Contents

Preface xvii

1 3D/4D Printing in Additive Manufacturing: Process Engineering and Novel Excipients 1 Christian Muchanfold and Simon A. Poherte

Christian Muehlenfeld and Simon A. Roberts

- 1.1 Introduction 1
- 1.2 The Process of 3D and 4D Printing Technology 1
- 1.3 3D/4D Printing for Biomedical Applications 2
- 1.4 Smart or Responsive Materials for 4D Biomedical Printing 3
- 1.5 Classification of 3D and 4D Printing Technologies 7
- 1.5.1 Fused Filament Fabrication (FFF) Extrusion-Based Systems 7
- 1.5.2 Powder Bed Printing (PBP) Droplet-Based Systems 10
- 1.5.3 Stereolithographic (SLA) Printing Resin-Based Systems 12
- 1.5.4 Selective Laser Sintering (SLS) Printing Laser-Based Systems 15
- 1.6 Conclusions and Perspectives 17 References 17
- 2 3D and 4D Printing Technologies: Innovative Process Engineering and Smart Additive Manufacturing 25 Deck Tan, Ali Nokhodchi, and Mohammed Maniruzzaman
- 2.1 Introduction 25
- 2.2 Types of 3D Printing Technologies 25
- 2.2.1 Stereolithographic 3D Printing (SLA) 25
- 2.2.2 Powder-Based 3D Printing 26
- 2.2.3 Selective Laser Sintering (SLS) 27
- 2.2.4 Fused Deposition Modeling (FDM) 28
- 2.2.5 Semisolid Extrusion (EXT) 3D Printing 29
- 2.2.6 Thermal Inkjet Printing 30
- 2.3 FDM 3D Printing Technology 31
- 2.3.1 FDM 3D Printing Applications in Unit Dose Fabrications and Medical Implants 33
- 2.4 Hot Melt Extrusion Technique to Produce 3D Printing Polymeric Filaments *34*

- 2.5 Smart Medical Implants Integrated with Sensors 35
- 2.5.1 Examples of Medical Implants with Sensors 36
- 2.6 4D Printing and Future Perspectives 38
- 2.6.1 4D Printing and Its Transition in Material Fabrication 38
- 2.6.2 Shape Memory or Stimuli-Responsive Mechanism of 4D Printing 39
- 2.6.3 Factors Affecting 4D Printing 40
- 2.6.3.1 Humidity-Responsive Materials 40
- 2.6.3.2 Temperatures 41
- 2.6.3.3 Electronic and Magnetic Stimuli 43
- 2.6.3.4 Light 45
- 2.6.4 Future Perspectives of 4D Printing 45
- 2.7 Regulatory Aspects 46
- 2.8 Conclusions 48 References 48

3 3D Printing: A Case of ZipDose[®] Technology – World's First 3D Printing Platform to Obtain FDA Approval for a Pharmaceutical Product 53

Thomas G. West and Thomas J. Bradbury

- 3.1 Introduction 53
- 3.2 Terminology 53
- 3.3 Historical Context for This Form of 3D Printing 54
- 3.4 ZipDose[®] Technology 56
- 3.5 3D Printing Machines and Pharmaceutical Process Design 60
- 3.5.1 Overview 60
- 3.5.2 Generalized Process in the Pharmaceutical Context 62
- 3.5.3 Exemplary 3DP Machine Designs 65
- 3.6 Development of SPRITAM[®] 70
- 3.6.1 Product Concept and Need 70
- 3.6.2 Regulatory Approach 71
- 3.6.3 Introduction of the Technology to FDA 72
- 3.6.4 Target Product Profile 72
- 3.6.5 Synopsis of Formulation and Clinical Development 73
- 3.7 Conclusion 76 Acknowledgments 77 References 77

4 Manufacturing of Biomaterials via a 3D Printing Platform 81

- Patrick Thayer, Hector Martinez, and Erik Gatenholm
- 4.1 Additive Manufacturing and Bioprinting 81
- 4.2 Bioinks 83
- 4.2.1 Printability Control Bioink Composition and Environmental Factors 83
- 4.2.2 Mechanisms for Filament Formation and Stability 85
- 4.3 3D Bioprinting Systems 87
- 4.3.1 Multifaceted Systems 88

