Handbook of Polymers for Pharmaceutical Technologies
Scrivener Publishing
100 Cummings Center, Suite 541J
Beverly, MA 01915-6106

Publishers at Scrivener
Martin Scrivener (martin@scrivenerpublishing.com)
Phillip Carmical (pcarmical@scrivenerpublishing.com)
To my parents and teachers who helped me become what I am today.

Vijay Kumar Thakur
Contents

Preface xvii

1 Particle Engineering of Polymers into Multifunctional Interactive Excipients 1
   Sharad Mangal, Ian Larson, Felix Meiser and David AV Morton
   1.1 Introduction 1
   1.2 Polymers as Excipients 3
   1.3 Material Properties Affecting Binder Activity 6
      1.3.1 Particle Size 6
      1.3.2 Deformation Mechanisms 7
      1.3.3 Glass Transition Temperature (Tg) 8
   1.4 Strategies for Improving Polymeric Filler-Binder Performance for Direct Compression 8
      1.4.1 Interactive Mixing 12
      1.4.2 Challenges to Interactive Mixing 13
      1.4.3 Controlling Interparticle Cohesion 14
   1.5 Preparation and Characterization of Interactive Excipients 14
      1.5.1 Particle Size and Size Distribution of Excipients 15
      1.5.2 Effect of L-leucine on Surface Morphology 16
      1.5.3 Effect of L-leucine on Surface Composition 16
      1.5.4 Effect of L-leucine on Surface Energy 17
      1.5.5 Effect of L-leucine on Interparticle Cohesion 18
   1.6 Performance of Interactive Excipients 18
      1.6.1 Blending Ability 18
      1.6.2 Effect on Flow 20
      1.6.3 Binder Activity 20
   1.7 Investigation of the Effect of Polymer Mechanical Properties 23
   1.8 Conclusion 25
   References 26

2 The Art of Making Polymeric Membranes 33
   K.C. Khulbe, T. Matsuura and C. Feng
   2.1 Introduction 33
   2.2 Types of Membranes 35
      2.2.1 Porous Membranes 35
      2.2.2 Nonporous Membranes 36
      2.2.3 Liquid Membranes (Carrier Mediated Transport) 36
      2.2.4 Asymmetric Membranes 36
   2.3 Preparation of Membranes 36
      2.3.1 Phase Inversion/Separation 37
      2.3.2 Vapor-Induced Phase Separation (VIPS) 37
      2.3.3 Thermally-Induced Phase Separation (TIPS) 37
      2.3.4 Immersion Precipitation 38
      2.3.5 Film/Dry Casting Technique 38
2.3.6 Track Etching 39
2.3.7 Electrospinning 39

2.3.7.1 Preparation of Electrospun Nanofiber Membranes (ENMs) with Single Component 40
2.3.7.2 Preparation of Nanofibers with Two Side-by-Side Components 40
2.3.7.3 Preparation of Core-Sheath and Hollow Nanofibers 41

2.3.8 Spraying 42
2.3.9 Foaming 42
2.3.10 Particle Leaching 43
2.3.11 Precipitation from the Vapor Phase 43
2.3.12 Emulsion Freeze-Drying 43
2.3.13 Sintering 44
2.3.14 Stretching 44
2.3.15 Composite/Supported 44
2.3.16 Mixed Matrix Membranes (MMMs) 45
2.3.17 Hollow Fiber Membranes 46
  2.3.17.1 Methods for Spinning 46
2.3.18 Metal-Organic Frameworks (MOFs) 48

2.4 Modification of Membranes 49
  2.4.1 Modification of Polymeric Membrane by Additives/Blending 49
  2.4.2 Coating 50
  2.4.3 Surface Modification by Chemical Reaction 50
  2.4.4 Interfacial Polymerization (IP)/Copolymerization 50
  2.4.5 Plasma Polymerization/Treatment 52
  2.4.6 Surface Modification by Irradiation of High Energy Particles 52
  2.4.7 UV Irradiation 53
  2.4.8 Ion-Beam Irradiation 53
  2.4.9 Surface Modification by Heat Treatment 53
  2.4.10 Graft Polymerization/Grafting 53
  2.4.11 Other Techniques 53

2.5 Characterization of Membrane by Different Techniques 54
  2.5.1 Conventional Physical Methods to Determine Pore Size and Pore Size Distribution 55
    2.5.1.1 Bubble Gas Transport Method 55
    2.5.1.2 Mercury Intrusion Porosimetry 56
    2.5.1.3 Gas Liquid Equilibrium Method (Permporometry) 56
    2.5.1.4 Adsorption-Desorption Method: Barrett-Joyner-Halenda (BJH) Method 57
    2.5.1.5 Permeability Methods 57
  2.5.2 Morphology 58
    2.5.2.1 Microscopic Method 58
    2.5.2.2 Spectroscopic Method 59
    2.5.2.3 Positron Annihilation Spectroscopy (PAL) 59
    2.5.2.4 X-Ray Analysis and Other Methods 59
  2.5.3 Thermal Properties 60
5 Polymers as Formulation Excipients for Hot-Melt Extrusion Processing of Pharmaceuticals

