Handbook of Polymers for Pharmaceutical Technologies
To my parents and teachers who helped me become what I am today.

Vijay Kumar Thakur
Contents

Preface xix

1 Bioactive Polysaccharides of Vegetable and Microbial Origins: An Overview

Giuseppina Tommonaro, Annarita Poli, Paola Di Donato,
Roberto Abbamondi Gennaro, Ilaria Finore and Barbara Nicolaus

1.1 Introduction 1
1.2 Anticarcinogenic Polysaccharides 3
  1.2.1 Microbial Sources 3
  1.2.2 Vegetable Sources 7
1.3 Anti-inflammatory/Immunostimulating Polysaccharides 8
  1.3.1 Microbial Sources 9
  1.3.2 Vegetable Sources 11
1.4 Antiviral Polysaccharides 13
  1.4.1 Microbial Sources 13
  1.4.2 Vegetable Sources 15
1.5 Antioxidant Polysaccharides 17
  1.5.1 Microbial Sources 17
  1.5.2 Vegetable Sources 19
1.6 Other Biotechnological Applications 21
1.7 Conclusions and Future Perspectives 23
Acknowledgments 23
Reference 24

2 Chitosan: An Emanating Polymeric Carrier for Drug Delivery

Priti Girotra and Shailendra Kumar Singh

2.1 Introduction 33
2.2 Preparation of Chitosan 34
2.3 Physicochemical Properties of Chitosan 35
2.4 Biological Activities of Chitosan 36
  2.4.1 Antimicrobial Activity 37
  2.4.2 Hypolipidemic and Hypocholesterolemic Activity 37
  2.4.3 Immunostimulatory Activity 37
  2.4.4 Anti-Cancer Activity 38
  2.4.5 Antioxidant Activity 38
  2.4.6 Anti-Inflammatory Activity 38
2.4.7 Burn and Wound Healing Promoter 38
2.4.8 Antiulcer Potential 39
2.5 Pharmaceutical Applications of Chitosan 39
  2.5.1 Mucoadhesive Drug Delivery Systems 44
    2.5.1.1 Ophthalmic Drug Delivery 44
    2.5.1.2 Buccal and Sublingual Drug Delivery 44
    2.5.1.3 Nasal Drug Delivery 44
    2.5.1.4 Gastro-Retentive Drug Delivery 45
    2.5.1.5 Intravesicle Drug Delivery 45
    2.5.1.6 Vaginal Drug Delivery 45
    2.5.1.7 Rectal Drug Delivery 45
  2.5.2 Targeted Drug Delivery 46
    2.5.2.1 Brain Targeting 46
    2.5.2.2 Colon Targeted Drug Delivery 46
  2.5.3 Parenteral Drug Delivery 46
  2.5.4 Transdermal Drug Delivery 46
  2.5.5 Topical Drug Delivery 47
  2.5.6 Proteins and Peptides Drug Delivery 47
  2.5.7 Vaccine Delivery 47
  2.5.8 Gene Delivery 48
  2.5.9 Pharmaceutical Excipient in Tablets 48
  2.5.10 Miscellaneous Applications 48
    2.5.10.1 Wetting Agent 48
    2.5.10.2 Coating Agent 49
    2.5.10.3 Hair/Skin Care Cosmetics 49
    2.5.10.4 Water Treatment 49
    2.5.10.5 Food Industry Applications 49
    2.5.10.6 Biomedical Applications 49
  2.6 Functionalization of Chitosan 49
  2.7 Conclusion and Future Perspectives 49
  Reference 51