- 4.3.2 Major Components 88
- 4.3.3 Pneumatic Printhead 89
- 4.3.4 Mechanical Displacement Printhead 89
- 4.3.5 Inkjet Printhead 91
- 4.3.6 Heated and Cooled Printheads 91
- 4.3.7 High-Temperature Extruder 92
- 4.3.8 Multimaterial Printhead 92
- 4.3.9 Heated and Cooled Printbed 94
- 4.3.10 Clean Chamber Technology 94
- 4.3.11 Video-Capture Printhead and Sensors 94
- 4.3.12 Integrated Intelligence 95
- 4.4 Applications 95
- 4.4.1 Internal Architecture 96
- 4.4.2 Integrated Vascular Networks and Microstructure Patterning 98
- 4.4.3 Personalized Medicine 99
- 4.5 Steps Necessary for Broader Application *101* References *102*
- 5 Bioscaffolding: A New Innovative Fabrication Process 113 Rania Abdelgaber, David Kilian, and Hendrik Fiehn
- 5.1 Introduction: From Bioscaffolding to Bioprinting 113
- 5.2 Scaffolding 115
- 5.2.1 Properties of Scaffolds 115
- 5.2.2 Bioprinters vs Common 3D Printers: Approaches for Extrusion of Polymers *116*
- 5.2.3 Comparing Cell Seeding Techniques to 3D Bioprinting or Cell-Laden Hydrogels *117*
- 5.2.3.1 From Printing to Bioprinting 117
- 5.2.3.2 Approaches of Stabilizing Printed Constructs 118
- 5.2.4 Examples/Applications of Cell-Seeded Scaffolds 119
- 5.2.5 Data Processing of 3D CAD Data for Bioscaffolds 119
- 5.3 Bioprinted Scaffolds 120
- 5.3.1 Bioinks 120
- 5.3.2 Tools for Multimaterial Printing 123
- 5.3.3 Multimaterial Scaffold 124
- 5.3.4 Core–Shell Scaffolds 126
- 5.3.5 Additional Technical Equipment 128
- 5.3.6 Piezoelectric Pipetting Technology 128
- 5.3.7 Usage of Piezoelectric Inkjet Technology with Bioscaffolds 130
- 5.4 Applications of Bioscaffolder and Bioprinting Systems 132
- 5.4.1 Individualized Implants and Tissue Constructs 132
- 5.4.2 Green Bioprinting 133
- 5.4.3 Challenges for Clinical Applications of Bioprinted Scaffolds in Tissue and Organ Engineering *134*
- 5.4.4 4D Printing 135
- 5.5 Conclusion 137 References 137

