# Contents

1 Introduction 1

Alex Langford, Satoshi Ohtake, David Lechuga-Ballesteros, and Ken-ichi Izutsu Acknowledgement 5 References 6

v |

# 2 A Concise History of Drying 9

Sakamon Devahastin and Maturada Jinorose

- 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 Paroma Chakravarty and Karthik Nagapudi

- Paroma Chakravarty and Karthik Nagapudi
- 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

- vi Contents
  - 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

Jacqueline Horn, Hanns-Christian Mahler, and Wolfgang Friess

- 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- $\beta$ -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

Akhilesh Bhambhani and Valentyn Antochshuk

- 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
```

Bakul Bhatnagar and Serguei Tchessalov

- 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<sup>TM</sup> 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

Reinhard Vehring, Herm Snyder, and David Lechuga-Ballesteros

- 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

**x** Contents

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 Phillip M. Lovalenti and Vu Truong-Le

- 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

Contents xi

- 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 Protein: IgG1 Monoclonal Antibody 273
- 10.5.2.2 Viral Vaccine: Influenza 274
- 10.5.2.3 Bacterial Vaccine: Ty21a 275
- 10.5.2.4 Human Cells: T Cells 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 Arun S. Mujumdar and Meng W. Woo
- 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 Howard Stamato and Jim Searles
- 12.1 Introduction 303
- 12.2 Measuring Dryness 305
- 12.3 Process Considerations 306
- 12.4 Product Considerations 307

xii Contents

- 12.5 Scale-Up Considerations 30912.6 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  $\beta$ -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