Kyriakos Kachrimanis and Ioannis Nikolakakis

5.1 Introduction

5.1.1 Overview of Hot-Melt Extrusion (HME)

5.1.2 Solubility/Dissolution Enhancement by Solid Dispersions

5.2 Polymers for HME Processing

5.2.1 Basic Requirements

5.2.2 Suitability – Examples

5.3 Polymer Selection for the HME Process

5.3.1 Thermodynamic Considerations – Drug-Polymer Solubility and Miscibility

5.4 Processing of HME Formulations

5.4.1 Physical Properties of Feeding Material – Flowability, Packing and Friction

5.4.1.1 Crystallinity

5.4.1.2 Molecular Weight and Viscosity

5.5 Improvements in Processing

5.5.1 Equipment Modifications

5.5.2 Plasticizers

5.5.2.1 Drugs Acting as Plasticizers

5.5.2.2 Extrusion Based on Use of Plasticizers

5.6 Conclusion and Future Perspective

References

6 Poly Lactic-Co-Glycolic Acid (PLGA) Copolymer and Its Pharmaceutical Application

Abhijeet Pandey, Darshana S. Jain, Subhashis Chakraborty

6.1 Introduction

6.2 Physicochemical Properties

6.3 Biodegradation

6.4 Biocompatibility, Toxicity and Pharmacokinetics

6.5 Mechanism of Drug Release

6.6 PLGA-Based DDS

6.7 Bone Regeneration

6.8 Pulmonary Delivery

6.9 Gene Therapy

6.10 Tumor Trageting

6.11 Miscellaneous Drug Delivery Applications

6.12 Conclusion

References

7 Pharmaceutical Applications of Polymeric Membranes

Stefan Ioan Voicu

7.1 Introduction

7.2 Obtaining Pure and Ultrapure Water for Pharmaceutical Usage

References
7.3 Wastewater Treatment for Pharmaceutics 180
7.4 Controlled Drug Delivery Devices Based on Membrane Materials 183
7.5 Molecularly Imprinted Membranes 185
7.6 Conclusions 190
References 191
8 Application of PVC in Construction of Ion-Selective Electrodes for Pharmaceutical Analysis: A Review of Polymer Electrodes for Nonsteroidal, Anti-Inflammatory Drugs 195
Joanna Lenik
8.1 Introduction 195
8.2 Properties and Usage of Poly(vinyl)chloride (PVC) 197
8.3 PVC Application and Properties in Construction of Potentiometric Sensors for Drug Detection 199
8.3.1 Role of Polymer Membrane Components 202
8.4 Ion-Selective, Classic, Liquid Electrodes (ISEs) 205
8.5 Ion-Selective Solid-State Electrodes 206
8.5.1 Ion-Selective Coated-Wire Electrodes (CWE) 206
8.5.2 Ion-Selective BMSA Electrodes 207
8.5.3 Electrodes Based on Conductive Polymers (SC-ISEs) 208
8.6 Application of Polymer-Based ISEs for Determination of Analgetic, Anti-Inflammatory and Antipyretic Drugs: Literature Review (2000-2014) 211
8.6.1 Electrodes for Determination of Narcotic Medicines 211
8.6.2 Electrode Sensitive to Dextromethorphan 211
8.6.3 Electrode Sensitive to Tramadol 212
8.6.4 Electrodes for Determination of Non-Narcotic Drugs 212
8.6.5 Salicylate Electrode 214
8.6.6 Ibuprofen Electrode 214
8.6.7 Ketoprofen Electrodes 216
8.6.8 Piroxicam Electrode 216
8.6.9 Tenoxicam Electrode 217
8.6.10 Naproxen Electrodes 217
8.6.11 Indomethacin Electrodes 217
8.6.12 Sulindac Electrode 218
8.6.13 Diclofenac Electrodes 218
8.7 Conclusion 218
References 222
9 Synthesis and Preservation of Polymer Nanoparticles for Pharmaceutical Applications 229
Antonello A. Barresi, Marco Vanni, Davide Fissore and Tereza Zelenková
9.1 Introduction: Polymer Nanoparticles Production 229
9.2 Production of Polymer Nanoparticles by Solvent Displacement Using Intensive Mixers 238
9.2.1 Influence of Polymer-Solvent Type and Hydrodynamics on Particle Size 243
9.2.2 Dependence on Operating Conditions – Polymer and Drug Concentration, Solvent/Antisolvent Ratio, Processing Conditions 248
9.2.3 Process Design: Selection of Mixing Device, Scale Up and Process Transfer 256
9.3 Freeze-Drying of Nanoparticles 264
9.4 Conclusions and Perspectives 268
Acknowledgements 272
References 272

10 Pharmaceutical Applications of Maleic Anhydride/Acid Copolymers 281
Irina Popescu
10.1 Introduction 281
10.2 Maleic Copolymers as Macromolecular Drugs 283
10.3 Maleic Copolymer Conjugates 285
  10.3.1 Polymer-Protein Conjugates 286
  10.3.2 Polymer-Drug Conjugates 288
10.4 Noncovalent Drug Delivery Systems 291
  10.4.1 Enteric Coatings 291
  10.4.2 Solid Dispersions 292
  10.4.3 Polymeric Films and Hydrogels 293
  10.4.4 Microspheres and Microcapsules 294
  10.4.5 Nanoparticles 295
  10.4.6 Micelles 295
10.5 Conclusion 296
References 296