x Contents

6	Potential of 3D Printing in Pharmaceutical Drug Delivery and
	Manufacturing 145
	Maren K. Preis
6.1	Introduction 145
6.2	Pharmaceutical Drug Delivery 145
6.3	Conventional Manufacturing vs 3D Printing 146
6.4	Advanced Applications for Improved Drug Delivery 148
6.5	Instrumentations 148
6.6	Location of 3D Printing Manufacturing 149
661	Pharmaceutical Industry 149
662	At the Point of Care 150
663	Print-at-Home 150
67	Regulatory Aspects 151
6.8	Summary 151
0.0	Pafarancas 151
	References 151
_	
7	Emerging 3D Printing Technologies to Develop Novel
	Pharmaceutical Formulations 153
	Christos I. Gioumouxouzis, Georgios K. Eleftheriadis, and
	Dimitrios G. Fatouros
7.1	Introduction 153
7.2	FDM 3D Printing 153
7.3	Pressure-Assisted Microsyringe 173
7.4	SLA 3D Printing 175
7.5	Powder Bed 3D Printing 175
7.6	SLS 3D Printing 178
7.7	3D Inkjet Printing 179
7.8	Conclusions 180
	Defense 190
	Kelerences 180
	References 180
8	Modulating Drug Release from 3D Printed Pharmaceutical
8	Modulating Drug Release from 3D Printed Pharmaceutical Products 185
8	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach
8 8.1	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach Introduction 185
8 8.1 8.2	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach Introduction 185 Pharmaceutically Used 3D Printing Processes and
8 8.1 8.2	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach Introduction 185 Pharmaceutically Used 3D Printing Processes and Techniques 186
8 8.1 8.2 8.2 1	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach Introduction 185 Pharmaceutically Used 3D Printing Processes and Techniques 186 Process Elow of 3D Printing Processes 186
8 8.1 8.2 8.2.1 8.2.2	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach Introduction 185 Pharmaceutically Used 3D Printing Processes and Techniques 186 Process Flow of 3D Printing Processes 186 Inkiet-Based Printing Technologies 187
8 8.1 8.2 8.2.1 8.2.2 8.2.3	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach Introduction 185 Pharmaceutically Used 3D Printing Processes and Techniques 186 Process Flow of 3D Printing Processes 186 Inkjet-Based Printing Technologies 187 Extrusion-Based Printing Technologies 187
8 8.1 8.2 8.2.1 8.2.2 8.2.3 8.2.4	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach Introduction 185 Pharmaceutically Used 3D Printing Processes and Techniques 186 Process Flow of 3D Printing Processes 186 Inkjet-Based Printing Technologies 187 Extrusion-Based Printing Techniques 187 Laser-Based Techniques 188
8 8.1 8.2 8.2.1 8.2.2 8.2.3 8.2.4 8.3	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach Introduction 185 Pharmaceutically Used 3D Printing Processes and Techniques 186 Process Flow of 3D Printing Processes 186 Inkjet-Based Printing Technologies 187 Extrusion-Based Printing Techniques 187 Laser-Based Techniques 188 Modifying the Drug Release Profile from 3D Printed Decage
8 8.1 8.2 8.2.1 8.2.2 8.2.3 8.2.4 8.3	Kelerences180Modulating Drug Release from 3D Printed PharmaceuticalProducts185Julian QuodbachIntroduction185Pharmaceutically Used 3D Printing Processes andTechniques186Process Flow of 3D Printing Processes186Inkjet-Based Printing Technologies187Extrusion-Based Printing Techniques187Laser-Based Techniques188Modifying the Drug Release Profile from 3D Printed DosageFormer180
8 8.1 8.2 8.2.1 8.2.2 8.2.3 8.2.4 8.3 8.2.4	Modulating Drug Release from 3D Printed Pharmaceutical Products 185 Julian Quodbach Introduction 185 Pharmaceutically Used 3D Printing Processes and Techniques 186 Process Flow of 3D Printing Processes 186 Inkjet-Based Printing Technologies 187 Extrusion-Based Printing Techniques 187 Laser-Based Techniques 188 Modifying the Drug Release Profile from 3D Printed Dosage Forms 189
 8 8.1 8.2 8.2.1 8.2.2 8.2.3 8.2.4 8.3 8.3.1 8.2.2 	Kelerences180Modulating Drug Release from 3D Printed PharmaceuticalProducts185Julian QuodbachIntroduction185Pharmaceutically Used 3D Printing Processes andTechniques186Process Flow of 3D Printing Processes186Inkjet-Based Printing Technologies187Extrusion-Based Printing Techniques187Laser-Based Techniques188Modifying the Drug Release Profile from 3D Printed DosageForms189Approaches to Modify the Drug Release189
 8 8.1 8.2 8.2.1 8.2.2 8.2.3 8.2.4 8.3 8.3.1 8.3.2 8.2.1 	Kelerences180Modulating Drug Release from 3D Printed PharmaceuticalProducts185Julian QuodbachIntroduction185Pharmaceutically Used 3D Printing Processes andTechniques186Process Flow of 3D Printing Processes186Inkjet-Based Printing Technologies187Extrusion-Based Printing Techniques187Laser-Based Techniques188Modifying the Drug Release Profile from 3D Printed DosageForms189Approaches to Modify the Drug Release189Modifying the Drug Release by Formulation Variation189Eugad Filoment Febrication180
 8 8.1 8.2 8.2.1 8.2.2 8.2.3 8.2.4 8.3 8.3.1 8.3.2 8.3.2.1 8.3.2.1 8.3.2.2 	Kelerences180Modulating Drug Release from 3D Printed PharmaceuticalProducts185Julian QuodbachIntroduction185Pharmaceutically Used 3D Printing Processes andTechniques186Process Flow of 3D Printing Processes186Inkjet-Based Printing Technologies187Extrusion-Based Printing Techniques187Laser-Based Techniques188Modifying the Drug Release Profile from 3D Printed DosageForms189Approaches to Modify the Drug Release189Modifying the Drug Release by Formulation Variation189Cub er Drinting Tachnigung104
 8 8.1 8.2 8.2.1 8.2.2 8.2.3 8.2.4 8.3 8.3.1 8.3.2 8.3.2.1 8.3.2.1 8.3.2.2 	Kelerences180Modulating Drug Release from 3D Printed PharmaceuticalProducts185Julian QuodbachIntroduction185Pharmaceutically Used 3D Printing Processes andTechniques186Process Flow of 3D Printing Processes186Inkjet-Based Printing Technologies187Extrusion-Based Printing Techniques187Laser-Based Techniques188Modifying the Drug Release Profile from 3D Printed DosageForms189Approaches to Modify the Drug Release189Modifying the Drug Release by Formulation Variation189Fused Filament Fabrication189Other Printing Techniques194

