# Contents

**List of Contributors**

**Preface**

   *Keith Luker*
   
   1.1 Introduction 1
   1.2 Ideal Compounding 2
   1.3 Basics of the Single-screw Extruder 3
     - 1.3.1 Screw Feed Section 5
     - 1.3.2 Screw Compressor Section 9
     - 1.3.3 Screw Metering Section 11
     - 1.3.4 Mixers 11
     - 1.3.5 Limitations of Conventional Single-screw Mixers 13
   1.4 SSE Elongational Mixers 13
   1.5 Summary 20
   References 21

   *Dirk Leister, Tom Geilen and Thobias Geissler*
   
   2.1 Introduction 23
   2.2 Extruder Types and Working Principle 24
   2.3 Individual Parts of a TSE 25
     - 2.3.1 Drive Unit 25
     - 2.3.2 Screws 25
     - 2.3.3 Screw Elements 27
     - 2.3.4 Distributive Flow Elements 28
     - 2.3.5 Discharge Feed Screw 28
     - 2.3.6 Barrel 29
   2.4 Downstreaming 30
   2.5 Individual Processing Sections of the TSE 31
     - 2.5.1 Feeding Section 32
     - 2.5.2 Conveying/Melting Section 32
     - 2.5.3 Mixing Section 33
     - 2.5.4 Venting Section 33
## Contents

2.5.5 Extrusion Section 33

2.6 Feeding of Solids 34

2.7 TSE Operating Parameters 34
   2.7.1 Filling Level 36
   2.7.2 Screw Speed 36
   2.7.3 Feed Rate 37
   2.7.4 Residence Time Distribution 37
   2.7.5 Effect of Screw Speed and Feed Rate on Melt Temperature 39

2.8 Setting up an HME Process using QbD Principles 40
   2.8.1 Understanding Knowledge Space 40
   2.8.2 Defining Design Space 40
   2.8.3 Determining Control Space 41

2.9 Summary 42

References 42

3. Hot-melt Extrusion Developments in the Pharmaceutical Industry 43

Ana Almeida, Bart Claeys, Jean Paul Remon and Chris Vervaet

3.1 Introduction 43

3.2 Advantages of HME as Drug Delivery Technology 44

3.3 Formulations used for HME Applications 45
   3.3.1 Active Pharmaceutical Ingredient 46
   3.3.2 Solid Dispersions 48
   3.3.3 Bioavailability Improvement 49
   3.3.4 Controlled Delivery Systems 51
   3.3.5 Plasticizers 53

3.4 Characterization of Extrudates 55
   3.4.1 Thermal Analysis 55
   3.4.2 Atomic Force Microscopy 56
   3.4.3 Residence Time 57
   3.4.4 Spectroscopic Techniques 57
   3.4.5 X-ray Diffraction (XRD) 58
   3.4.6 Microscopy 58
   3.4.7 Drug Release 58

3.5 Hot-melt Extruded Dosage Forms 58
   3.5.1 Oral Drug Delivery 59
   3.5.2 Films 61
   3.5.3 Vaginal Rings and Implants 61

3.6 A View to the Future 63

References 64

4. Solubility Parameters for Prediction of Drug/Polymer Miscibility in Hot-melt Extruded Formulations 71

Andreas Gryczke

4.1 Introduction 71

4.2 Solid Dispersions 72
Contents

4.3 Basic Assumptions for the Drug–polymer Miscibility Prediction 77
4.4 Solubility and the Flory–Huggins Theory 78
4.5 Miscibility Estimation of Drug and Monomers 83
4.6 Summary 89
References 90

5. The Influence of Plasticizers in Hot-melt Extrusion 93
Geert Verreck
5.1 Introduction 93
5.2 Traditional Plasticizers 94
5.3 Non-traditional Plasticizers 95
5.4 Specialty Plasticizers 104
5.5 Conclusions 107
References 108