11 Stimuli-Sensitive Polymeric Nanomedicines for Cancer Imaging and Therapy 311
F. Perche, S. Biswas and V. P. Torchilin
11.1 Introduction 311
11.2 Pathophysiological and Physical Triggers 314
  11.2.1 Acidosis 314
    11.2.1.1 pH-Sensitive Tumor Imaging 314
    11.2.1.2 pH-Sensitive Prodrugs 315
    11.2.1.3 pH-Dependent Change of Structure/Size or Shape 315
    11.2.1.4 pH-Induced Exposure of an Internalization Moiety 315
    11.2.1.5 pH-Sensitive Coordination Bonds 317
    11.2.1.6 pH-Sensitive Dendrimer Nanoparticles 317
    11.2.1.7 Drug Conjugated to Dendrimer via pH-Sensitive Linkages 318
  11.2.2 Reductive Stress 319
    11.2.2.1 Reduction-Sensitive Prodrug 319
    11.2.2.2 Reduction-Induced Exposure of an Internalizing Moiety 320
    11.2.2.3 Reduction-Sensitive Crosslinking 320
  11.2.3 Tumor Hypoxia 320
    11.2.3.1 Hypoxia-Induced Drug Release or Exposure of Positive Charge 321
11.2.4 Cancer Associated Extracellular Enzymes
   11.2.4.1 Activatable Cell Penetrating Peptides for Tumor Imaging
   11.2.4.2 MMP-Induced Exposure of Internalization Moiety
   11.2.4.3 MMP-Induced Exposure of Positive Charge
   11.2.4.4 Combination Therapy
   11.2.4.5 Enzyme-Sensitive Dendrimers
11.2.5 Magneto-Responsive Polymers
11.2.6 Temperature-Sensitive Dendrimers
11.2.7 Photoresponsive Polymers
   11.2.7.1 Photodynamic Therapy
   11.2.7.2 Photosensitive Dendrimers
   11.2.7.3 Photoimmunotherapy
11.3 Stimuli-Responsive Polymers for Patient Selection and Treatment Monitoring
   11.3.1 Selection of Patients Amenable to Nanomedicine Treatment
   11.3.2 Selection of Patients for pH-Sensitive Nanocarriers
   11.3.3 Selection of Patients for Redox-Sensitive Nanocarriers
   11.3.4 Mapping of Dominant Active Pathways Using Enzyme-Sensitive Probes
   11.3.5 Selection of Patients for Molecularly-Targeted Therapies
   11.3.6 Evaluation of Response to Treatment
11.4 Conclusions and Future Perspectives
Acknowledgments
References

12 Artificial Intelligence Techniques Used for Modeling of Processes Involving Polymers for Pharmaceutical Applications
   Silvia Curteanu
12.1 Introduction
12.2 Artificial Neural Networks
   12.2.1 Elements and Structure
   12.2.2 Working Methodology
   12.2.3 Variants of ANN Modeling
12.3 Support Vector Machines
   12.3.1 General Aspects
   12.3.2 SVM Modeling Methodology
12.4 Modeling of Processes Involving Polymers for Pharmaceutical Applications
   12.4.1 Neural Networks Used for Modeling of Processes Involving Pharmaceutical Polymers
   12.4.2 Support Vector Machines Used for Modeling of Processes Involving Pharmaceutical Polymers
12.5 Conclusion and Future Perspective
References
13 Review of Current Pharmaceutical Applications of Polysiloxanes (Silicones) 363

Krystyna Mojsiewicz-Pieńkowska

13.1 Introduction 363
13.2 Variety of Polysiloxane – Structure, Synthesis, Properties 364
  13.2.1 Basic Silicone Chemistry 364
  13.2.2 Properties of Silicones 364
13.3 Polysiloxanes as Active Pharmaceutical Ingredient (API) 368
  13.3.1 Mechanism of Action of Dimethicone and Simethicone 370
  13.3.2 Current Legislative Standards Related to Oral Application of Dimethicone and Simethicone (PDMS) 370
  13.3.3 Admissible Doses for Dimethicone and Simethicone (PDMS) 372
13.4 Polysiloxanes as Excipients 373
  13.4.1 Skin Adhesive Patches 375
  13.4.2 Carrier for Controlled-Release Drugs 375
    13.4.2.1 Transdermal Drug Delivery System 377
13.5 Conclusion and Future Perspective 377

References 378

14 Polymer-Doped Nano-Optical Sensors for Pharmaceutical Analysis 383

M. S. Attia and M. S. A. Abdel-Mottaleb

14.1 Introduction 383
  14.1.1 Sol-Gel Process 384
    14.1.1.1 Mechanism of Sol-Gel Formation 384
    14.1.1.2 Hybrid Nanomaterials 385
  14.1.2 Molecular Imprinting Nanomaterial Polymer 386
    14.1.2.1 Approach of Molecular Imprinted Polymer Formation 387
  14.1.3 Poly(methyl methacrylate) Polymer (PMMA) 390
14.2 Processing 392
  14.2.1 Sol-Gel Technique 392
    14.2.1.1 Preparation of Optical Sensor Doped in TEOS 392
    14.2.1.2 Preparation of Thin Film Nano-Optical Sensor Doped in Sol-Gel Matrix 393
  14.2.2 Molecular Imprinted Nanomaterials 394
    14.2.2.1 Imprinted Nanoparticles (Imp-NPs) 394
    14.2.2.2 Imprinted Nanospheres 394
    14.2.2.3 Imprinted Nanoshells 395
    14.2.2.4 Imprinted Nanofibers 396
  14.2.3 Preparation of Optical Sensor Doped in PMMA Matrix 396
  14.2.4 Determination of Pharmaceutical Drug in Pharmaceutical Preparations 396
  14.2.5 Determination of Pharmaceutical Drug in Serum Solution 397
14.3 Application of Optical Sensor for Pharmaceutical Drug Determination 397
  14.3.1 TEOS-Doped Nano-Optical Sensor for Pharmaceutical Determinations 397
    14.3.1.1 Determination of Ramipril by Using Sm3⁺-Doxycycline Doped in TEOS matrix 397
14.3.1.2 Determination of Metoclopramide Hydrochloride by Using Europium Doped in TEOS Matrix 398
14.3.1.3 Nano-Optical Sensor for Chlorzoxazone and Ibuprofen Determination 399
14.3.1.4 Nano-Optical Sensor for Norfloxacin and Gatifloxacin Determination 399