Contents xi

- 8.3.3 Manipulating the Dosage Form Geometry as a Means to Modify API Release 195
- 8.3.3.1 Fused Filament Fabrication 196
- 8.3.3.2 Drop-on-Drop Printing 197
- 8.3.4 Dissolution Control via Directed Diffusion and Compartmentalization *199*
- 8.3.4.1 Drop-on-Powder Printing 199
- 8.3.4.2 Fused Filament Fabrication 202
- 8.3.4.3 Printing with Pressure-Assisted Microsyringes 205
- 8.4 Conclusion 206 References 207
- 9 Novel Excipients and Materials Used in FDM 3D Printing of Pharmaceutical Dosage Forms 211 Ming Lu
- 9.1 Introduction 211
- 9.2 Biodegradable Polyester 219
- 9.2.1 Polylactic Acid (PLA) 219
- 9.2.2 Poly(ε-caprolactone) (PCL) 220
- 9.3 Polyvinyl Polymer 221
- 9.3.1 Polyvinyl Alcohol (PVA) 221
- 9.3.2 Ethylene Vinyl Acetate (EVA) 223
- 9.3.3 Polyvinylpyrrolidone (PVP) 224
- 9.3.4 Soluplus 225
- 9.4 Cellulosic Polymers 225
- 9.4.1 Hydroxypropyl Cellulose (HPC) 226
- 9.4.2 Hydroxypropyl Methylcellulose (HPMC) 227
- 9.4.3 Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS) 228
- 9.5 Polymethacrylate-Based Polymers 229
- 9.5.1 Eudragit RL/RS 230
- 9.5.2 Eudragit L100-55 231
- 9.5.3 Eudragit E 100 232
- 9.6 Conclusion 233 References 234
- 10Recent Advances of Novel Materials for 3D/4D Printing in
Biomedical Applications239

Jasim Ahmed

- 10.1 Introduction 239
- 10.2 Materials for 3DP 240
- 10.3 Rheology 241
- 10.4 Ceramics for 3D Printing 241
- 10.5 Polymers and Biopolymers for 3D Printing 243
- 10.5.1 Polylactide (PLA) 245
- 10.5.2 Poly(ε-caprolactone) (PCL) 245
- 10.5.3 Hyaluronic Acid 245

