</i>	
11.1	Introduction	283
11.2	The Different Stages and Parameters of Freezing	284
11.3	Effect of Electric Field on Freezing	285
11.3.1	Application to Water and Systems with Dissolved Solute	285
11.3.2	Application to Solid Materials	287
11.3.3	Application of AC Field to Freezing	288
11.3.4	Important Additional Considerations	289
11.4	Effect of Magnetic Field on Freezing	290
11.4.1	Patent Claims and Studies on Magnetic Field Assisted Freezing	290
11.4.2	Debate on the Possible Nonsignificant Effect of Magnetic Field to Freezing	291
11.5	Possible Effect of Electric and Magnetic Field on the Sublimation Process	294
11.6	Future Outlook for Pharmaceutical Application	296
	References	296
12	Desired Attributes and Requirements for Implementation	303
	<i>Howard Stamato and Jim Searles</i>	
12.1	Introduction	303
12.2	Measuring Dryness	305
12.3	Process Considerations	306
12.4	Product Considerations	307

- 12.5 Scale-Up Considerations 309
- 12.6 Implementation 309
- References 310

Part IV Formulation Considerations for Solid Dosage Preparation 315

- 13 The Roles of Acid–Base Relationships, Interfaces, and Molecular Mobility in Stabilization During Drying and in the Solid State 317**
Danforth P. Miller, Evgenyi Shalaev, and Jim Barnard
- 13.1 Introduction 317
- 13.2 Acid–Base Relationships and Change in Ionization During Freezing and Drying 318
- 13.3 Role of Interfaces in Instability During Freeze Drying and Spray Drying 323
- 13.4 Influence of Molecular Mobility on Physicochemical Stability 325
- 13.5 Fast β -Relaxation in Practice 332
- 13.6 Conclusions and Advice to the Formulator 336
- References 337

Part V Implementation 347

- 14 Challenges and Considerations for New Technology Implementation and Synergy with Development of Process Analytical Technologies (PAT) 349**
Howard Stamato and Jim Searles
- References 353

Part VI Future Perspectives 355

- 15 Future Directions: Lyophilization Technology Roadmap to 2025 and Beyond 357**
Alina Alexeenko and Elizabeth Topp
- 15.1 Introduction 357
- 15.2 Overview of the Roadmapping Process 358
- 15.2.1 Roadmap Framework and Development 358
- 15.2.2 Roadmap Summary 360
- 15.3 Trends and Drivers 363
- 15.4 Lyophilized Products 364
- 15.4.1 New and Improved Analytical Methods 365
- 15.4.2 Improved Container/Closure Systems 365
- 15.4.3 Adapt Lyophilization to New Product Types 366

- 15.5 Process 366
 - 15.5.1 Process Monitoring Instrumentation 366
 - 15.5.2 Process Modeling and Simulation 367
 - 15.5.3 Process Control and Automation 367
- 15.6 Equipment 367
 - 15.6.1 Equipment Harmonization and Scale-Up 368
 - 15.6.2 Improve Lyophilized Technologies and Equipment for Existing and New Products 369
 - 15.6.3 Disruptive Lyophilization/Drying Technologies and Equipment 369
- 15.7 Regulatory Interface 370
- 15.8 Workforce Development 371
- References 372

- Index 373**