14.3.2 Molecular Imprinted Nano-Polymer 401
14.3.2.1 Hollow Molecular Imprinting Polymer for Ofloxacin Determination 401
14.3.2.2 Molecular Imprinted Solid-Phase Extraction for Determination of Ofloxacin (OFL) and Lomefloxacin 401
14.3.2.3 Ofloxacin-Imprinted Polymer Using Poly(glycidyl methacrylate-co-ethylenedimethacrylate) Particles as a Support 402
14.3.2.4 Molecular Imprinted Polymer Nanoparticles for Ofloxacin Determination 402
14.3.2.5 Molecular Imprinted Polymer for Ciprofloxacin Determination 403
14.3.2.6 Molecular Imprinted Polymeric Membrane on a Porous Silica-Gel for Norfloxacin Determination 403
14.3.2.7 Electrochemical Sensor Combined with Molecular Imprinted Polymer for Paracetamol Determination 403

14.3.3 Sensor Embedded in Polymethymethacrylate 404
14.3.3.1 Metoclopramide Hydrochloride Determination by Using an Optical Sensor Tb\(^{3+}\) Embedded in PMMA 404
14.3.3.2 Hydrochlorothiazide Determination by Using an Optical Sensor Eu\(^{3+}\) Embedded in PMMA 404

14.4 Conclusion 405

References 405

15 Polymer-Based Augmentation of Immunosuppressive Formulations:
Application of Polymer Technology in Transplant Medicine 411
Ian C. Doyle and Ashim Malhotra

15.1 Introduction 411
15.2 Polymer-Based Immunosuppressive Formulations 414
  15.2.1 Sirolimus 414
    15.2.1.1 Oral and Injectable Formulations 414
    15.2.1.2 Device Slow-Release Formulations 415
  15.2.2 Cyclosporine A 424
    15.2.2.1 CsA Delivery via Polymeric Micelles 425
    15.2.2.2 CsA Delivery via Nanoparticles 426
    15.2.2.3 CsA Delivery via Biodegradable Matrices 428
    15.2.2.4 Ophthalmic CsA Delivery Systems 429
  15.2.3 Tacrolimus 429
    15.2.3.1 Polymer Applications for Oral Tacrolimus Formulations 430
    15.2.3.2 Other Polymer Applications for Tacrolimus 431
15.2.4 Mycophenolic Acid 431
15.3 Conclusion and Future Perspective 433
References 434

16 Polymeric Materials in Ocular Drug Delivery Systems 439
M. E. Pina, P. Coimbra, P. Ferreira, P. Alves, A. I. Figueiredo and M. H. Gil
16.1 Introduction 439
16.2 A Brief Description of Ocular Anatomy and Physiology 440
16.2.1 Anatomy of the Human Eye 440
16.2.2 Routes of Ocular Drug Delivery 441
16.2.3 Barriers in Ocular Drug Delivery 444
16.2.3.1 Lacrimation, Drainage and Blood Vessels 444
16.2.3.2 Corneal–Aqueous Barrier 444
16.3 Polymeric Ocular Drug Delivery Systems 445
16.3.1 Non-Biodegradable Polymeric Ocular Drug Delivery Systems 446
16.3.1.1 Non-Biodegradable Synthetic Polymers 446
16.3.2 Biodegradable Polymeric Ocular Drug Delivery Systems 449
16.3.2.1 Biodegradable Synthetic Polymers 450
16.4 Conclusion and Future Perspective 455
References 455

Index 459
The modern pharmaceutical market is under relentless pressure from slowing new drug product approvals, blockbuster drug patent expiry, price pressure and global competition. In addition, new opportunities exist due to an evolving patient population, numerous unmet medical needs and growing disease awareness. In order to sustain performance, the pharmaceutical industry must evolve and improve product development and processing efficiencies. Therefore, efficient and cost-effective product development and processing are continually being explored to meet the challenge of not only reducing cost, but also the risk of product recalls. In the last few decades, much importance has been given to the use of polymers in pharmaceutical systems. Huge opportunities in the design, synthesis and modification of the physical and chemical properties of polymers have made them the most rapidly growing group of materials with great importance and possible applications in pharmacy, medicine and cosmetology. Polymeric materials having biomedical applications can be classified into different groups depending upon the application. For example, they are generally divided into two major groups according to use: those employed in prosthetic devices such as cardiovascular and orthopedic prostheses; and those employed as therapeutic systems such as drug carriers. Among the prosthetic systems, polymeric materials can be used as coatings or as cemented prostheses. Some of the major advantages in using polymeric materials for biomedical applications are their flexibility, biocompatibility, the possibility of tailoring their mechanical properties and their ability to incorporate therapeutic agents into their matrix in order to allow drug administration at a specific site.