6. Applications of Poly(meth)acrylate Polymers in Melt Extrusion 113
Kathrin Nollenberger and Jessica Albers
6.1 Introduction 113
6.2 Polymer Characteristics 116
6.2.1 Chemical Structure and Molecular Weight 116
6.2.2 Glass Transition Temperature 119
6.2.3 Plasticizers 120
6.2.4 Thermostability 121
6.2.5 Viscosity 122
6.2.6 Specific Heat Capacity 124
6.2.7 Hygroscopicity 126
6.3 Melt Extrusion of Poly(methacrylates) to Design Pharmaceutical Oral Dosage Forms 128
6.4 Solubility Enhancement 128
6.5 Bioavailability Enhancement of BCS Class IV Drugs 132
6.5.1 Controlled Release 135
6.5.2 Time-controlled-release Dosage Forms 136
6.5.3 pH-dependent Release 138
6.5.4 Taste Masking 139
6.6 Summary 140
References 140

7. Hot-melt Extrusion of Ethylcellulose, Hypromellose and Polyethylene Oxide 145
Mark Hall and Michael Read
7.1 Introduction 145
7.2 Background 146
x Contents

7.3  Thermal Properties 147
7.4  Processing Aids/Additives 147
7.5  Unconventional Processing Aids: Drugs, Blends 149
7.6  Case Studies 151
  7.6.1  Ethylcellulose 151
  7.6.2  Combinations of Excipients 151
  7.6.3  Solubilization 155
  7.6.4  Film 159
  7.6.5  Unique Dosage Forms 163
  7.6.6  Abuse Resistance 163
  7.6.7  Controlled Release 164
  7.6.8  Solubility Parameters 166
7.7  Milling of EC, HPMC and PEO Extrudate 168
References 170

8.  Bioadhesion Properties of Polymeric Films Produced by Hot-melt Extrusion 177

Joshua Boateng and Dennis Douroumis

8.1  Introduction 177
8.2  Anatomy of the Oral Cavity and Modes of Drug Transport 180
  8.2.1  Structure 180
  8.2.2  Modes of Drug Transport and Kinetics 180
  8.2.3  Factors Affecting Drug Absorption 181
8.3  Mucoadhesive Mechanisms 182
8.4  Factors Affecting Mucoadhesion in the Oral Cavity 183
8.5  Determination of Mucoadhesion and Mechanical Properties of Films 183
8.6  Bioadhesive Films Prepared by HME 184
8.7  Summary 194
References 194

9.  Taste Masking Using Hot-melt Extrusion 201

Dennis Douroumis, Marion Bonnefille and Attila Aranyos

9.1  The Need and Challenges for Masking Bitter APIs 201
9.2  Organization of the Taste System 203
  9.2.1  Taste Perception in Humans and Organization of Peripheral System 203
  9.2.2  Transduction of Taste Signals 205
9.3  Taste Sensing Systems (Electronic Tongues) for Pharmaceutical Dosage Forms 206
  9.3.1  Alpha MOS Electronic Tongue: Instrumentation and Operational Principles 206
  9.3.2  Taste Analysis 208
  9.3.3  Taste Masking Efficiency Testing 209
  9.3.4  Advantages of E-tongue Taste Analysis 211
9.4 Hot-melt Extrusion: An Effective Means of Taste Masking 212
9.4.1 Taste Masking via Polymer Extrusion 212
9.4.2 Taste Masking via Solid Lipid Extrusion 216
9.5 Summary 219
References 219

10. Clinical and Preclinical Studies, Bioavailability and Pharmacokinetics of Hot-melt Extruded Products 223
Sandra Guns and Guy Van den Mooter
10.1 Introduction to Oral Absorption 223
10.2 In Vivo Evaluation of Hot-melt Extruded Solid Dispersions 225
10.2.1 Oral Immediate Release 225
10.2.2 Oral Controlled Release 232
10.2.3 Implants 233
10.3 Conclusion 234
References 234