3 Fungi as Sources of Polysaccharides for Pharmaceutical and Biomedical Applications 61
  Filomena Freitas, Christophe Roca and Maria A. M. Reis 61
  3.1 Introduction 61
  3.2 The Fungal Cell 62
    3.2.1 Cell Wall Structure 62
    3.2.2 Capsular and Extracellular Polysaccharides 63
    3.2.3 Polysaccharides Biosynthesis in Fungi 66
      3.2.3.1 Carbohydrate Synthesis 66
      3.2.3.2 Carbohydrate Polymerization 68
      3.2.3.3 Polysaccharide Secretion 69
  3.3 Polysaccharides Produced by Fungi 69
    3.3.1 Glucans 69
    3.3.2 Chitin, Chitosan and Their Complexes 73
3.3.3 Mannan-Containing Polysaccharides 75
3.3.4 Other Polysaccharides 77
3.4 Production and Extraction of Polysaccharides from Fungi 77
3.4.1 Fungal Sources and Cultivation Conditions 77
3.4.2 Fractionation and Isolation of Cell Wall Polysaccharides 79
3.4.3 Extraction of Extracellular Polysaccharides 80
3.5 Fungal Polysaccharides in Biomedical and Pharmaceutical Applications 81
3.5.1 Bioactive Compounds 82
  3.5.1.1 Immunomodulating Activity 82
  3.5.1.2 Antimicrobial and Antiviral Properties 84
  3.5.1.3 Anticancer Effect 84
  3.5.1.4 Antioxidants 85
  3.5.1.5 Other Biological Activities 86
3.5.2 Excipients 86
3.5.3 Drug Delivery Agents 87
3.6 Commercial Exploitation of Fungal Polysaccharides in Biomedical and Pharmaceutical Applications 89
3.7 Conclusion and Future Perspective 91
Reference 91

4 Environmentally Responsive Chitosan-based Nanocarriers (CBNs) 105
Ankit Jain and Sanjay K. Jain
4.1 Introduction 105
4.2 Graft Copolymerized CBNs 107
4.3 pH-Sensitive CBNs 109
4.4 Thermosensitive CBNs 111
4.5 pH-Sensitive and Thermosensitive CBNs 112
4.6 pH- and Ionic-Sensitive CBNs 113
4.7 Photosensitive CBNs 114
4.8 Electrical-Sensitive CBNs 115
4.9 Magneto-Responsive CBNs 115
4.10 Chemo-Sensitive CBNs 115
4.11 Biodegradation of Chitosan and Its Derivatives 116
  4.11.1 Enzymatic Degradation 116
  4.11.2 Chemical Degradation 118
  4.11.3 In-Vitro Biodegradation 119
  4.11.4 In-Vivo Biodegradation of CBNs 119
4.12 Toxicity of CBNs 120
4.13 Conclusions and Future Perspectives 120
References 120

5 Biomass Derived and Biomass Inspired Polymers in Pharmaceutical Applications 127
Elisavet D. Bartzoka, Claudia Crestini and Heiko Lange
5.1 Introduction 127
5.2 Biodegradable Polymers in Biomedical Applications – Relevant Aspects 129
5.3 Biodegradable Natural Polymers in Pharmaceutical Applications 133
5.3.1 Polyethers 133
5.3.1.1 Cellulose 133
5.3.1.2 Hemicelluloses and Other Pectic Substances 137
5.3.1.3 Cyclodextrin 145
5.3.1.4 Alginate 147
5.3.1.5 Carrageenan 149
5.3.1.6 Chitin and Chitosan 149
5.3.1.7 Hyaluronic Acid 151
5.3.1.8 Microbial Exopolysaccharides 152
5.3.1.9 Natural Gums 155
5.3.1.10 Poly(ethylene glycol) 157
5.3.2 Polyesters 157
5.3.2.1 Polyhydroxyalkanoates (PHA) 157
5.3.2.2 Hydroxyapatite 159
5.3.2.3 Lactide Polymers 160
5.3.2.4 Glycolides 161
5.3.2.5 Lactide-Glycolide Copolymers 161
5.3.2.6 Poly(orthoesters) 162
5.3.2.7 Poly(ε-caprolactone) 163
5.3.3 Polyamides 163
5.3.3.1 Collagen 163
5.3.3.2 Gelatin 165
5.3.3.3 Albumin 165
5.3.3.4 Fibrin 166
5.3.3.5 Synthetic Polyamides 167
5.3.4 Polyanhydrides 168
5.3.5 Polyurethanes 170
5.3.6 Polymers with Mixed Linkage Motifs 170
5.3.6.1 Polydioxanone 170
5.3.6.2 Polyfumarates 171
5.3.6.3 Lignin 172
5.4 Micro- and Nanocrystalline Natural Polymers and Fibrils – General Regulative Considerations 175
5.5 Concluding Remarks and Outlook 176
Reference 177