Both natural and man-made polymers have been widely utilized as tablet binders and filler-binders in the pharmaceutical industry. The physico-chemical and mechanical properties such as particle size, shape and deformation behavior of polymeric binders are key to their effective use. Polymeric membranes are also becoming increasingly important in the field of separation processes in the pharmaceutical industry and artificial organs. Some polymers are obtained from natural sources (natural polymer) and then chemically modified for various applications, while others are chemically synthesized (synthetic polymer). Polymeric membranes can be fabricated in different configurations, such as flat sheet, tubular hollow fibers, nanofibers, etc., via different techniques. Since the performance of the membrane is largely controlled by its surface (active layer), the design of membrane surface and its characterization, either by chemistry or morphology, are extremely important. Hence, emphasis is being placed on the membrane surface. Hot-melt extrusion (HME) technique is used to create a dispersion of the active pharmaceutical ingredient (API) in a polymer matrix in order to achieve solubility enhancement, release rate modulation, mask taste, or to develop a new dosage form. However, polymers must fulfill a number of requirements in order to be suitable for HME processing. The relatively recent introduction of
HME in the pharmaceutical industry has opened new areas of applications for old and newly synthesized polymers, and enabled drug manufacturers to scale up the production of solid dispersions. A variety of chemically diverse polymers with different physico-chemical properties are available, which enable formulators to fine-tune the solid form of the extruded product by the selection of suitable polymer, drug-polymer ratio and operating conditions. Scientists in collaboration with pharmaceutical industries are extensively developing new classes of pharmaceutical materials. This second volume of *Handbook of Polymers for Pharmaceutical Technologies* is primarily focused on the pharmaceutical polymers and deals with the processing and applications of these polymers. Numerous critical issues and suggestions for future work are comprehensively discussed in this book with the hope that it will provide a deep insight into the state-of-art of pharmaceutical polymers. The prime topics extensively described in this book include: particle engineering of polymers into multifunctional interactive excipients; the art of making polymeric membranes; pharmaceutical applications of polymeric membranes; development of microstructuring technologies of polycarbonate for establishing advanced cell cultivation systems; *in-situ* gelling thermosensitive hydrogels for protein delivery applications; polymers as formulation excipients for the hot-melt extrusion processing of pharmaceuticals; poly lactic-co-glycolic acid (PLGA) copolymer and its pharmaceutical application; application of PVC in construction of ion-selective electrodes for pharmaceutical analysis; a review of polymer electrodes for nonsteroidal, anti-inflammatory drugs; synthesis and preservation of polymer nanoparticles for pharmaceutical applications; pharmaceutical applications of maleic anhydride/acid copolymers; stimuli-sensitive polymeric nanomedicines for cancer imaging and therapy; artificial intelligence techniques used for modeling of processes involving polymers for pharmaceutical applications; a review of current pharmaceutical applications of polysiloxanes (silicones); polymer-doped nano-optical sensors for pharmaceutical analysis; and finally, polymer-based augmentation of immunosuppressive formulations – application of polymer technology in transplant medicine.

Several critical issues and suggestions for future work are comprehensively discussed in this book with the hope that it will provide a deep insight into the state-of-art of processing and applications of pharmaceutical polymers. We would like to thank the publisher and Martin Scrivener for their invaluable help in the organization of the editing process. Finally, we would like to thank our parents for their continuous encouragement and support.

Vijay Kumar Thakur, PhD
Washington State University, USA

Manju Kumari Thakur, MSc, MPhil, PhD
Himachal Pradesh University, Shimla, India

May 2015
About the Editors

Vijay Kumar Thakur, Ph.D.

Email: vijayisu@hotmail.com

Dr. Vijay Kumar Thakur has been working as Research Faculty (staff scientist) in the School of Mechanical and Materials Engineering at Washington State University, USA, since September 2013. His former appointments include being a research scientist in Temasek Laboratories at Nanyang Technological University, Singapore, and a visiting research fellow in the Department of Chemical and Materials Engineering at LHU-Taiwan. His research interests include the synthesis and processing of biobased polymers, nanomaterials, polymer micro/nanocomposites, nanoelectronic materials, novel high dielectric constant materials, electrochromic materials for energy storage, green synthesis of nanomaterials, and surface functionalization of polymers/nanomaterials. He did his post doctorate in Materials Science at Iowa State University and his PhD in Polymer Science (2009) at the National Institute of Technology. In his academic career, he has published more than 80 SCI journal research articles in the field of polymers/materials science and holds one United States patent. He has also published 15 books and thirty book chapters on the advanced state-of-the-art of polymers/materials science with numerous publishers.

Manju Kumari Thakur, M.Sc., M.Phil., Ph.D.

Email: shandilyamn@gmail.com

Dr. Manju Kumar Thakur has been working as an Assistant Professor of Chemistry at the Division of Chemistry, Govt. Degree College Sarkaghat Himachal Pradesh University, Shimla, India, since June 2010. She received her BSc in Chemistry, Botany and Zoology; MSc, MPhil in Organic Chemistry and PhD in Polymer Chemistry from the Chemistry Department at Himachal Pradesh University, Shimla, India. She has rich experience in the field of organic chemistry, biopolymers, composites/nanocomposites, hydrogels, applications of hydrogels in the removal of toxic heavy metal ions, drug delivery, etc. She has published more than 30 research papers in several international journals, co-authored five books and has also published 25 book chapters in the field of polymeric materials.
Particle Engineering of Polymers into Multifunctional Interactive Excipients

Sharad Mangal, Ian Larson, Felix Meiser and David AV Morton*

Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia

Abstract
Both natural and man-made polymers are widely utilized as tablet binders and filler-binders. The physicochemical and mechanical properties such as particle size, shape and deformation behavior of polymeric binders are key in their effective use. Many such binders are applied as solution in a wet granulation process, which facilitate its facile distribution leading to improved effectiveness as a binder. Direct compression and dry granulation are recognized as routes with reduced process complexity and cost. These processes require a binder to be employed in a dry form and it can be more difficult to obtain a homogeneous distribution of a dry binder in a powder formulation. Therefore, these binders are required in high proportions to generate mechanically strong tablets. At lower proportions, they often are insufficient to create mechanically strong tablets. Recently, innovations in the generation of co-processed excipients have been proposed. Co-processing is a popular means of improving excipient functionalities, where two or more existing excipients are combined by some suitable means to generate new structures with improved and often combined functionalities as compared to the component excipients. Particle size reduction is known to improve the binder properties of an excipient, but also makes it highly cohesive and hard to blend. Via particle engineering, surface structure of smaller particles can be tailored to optimize the cohesive-adhesive balance (CAB) of the powder, allowing formation of interactive mixtures. This chapter reviews recent efforts to engineer surface-modified polymeric micro-excipient structures with the inherent ability to not only form an interactive mixture efficiently and provide flow enhancement, but also to create harder tablets at lower proportions. Hence, this approach represents a potential novel multifunctional prototype polymeric micro-excipient for direct compression and dry granulation processes.