11. Injection Molding and Hot-melt Extrusion Processing for Pharmaceutical Materials 239
Pernille Høyrup Hemmingsen and Martin Rex Olsen
11.1 Introduction 239
11.2 Hot-melt Extrusion in Brief 240
11.3 Injection Molding 241
11.4 Critical Parameters 242
11.4.1 Melt Temperature 242
11.4.2 Barrel Temperature 243
11.4.3 Cooling Temperature 243
11.4.4 Holding Pressure 243
11.4.5 Holding Time 243
11.4.6 Back Pressure 244
11.4.7 Injection Speed 244
11.4.8 Cooling Time/Cycle Time 244
11.5 Example: Comparison of Extruded and Injection-molded Material 245
11.6 Development of Products for Injection Molding 246
11.6.1 Excipients 246
11.6.2 Stability 248
11.6.3 Process Development 248
11.7 Properties of Injection-molded Materials 251
11.7.1 Egalet® Technology 251
11.7.2 Controlling Physical State by Means of Hot-melt Extrusion and Injection Molding 253
11.7.3 Anti-tamper Properties of Injection-molded Tablets 254
11.8 Concluding Remarks 257
References 257
12. Laminar Dispersive and Distributive Mixing with Dissolution and Applications to Hot-melt Extrusion 261

Costas G. Gogos, Huiju Liu and Peng Wang

12.1 Introduction 261

12.2 Elementary Steps in HME 263

12.2.1 Particulate Solids Handling (PSH) 263

12.2.2 Melting 263

12.2.3 Devolatilization 264

12.2.4 Pumping and Pressurization 265

12.3 Dispersive and Distributive Mixing 265

12.4 HME Processes: Cases I and II 265

12.4.1 Case I 266

12.4.2 Case II 268

12.5 Dissolution of Drug Particulates in Polymeric Melt 270

12.5.1 Process Variables 270

12.5.2 Equipment Variables 273

12.5.3 Material Variables 275

12.6 Case Study: Acetaminophen and Poly(ethylene oxide) 278

12.7 Determination of Solubility of APAP in PEO 280

References 282

13. Technological Considerations Related to Scale-up of Hot-melt Extrusion Processes 285

Adam Dreblatt

13.1 Introduction 285

13.2 Scale-up Terminology 287

13.2.1 Scale-up: Batch Size 287

13.2.2 Scale-up: Feed Rate 288

13.2.3 Scale-up: Extruder Diameter 290

13.3 Volumetric Scale-up 290

13.3.1 Volumetric Scale-up: Length/Diameter (L/D) 292

13.3.2 Volumetric Scale-up: Diameter Ratio 292

13.3.3 Volumetric Scale-up: Screw Design 294

13.4 Power Scale-up 296

13.5 Heat Transfer Scale-up 298

13.6 Die Scale-up 299

13.7 Conclusion 299

References 300

14. Devices and Implant Systems by Hot-melt Extrusion 301

Andrew Loxley

14.1 Introduction 301

14.2 HME in Device Development 302

14.3 Hot-melt Extruder Types 303
Contents

14.4 Comparison of HME Devices and Oral Dosage Forms 305
14.5 HME Processes for Device Fabrication 306
  14.5.1 Issues with HME in preparing Drug-eluting Devices 308
14.6 Devices and Implants 310
  14.6.1 Anatomical Device Locations 310
  14.6.2 Simple Devices 310
  14.6.3 Non-medicated Prolonged Tissue Contact Devices 312
  14.6.4 Medicated (Drug-eluting) Prolonged Tissue Contact Devices 313
14.7 Release Kinetics 318
  14.7.1 Mechanisms of API Release 318
  14.7.2 Example In Vitro Drug Elution Profiles 319
14.8 Conclusions 321
References 321

15. Hot-melt Extrusion: An FDA Perspective on Product and Process Understanding 323
   Abhay Gupta and Mansoor A. Khan
   15.1 Introduction 323
   15.2 Quality by Design 325
   15.3 Utilizing QbD for HME Process Understanding 328
     References 331

   Chris Heil and Jeffrey Hirsch
   16.1 Vibrational Spectroscopy Introduction 333
   16.2 Near-infrared Method Development 339
   16.3 Near-infrared Probes and Fiber Optics 344
   16.4 NIR for Monitoring the Start-up of a HME Process 347
   16.5 NIR for Improved Process Understanding and Control 350
     References 353

Index 355