ii Contents

- 4D Printing 246 10.6
- 10.6.1 Bioprinting 246
- 10.6.2 Smart or Intelligent Materials 249
- 10.6.2.1 Thermal Stimuli-Induced Transformation 249
- 10.6.2.2 Hydrogel 253
- 3D and 4D Printed Bone Scaffolds with Novel Materials 255 10.7
- 10.7.1 3DP/4DP for Drug Delivery and Bioprinting 259
- 10.7.2 Polvurethane-Based Scaffolds for Tissue Engineering 260
- Future and Prospects 263 10.8 References 264
- 11 Personalized Polypills Produced by Fused Deposition Modeling **3D Printing** 273
 - Sheng Qi, Jehad Nasereddin, and Fahad Algahtani
- 11.1 Introduction 273
- Polypharmacy and Polypills 275 11.2
- Clinical Evidence and Current State of the Art 275 11.2.1
- 11.2.2 Future Personalization 276
- FDM 3D Printing of Pharmaceutical Solid Dosage Forms 279 11.3
- 11.3.1 Basic Principle of FDM 3D Printing 279
- Printing Parameter Control 281 11.3.2
- 11.3.3 Drug-Loading Methods 285
- Key Challenges in the Development of FDM 3D Printed Personalized 11.4 Polypills 287
- 11.4.1 Printable Pharmaceutical Materials 287
- Printing Precision and Printer Redesign 288 11.4.2
- Regulatory Barriers for Personalized Polypill Printing 290 11.4.3
- Conclusions and Future Remarks 292 11.5 References 292
- 12 3D Printing of Metallic Cellular Scaffolds for Bone Implants 297
 - Xipeng Tan and Yu Jun Tan
- 12.1Introduction 297
- Metal 3D Printing Techniques for Bone Implants 299 12.2
- 12.2.1 Selective Laser Melting 301
- 12.2.2 Selective Electron Beam Melting 302
- 12.3 Biometals for Bone Implants 303
- 12.3.1 Nondegradable Biometals 304
- Biodegradable Biometals 305 12.3.2
- 12.3.3 3D Printing of Biometals 306
- 12.3.3.1 Ti-6Al-4V ELI Alloy 306
- 12.3.3.2 CoCrMo Alloy 307
- 12.3.3.3 Stainless Steel 316L Alloy 307
- 12.3.3.4 NiTi Shape Memory Alloy 308
- 12.3.3.5 Tantalum 309
- 12.3.3.6 Mg and Its Alloy 309

х

- 12.4 Cellular Structure Design 310
- 12.4.1 Stochastic and Reticulated Cellular Design 311
- 12.4.2 Bend- and Stretch-Dominated Cellular Design 312
- 12.4.3 Scaffold Design Feasibility *312*
- 12.5 Outlook 313 References 314

3D and 4D Scaffold-Free Bioprinting *317*

Chin Siang Ong, Pooja Yesantharao, and Narutoshi Hibino

- 13.1 Introduction 317
- 13.2 3D Scaffold-Free Bioprinting 318
- 13.2.1 Principles 318
- 13.2.2 Spheroid Optimization 318
- 13.2.3 3D Bioprinting 322
- 13.2.4 Decannulation and Functional Assessment 325
- 13.3 4D Bioprinting 326
- 13.3.1 Properties of "Smart" Materials 328
- 13.3.2 General Approaches 328
- 13.3.2.1 "Smart" Scaffolds 328
- 13.3.2.2 In Vivo Bioprinting 331
- 13.3.2.3 Hybrid Techniques 332
- 13.3.3 4D Bioprinting Technologies 332
- 13.3.4 Applications 334
- 13.3.5 Limitations and Future Directions 336
- 13.4 4D Scaffold-Free Bioprinting 337
- 13.5 Conclusion 338 Acknowledgments 338 References 338

14 4D Printing and Its Biomedical Applications 343

- Saeed Akbari, Yuan-Fang Zhang, Dong Wang, and Qi Ge
- 14.1 Introduction 343
- 14.2 3D Printing Technologies with Potential for 4D Printing 344
- 14.2.1 Fused Deposition Modeling (FDM) 344
- 14.2.2 Direct Ink Writing (DIW) 345
- 14.2.3 Inkjet 347
- 14.2.4 Projection Stereolithography (pSLA) 348
- 14.3 Soft Active Materials for 4D Printing 349
- 14.3.1 Shape Memory Polymers 349
- 14.3.2 Hydrogels 354
- 14.3.3 Other SAMs 356
- 14.4 Biomedical Applications of 4D Printing 358
- 14.4.1 Temperature-Actuated 4D Printing 358
- 14.4.2 Humidity-Actuated 4D Printing 363
- 14.5 Conclusion and Outlook 365 References 366