Keywords: Particle engineering, powder technology, interactive mixtures, tablets, binder, multifunctional excipients

1.1 Introduction
The modern pharmaceutical market is under relentless pressure from slowing new product approvals, patent expirations and global competition. In addition, new opportunities
Handbook of Polymers for Pharmaceutical Technologies

exist with an evolving patient population, numerous unmet medical needs and growing disease awareness. The pharmaceutical industry must evolve and improve product developing and manufacturing efficiencies for sustainable performance. Efficient and cost-effective product development and manufacturing are continually being explored to meet the challenge of not only reducing cost but also reducing the risk of product recalls.

Tablets are the most commonly used pharmaceutical preparation, accounting for more than 80% of all dosage forms administered [1]. The principal reasons for their continued popularity include convenience of administration and patient preference, high-precision dosing, stability and cost effectiveness [2].

Tablets are typically manufactured by applying pressure to active pharmaceutical ingredient(s) (APIs) and excipients powder blends in a die using a punch, which compresses the powder into a coherent compact. Under compression, bonds are established between the particles, thus conferring a certain mechanical strength to the compact. A formulation must exhibit good flow and high compactability for an API to be transformed into tablets of satisfactory quality. Good flow is necessary to ascertain the rapid and reproducible filling of powder into the die to minimize weight variation; while high compactability is required to ensure that the tablets are sufficiently strong to withstand handling during manufacturing and transportation [3].

The majority of API(s) lack the requisite flow and compactability for direct tablet manufacturing [4]. Therefore, the flow and compactability of the API(s) need to be adjusted to ensure formation of high-quality tablets. Typically, the flow and compactability of a tablet formulation is improved by a granulation step (wet or dry granulation) in which the particles of API(s) and excipients are agglomerated into larger particulate structures referred to as granules. Wet granulation of the input materials can improve the flow properties for further processing and can create non-segregating blends of powder ingredients [5]. However, it involves multiple manufacturing steps, which can add significant time and cost to the process. Conversely, direct compression

Figure 1.1 The various steps involved in wet granulation, dry granulation and direct compression tablet manufacturing. Adapted and modified from [6].
merely involves mixing of API(s) and excipients followed by immediate compression (Figure 1.1). Therefore, direct compression is an attractive manufacturing process, with fewer steps, for reducing cost and improving manufacturing output.

### 1.2 Polymers as Excipients

Excipients form an integral part of any pharmaceutical tablet formulation. They play the fundamental role in creation of robust tablet formulations by carrying out an extensive range of functions such as fillers, binders, disintegrants, lubricants, glidants, coating agent and anti-adherents. Currently, a wide range of polymeric materials are used as excipients [6,7], and polymers are the largest overall consumed product segment for the global excipients market, accounting for over 30% [8]. The excipient market is expected to grow at an annual rate of 5.2% from 2013 to 2018, to reach around $7.35 billion by 2018 [8].

Polymers of natural, semi-synthetic and synthetic origin are used especially in the role of binder and filler-binder (see Table 1.1). Polymeric excipients are popular as they can be tailored for many applications by altering their chain length and by chemical functionalization. This can achieve new materials with various optimized physico-chemical and mechanical properties for such specific applications.

<table>
<thead>
<tr>
<th>Polymeric Excipient</th>
<th>Source</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zein</td>
<td>Extracted from corn gluten</td>
<td>Binder, Coating agent</td>
</tr>
<tr>
<td>Cellulose</td>
<td>Extracted from fibrous plant material</td>
<td>Diluent, Disintegrant</td>
</tr>
<tr>
<td>Alginic acid</td>
<td>Extracted from various species of brown seaweed</td>
<td>Binder, Disintegrant</td>
</tr>
<tr>
<td>Acacia</td>
<td>Exudate from the stems and branches of Acacia Senegal</td>
<td>Binder</td>
</tr>
<tr>
<td>Guar gum</td>
<td>Extracted from the endosperm of the Cyamopsis tetragonolobus</td>
<td>Binder, Disintegrant</td>
</tr>
<tr>
<td>Inulin</td>
<td>Extracted from the tubers of Dahlia variabilis, Helianthus</td>
<td>Binder</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Extracted from shells of crustaceans such as shrimps and crabs</td>
<td>Binder, Coating agent</td>
</tr>
</tbody>
</table>

Table 1.1 List of polymeric excipients, their source and functionalities. This table is compiled from the information given in the *Handbook of Pharmaceutical Excipients* [9].

(Continued)
### Table 1.1 (Cont.)

