

Contents

Preface to Third Edition and Acknowledgment *ix*

Preface to the Second Edition *xi*

1	Foundations and Process Engineering	1
1.1	Freezing	2
1.1.1	Amount of Heat, Heat Conductivity, Heat Transfer, and Cooling Rate	3
1.1.2	Structure of Ice, Solutions, and Dispersions	14
1.1.3	Influence of Excipients	22
1.1.4	Freezing of Cells and Bacteria	32
1.1.5	Methods of Structure Analysis	34
1.1.5.1	Measurements of Electrical Resistance (ER)	34
1.1.5.2	Differential Thermal Analysis (DTA)	45
1.1.5.3	Cryomicroscopy	51
1.1.5.4	Freeze-Dry Microscopy	59
1.1.5.5	Differential Scanning Calorimetry (DSC)	60
1.1.5.6	Nuclear Magnetic Resonance	68
1.1.5.7	Thermomechanical Analysis (TMA)	74
1.1.5.8	Dielectric Analysis (DEA)	76
1.1.5.9	XRPD Diffractometer–Raman Spectroscopy	77
1.1.6	Changes of Structure in Freezing or Frozen Products	78
1.2	Drying	79
1.2.1	Main Drying (Sublimation Drying)	82
1.2.2	Secondary Drying (Desorption Drying)	101
1.2.3	Temperature and Pressure Measurement	113
1.2.3.1	Wireless Temperature Measurement	135
1.2.4	Water Vapor Transport during Drying	136
1.2.4.1	Endpoint Determination of Main and Secondary Drying	144
1.2.5	Collapse and Recrystallization	145
1.2.6	Drying Processes without Vacuum	148
1.2.7	Microwave Freeze-Drying	149
1.2.8	Spray Freeze-Drying	150
1.3	Storage	150
1.3.1	Measurement of the Residual Moisture Content (RM)	151

1.3.1.1	Gravimetric Method	151
1.3.1.2	Karl Fischer (KF) Method	151
1.3.1.3	Thermogravimetry (TG, TG/MS)	153
1.3.1.4	Infrared Spectroscopy	154
1.3.2	Influence of Vial Stoppers on the Residual Moisture Content	156
1.3.3	Qualities of the Dry Substances and Their Changes	162
	References	165
2	Installation and Equipment Technique	177
2.1	Freezing Installation	177
2.1.1	Cooling by Liquids: Shell-Freezing and Spin-Freezing	177
2.1.2	Cooled Surfaces	178
2.1.3	Product in the Flow of Cold Air, Foaming, and Freezing of Extracts and Pulps	179
2.1.4	Droplet Freezing in Cold Liquids	181
2.1.5	Freezing by Evaporation of Product Water	184
2.1.6	Nucleation-on-Demand Technology – ControLyo™	184
2.2	Components of a Freeze-Drying Plant	185
2.2.1	Installations for Flasks and Manifolds	185
2.2.2	Drying Chambers and Forms of Trays	186
2.2.3	Shelves and Their Cooling and Heating	192
2.2.4	Water Vapor Condensers	192
2.2.5	Refrigerating Systems and Refrigerants	201
2.2.6	Vacuum Pumps	215
2.2.7	Inlet Venting Filters	221
2.2.8	Vacuum Measuring Systems	224
2.2.9	Leak Rate Detection	229
2.2.10	Process Control Systems	232
2.2.11	Problems, Failures, and Deviations	235
2.3	Installations Up to 10 kg Ice Capacity	238
2.3.1	Universal Laboratory Plants	238
2.3.2	Pilot Plants	240
2.3.3	Manipulators and Stoppering Systems for Vials	244
2.3.4	Cleaning Installations, Sterilization by Steam, and Vaporized Hydrogen Peroxide (VHP®)	248
2.4	Production Plants	264
2.4.1	Loading and Unloading Systems	269
2.4.2	What Is an Isolator?	274
2.4.3	Isolators: Validation of Decontamination Processes	280
2.5	Production Plants for Food	283
2.5.1	Discontinuous Plants	283
2.5.2	Continuous Plants with Tray Transport	284
2.5.3	Continuous Plants with Product Transport by Wipers or by Vibration	285
2.6	Process Automation	287
2.6.1	Prerequisites for Process and Related Plant Automation	287

2.6.2	Control of the Process and Related Plant Data by Thermodynamic Data Measured during the Process: Thermodynamic Lyophilization Control (TLC)	289
2.6.2.1	Control of the Process without Temperature Sensors in the Product	289
2.6.2.2	Measurement of the Ice Temperature at the Sublimation Front and the Desorption Rate as Process Guides	292
2.6.2.3	Measurement of the Residual Moisture Content (RM) during the Process	302
2.6.2.4	The Transfer of a Freeze-Drying Process from a Pilot to a Production Plant	304
2.6.2.5	Summary of Prerequisites, Limits, and Suggestions for Automated Thermodynamic Lyophilization Control	308
	References	309
	Further Reading	310
3	Pharmaceutical, Biological, and Medical Products	313
3.1	Proteins and Hormones	313
3.2	Viruses, Vaccines, Bacteria, and Yeasts	330
3.3	Antibiotics, Cytostatics, Ibuprofen	341
3.4	Liposomes and Nanoparticles	342
3.5	Antibody	350
3.6	Transplants, Collagen	351
3.7	Freeze-Drying Subject Terms – Overview and Summary	358
	References	360
4	Metal Oxides, Ceramic Powders	367
	References	372
5	Trouble Shooting	375
5.1	Prolonged Evacuation Time	375
5.2	Sublimation Front Temperature Too High	376
5.3	Sublimation Front Temperature Irregular	376
5.4	Slow Pressure Increase in the Chamber during Main Drying	376
5.5	Stoppers ›Pop Out‹ or Slide into the Vials	377
5.6	Traces of Highly Volatile Solvents (Acetone, Ethanol)	377
5.7	Different Structures of the Dried Product in the Center and Border of a Shelf	378
6	Regulatory Issues	379
	Qualification and Validation of Processes and Installations	379
6.1	PAT (Practical Analytical Technology)	385
6.2	Quality of the Product	388
6.3	Description of the Process Developed for Manufacturing of the Product	389
6.4	Description of Production Installations and Their Handling	391
6.5	Equipment Performance Tests	392

6.6	Quality of Installation to Document the Ability of Equipment to Operate Processes (Described in Section 6.3)	395
6.7	Documentation of the Quality of the Products Manufactured (in Comparison with Section 6.2)	396
	References	396

Appendix: Abbreviations, Symbols, and Unit of Measure	399
--	------------

Index	405
--------------	------------