xiv Contents

15	Current Trends and Challenges in Biofabrication Using
	Biomaterials and Nanomaterials: Future Perspectives for 3D/4D
	Bioprinting 373
	Luciano P. Silva
15.1	Introduction 373
15.2	Biofabrication as a Multidisciplinary to Interdisciplinary
	Research Field 375
15.3	Biofabrication as a Multifaceted Approach 377
15.4	Biofabrication Beyond Biomedical Pharmaceutical
	Applications 377
15.5	The Diversity of Techniques Used in Biofabrication 378
15.6	Natural Resources as Sources of Biomaterials Useful for
	Biofabrication 380
15.7	Nanomaterials as Much More Than Just New Building Blocks for
	Biofabrication 382
15.8	3D Bioprinting as the New Gold Standard for Biofabrication 383
15.9	When 3D Bioprinting Is Not Sufficient for Bioconstruction: 4D
	Bioprinting 385
15.10	An Overview About Current Bottlenecks in Biofabrication 385
15.10.1	Does 3D Model Matter in Biofabrication? 386
15.10.2	Does Size and Time Matter in Biofabrication? 386
15.10.3	Do Choice Materials and Cells Matters in Biofabrication? 387
15.10.4	Does Maturation of the Bioconstructs Matter in
	Biofabrication? 387
15.10.5	Do Characterization Methods Matters in Biofabrication? 388
15.10.6	Does Economic and Social Impact Matter Biofabrication? 388
15.10.7	Does Ethical and Legal Issues Matter in Biofabrication? 389
15.11	Conclusion 390
	References 390
16	Orthopedic Implant Design and Analysis: Potential of
	3D/4D Bioprinting 423
	Chang Jiang Wang and Kevin B. Hazlehurst
16.1	Orthopedic Implant Design with 3D Printing 423
16.1.1	Bone Properties and Orthopedic Implants 423
16.1.2	3D Printing and Porous Implant Design 426
16.2	Analysis of 3D Printed Orthopedic Implants 428
16.2.1	Mechanical Properties of Porous Structures 429
16.2.2	Experimental Testing of 3D Printed Femoral Stems 433
16.2.3	Finite Element Analysis of Porous Stems with 3D Printing 435
16.3	3D Printed Orthopedic Implant Installation and
	Instrumentation 437
16.4	Orthopedic Implants Manufactured with 4D Printing 439
16.5	Summary 439
	References 440

Contents xv

- 17Recent Innovations in Additive Manufacturing Across
Industries: 3D Printed Products and FDA's Perspectives443
Brett Rust, Olga Tsaponina, and Mohammed Maniruzzaman
- 17.1 Introduction 443
- 17.2 Current Widely Used Processes Across Industries 443
- 17.2.1 Fused Deposition Modeling (FDM) 443
- 17.2.2 Stereolithography (SLA) and Digital Light Processing (DLP) 444
- 17.2.3 Selective Laser Sintering (SLS) 445
- 17.3 Emerging 3D Printing Processes and Technologies 446
- 17.3.1 Continuous Liquid Interface Production (CLIP) 446
- 17.3.2 Multi Jet Fusion (MJF) 446
- 17.4 Industry Uses of Additive Manufacturing Technologies 447
- 17.5 Material and Processes for Medical and Motorsport Sectors 449
- 17.6 Medical Industry Usage and Materials Development 452
- 17.7 3D Printing of Medical Devices: FDA's Perspectives 455
- 17.7.1 FDA's Role in 3D Printing of Materials 455
- 17.7.2 Classifications of Medical Devices from FDA's Viewpoint 456
- 17.7.3 Medical Applications of 3D Printing and FDA's Expectations 457
- 17.7.4 Person-Specific Devices 458
- 17.7.5 Process of 3D Printing of Various Medical Devices 458
- 17.7.6 Materials Used in 3D Printed Devices Overall 459
- 17.7.7 Materials Used in Specific Application (Printed Dental Devices) 460
- 17.8 Conclusions 461
 - References 461

Index 463