<table>
<thead>
<tr>
<th>Polymeric Excipient</th>
<th>Source</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Semi-synthetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>By neutralized alginic acid with sodium bicarbonate</td>
<td>Binder, Disintegrant</td>
</tr>
<tr>
<td>Calcium alginate</td>
<td>By treating sodium alginate with calcium salts</td>
<td>Disintegrant</td>
</tr>
<tr>
<td>Methyl cellulose</td>
<td>By treating wood pulp with alkali followed by methylation</td>
<td>Binder, Disintegrant, Coating agent</td>
</tr>
<tr>
<td>Carboxymethyl cellulose sodium</td>
<td>By treating wood pulp with alkali followed by reaction with sodium monochloroacetate</td>
<td>Binder, Disintegrant</td>
</tr>
<tr>
<td>Carboxymethyl cellulose calcium</td>
<td>By treating wood pulp with alkali followed by methylation and then converting to calcium salt</td>
<td>Disintegrant</td>
</tr>
<tr>
<td>Cellulose acetate</td>
<td>By treating cellulose with acid catalysis and acetic anhydride</td>
<td>Diluent, Coating agent</td>
</tr>
<tr>
<td>Cellulose acetate phthalate</td>
<td>By reacting cellulose acetate with phthalic anhydride</td>
<td>Coating agent</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>By controlled hydrolysis of cellulose with mineral acid</td>
<td>Binder, Diluent, Disintegrant</td>
</tr>
<tr>
<td>Hydroxypropylmethyl cellulose</td>
<td>By treating alkali cellulose with chloromethane and propylene oxide</td>
<td>Binder, Coating agent</td>
</tr>
<tr>
<td>Hydroxypropylmethyl cellulose acetate succinate</td>
<td>By the esterification of hydroxypropylmethyl cellulose with acetic anhydride and succinic anhydride</td>
<td>Film coating, Enteric coating</td>
</tr>
<tr>
<td>Hydroxypropylmethyl cellulose phthalate</td>
<td>By the esterification of hydroxypropylmethyl cellulose with phthalic anhydride</td>
<td>Enteric coating</td>
</tr>
<tr>
<td>Ethylcellulose</td>
<td>By ethylation of the alkali cellulose with chloroethane</td>
<td>Binder, Diluent, Coating agent</td>
</tr>
<tr>
<td>Low substituted-hydroxypropyl cellulose</td>
<td>By reacting alkaline cellulose with propylene oxide</td>
<td>Binder, Disintegrant</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>By ethylation of the alkali cellulose with chloroethane</td>
<td>Binder, Diluent, Coating agent</td>
</tr>
<tr>
<td>Hydroxyethyl cellulose</td>
<td>By reacting alkali cellulose with ethylene oxide</td>
<td>Binder, Coating agent</td>
</tr>
</tbody>
</table>

(Continued)
### Table 1.1 (Cont.)

<table>
<thead>
<tr>
<th>Polymeric Excipient</th>
<th>Source</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maltodextrin</strong></td>
<td>By heating starch with acid and/or enzymes</td>
<td>Binder, Diluent, Coating agent</td>
</tr>
<tr>
<td><strong>Sodium starch glycolate</strong></td>
<td>By reacting starch with sodium chloroacetate followed by acidic neutralization</td>
<td>Disintegrant</td>
</tr>
<tr>
<td><strong>Hydroxypropyl starch</strong></td>
<td>By reacting starch with propylene oxide in the presence of alkali</td>
<td>Binder, Disintegrant</td>
</tr>
<tr>
<td><strong>Dextrates</strong></td>
<td>By controlled enzymatic hydrolysis of starch</td>
<td>Binder, Diluent</td>
</tr>
<tr>
<td><strong>Dextrin</strong></td>
<td>By the incomplete hydrolysis of starch</td>
<td>Binder, Diluent</td>
</tr>
<tr>
<td><strong>Lactose monohydrate</strong></td>
<td>By crystallization from supersaturated lactose solutions</td>
<td>Binder, Diluent</td>
</tr>
<tr>
<td><strong>Spray-dried lactose</strong></td>
<td>By spray drying a suspension of α-lactose monohydrate</td>
<td>Binder, Diluent</td>
</tr>
<tr>
<td><strong>Pregelatinized starch</strong></td>
<td>By heating an aqueous slurry of starch with salts or bases and surfactants</td>
<td>Binder, Diluent, Disintegrant</td>
</tr>
</tbody>
</table>

### Synthetic

<table>
<thead>
<tr>
<th><strong>Poloxamer</strong></th>
<th>By reacting propylene oxide with propylene glycol followed by addition of ethylene oxide</th>
<th>Lubricant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyethylene oxide</strong></td>
<td>By polymerization of ethylene oxide</td>
<td>Binder, Coating agent</td>
</tr>
<tr>
<td><strong>Polyethylene glycol</strong></td>
<td>By reacting ethylene oxide and water under pressure</td>
<td>Coating agent</td>
</tr>
<tr>
<td><strong>Polyvinyl acetate phthalate</strong></td>
<td>By reacting phthalic anhydride, sodium acetate, and a partially hydrolyzed polyvinyl alcohol</td>
<td>Coating agent</td>
</tr>
<tr>
<td><strong>Polyvinyl alcohol</strong></td>
<td>By hydrolyzing of polyvinyl acetate</td>
<td>Coating agent, Lubricant</td>
</tr>
<tr>
<td><strong>Polyvinylpyrrolidone (PVP)</strong></td>
<td>By reacting acetylene and formaldehyde followed by hydrogenation to form butyrolactone and reacting it with ammonia</td>
<td>Binder, Disintegrant</td>
</tr>
<tr>
<td><strong>Copovidone PVP/VA</strong></td>
<td>By free-radical polymerization of vinylpyrrolidone and vinyl acetate in a ratio of 6 : 4</td>
<td>Binder</td>
</tr>
<tr>
<td><strong>Crospovidone</strong></td>
<td>By polymerizing vinylpyrrolidone</td>
<td>Disintegrant</td>
</tr>
<tr>
<td><strong>Polymethcrylate</strong></td>
<td>By the polymerization of acrylic and methacrylic acids</td>
<td>Binder, Diluent</td>
</tr>
<tr>
<td><strong>Carbomer</strong></td>
<td>By crosslinking acrylic acid</td>
<td>Binder</td>
</tr>
</tbody>
</table>
In wet and dry granulation, the properties of the individual API and excipients particles are significantly altered by their agglomeration into granules. Such structures can hide the undesirable properties of individual components (of both API(s) and excipients) of the blend. In wet granulation, a binder can be sprayed into the powder as a solution, and so is easily distributed onto the particle interfaces, so facilitating the binding action. For dry granulation, a binder must be added in dry particulate form. Tablet formulations involving a granulation step can be less sensitive to binder excipient performance and variation than for direct compression. In direct compression, the original particle's structure remains largely unaltered, so individual particle properties (API(s) and excipient) have a more critical and direct impact on formulation properties, such as flow and compactability, and decide the success or otherwise of tablet formation. Consequently, excipients, particularly filler-binders, which play a critical role in direct compression, can be very different in nature to the excipients used in wet/dry granulation. Therefore, there is a great interest in generating ready-made multifunctional filler-binders with improved flowability and binder activity (API uptake capacity) for robust tablet manufacturing using direct compression.

The main focus of this chapter is to examine the critical material properties that influence polymeric binder and filler-binder performance of directly compressible excipients, and how these material properties can be optimized and integrated with other functionalities via particle engineering.

1.3 Material Properties Affecting Binder Activity

The material properties such as particle size and deformation mechanism (elasticity-plasticity and fragmentation) and compressibility have been identified as affecting the ability of a binder to create strong tablets [10–14].

1.3.1 Particle Size

Previous studies have indicated that the optimal amount of binder corresponds to that providing a surface area ratio of unity to the corresponding API, i.e., the amount needed to form a monoparticulate layer of binder particles around the API particles [10]. This suggests that if the particle size of the binder and API is similar (as desirable in direct compression powder blends to avoid segregation), higher proportions will be required to achieve monoparticulate layer of binder around the API particles. However, if the binder particles are smaller than the API, lower proportions of binder particles can form a monoparticulate layer. This concept is illustrated in Figure 1.2. The limited efficacy of the binders in direct compression formulations (and also in dry granulation) may partly be attributed to this concept, i.e., that the binder added in its dry state can be more difficult to disperse homogeneously than when added as a solution [10]. Other physical material properties such as shape and surface energy have also been demonstrated to have a significant impact on the tableting performance of the excipients [15–18].
Polymers are typically considered to be as excellent binders owing to their good bonding properties [6,7]. The polymers such as PVP and PEG are also available in a variety of molecular weights, and their deformation behavior under compression can be altered by altering their molecular weight [14]. However, the compaction of polymers is greatly affected by the speed of tableting. This has been attributed to the high elasticity of the excipients at high rates of strain [19]. Large stress relaxation yields porous and consequently weak tablets. Figure 1.3 schematically depicts relations between stress and strain for several materials. For a plastic solid, stress (σ) is directly proportional to deformation (strain, γ):

\[ \sigma = E \gamma \]  

(1.1)

The proportionality constant (E) is the elastic or Young’s modulus [20]. It is a measure of the stiffness or resistance against deformation. The material behaves elastically up to the yield point \( (P_y) \) at which the stress is called yield stress \( (\sigma_y) \). Beyond this point the material behaves as a plastic, rather than as an elastic solid. Brittle materials can be distinguished from plastic materials by the absence of the \( P_y \); stress increases proportionally with strain until the material breaks.

Figure 1.2 Effect of particle size on surface coverage of API particles with binder.

1.3.2 Deformation Mechanisms

Figure 1.3 Stress-strain behavior of brittle, plastic and rubbers. The point \( P_y \) indicates the yield point with corresponding yield strength. Adapted and modified from [21].
1.3.3 Glass Transition Temperature (Tg)

The amount of energy stored during densification is manifested as the stress relaxation propensity of the material. Large stress relaxation yields porous and consequently weak tablets. At a high temperature difference (i.e., tableting temperature is much lower than the Tg), the polymer exhibits higher resistance to deformation and the amount of stored energy is large, resulting in highly porous and weak tablets. The Tg of amorphous polymeric materials appears to be a critical parameter with respect to mechanical properties (i.e., plastic/elastic character) of polymers [20]. At temperatures substantially below the Tg, an amorphous material is in the glassy state and its Young’s modulus is high, resulting in greater resistance to deformation. However, at temperature close to the Tg a material undergoes the change from a hard glassy form to a more plastic structure or a viscous fluid and the resistance against deformation decreases dramatically. This change is related to the onset of a certain degree of movement in the main chain and the rotation of side segments. Consequently, the performance of polymeric excipients during processes such as compaction strongly depends on their Tg [21].

It was reported that the compaction at a temperature of about 20 K under Tg yields circumstances for which the amount of stored energy has a minimum [21]. The Tg of the material depends on its chemical structure, the presence of a plasticizer and, in the case of polymers, on the molecular weight [22]. Therefore, it may be expected that using polymers with lower Tg (preferably near room temperature) would be advantageous for improved binder activity.

1.4 Strategies for Improving Polymeric Filler-Binder Performance for Direct Compression

The development of excipients of new chemical composition requires extensive toxicology tests. This is a costly proposition and so, in the last three decades, only a few such new excipients have been introduced in the market [23]. Therefore, improved filler-binders have mainly been generated via physical manipulation of existing excipient materials, i.e., as the physical mixture of GRAS (generally regarded as safe) materials [24].

Particle size manipulation is a commonly used strategy to modify polymeric filler-binder performance. For example, microcrystalline cellulose, one of the most commonly used polymeric multifunctional excipients, is commercially available in a variety of particle size ranges [25]. In addition, a wide range of multifunctional excipients are also available in different particle size grades (Table 1.2).

The main objective of excipient engineering is to improve both flow and binder activity of the excipients. Flow and compactability both depend on particle size, and these characteristics often compete, making it difficult to achieve an optimum excipient performance [30]. For example, large particle size is typically associated with improved flow (Table 1.3). However, a smaller particle size is associated with improved compactability due to an increase in the surface area except for brittle materials (as shown in Figure 1.2) [31–33]. Hence there is a fundamental contradiction in designing