6 Modification of Cyclodextrin for Improvement of Complexation and Formulation Properties 205
Tapan K. Dash and V. Badireenath Konkimalla
Abbreviations 205
6.1 Introduction 206
6.2 Cyclodextrin and Its Degradation 206
6.3 Complexation by CDs and Release 207
6.4 Modifications and Scope with Respect to Pharmaceutical Application 208
6.4.1 Modification to Improve Complexation Efficacy 209
   6.4.1.1 Chemical Modification 209
   6.4.1.2 Ionic Modification or Salt Formation 210
   6.4.1.3 Environmental Modification 211
6.4.2 Modification for Improvement of Formulation Properties 213
   6.4.2.1 Modulation of Release and Formulations 213
   6.4.2.2 Targeting Features 216
   6.4.2.3 Fluorescence and Its Attenuation 217
6.5 Concluding Remarks 218
Acknowledgements 218
Reference 218

7 Cellulose-, Ethylene Oxide- and Acrylic-Based Polymers in Assembled Module Technology (Dome Matrix®) 225
Camillo Benetti, Paolo Colombo and Tin Wui Wong
7.1 Dome Matrix® Technology 225
   7.1.1 Advantages as Drug Carrier 227
   7.1.2 Preparation Methods 227
7.2 Polymers for Controlled Drug Release 228
7.3 Cellulose Derivatives 230
7.4 Acrylic Acid Polymers 232
7.5 Polymethacrylates 234
7.6 Polyethylene Oxide 236
7.7 Conclusions 237
Acknowledgments 237
Reference 237

8 Structured Biodegradable Polymers for Drug Delivery 243
Nishi Mody, Udita Agrawal, Rajeev Sharma and S. P. Vyas
8.1 Introduction 243
   8.1.1 Advantages of Biodegradable Polymers 244
   8.1.2 Disadvantages of Biodegradable Polymers 244
   8.1.3 Factors Governing Biodegradation of Polymers 244
      8.1.3.1 Effect of Polymer Structure 247
      8.1.3.2 Effect of Polymer Morphology 247
      8.1.3.3 Effect of Molecular Weight 248
      8.1.3.4 Effect of Physical Properties 248
8.2 Classification 249
   8.2.1 Polymer Classification 249
      8.2.1.1 On the Basis of Origin 249
      8.2.1.2 On the Basis of Polymerization 249
      8.2.1.3 On the Basis of Degradation 249
      8.2.1.4 On the Basis of Interaction of Polymer with Water 249
      8.2.1.5 On the Basis of Type of Degradation 250
      8.2.1.6 Smart Polymers 250
   8.2.2 Characterization of Polymers 253
8.3 Degradation Processes in Biodegradable Polymers 254
  8.3.1 Mechanism of Biodegradation 254
  8.3.2 Hydrolytically Degradable Polymers as Biomaterials 255
    8.3.2.1 Polyanhydrides 256
    8.3.2.2 Poly(Alkyl Cyanoacrylate)s 257
    8.3.2.3 Polylphosphoesters 257
  8.3.3 Enzymatically Degradable Polymers 257
    8.3.3.1 Proteins and Poly(Amino Acid)s 258
    8.3.3.2 Natural Poly(Amino Acid)s 258
    8.3.3.3 Synthetic Poly(Amino Acid)s 259
    8.3.3.4 Albumin 259
    8.3.3.5 Polysaccharides 259
8.4 Responsive Stimuli-Sensitive Polymers 260
  8.4.1 pH-Sensitive Polymers 262
    8.4.1.1 Applications 263
  8.4.2 Temperature Responsive Polymers 269
  8.4.3 Polymers with Dual Stimuli Responsiveness 270
  8.4.4 Phase-Sensitive Smart Polymers 270
  8.4.5 Light-Sensitive Smart Polymers 271
8.5 Conclusion and Future Prospects 271
References 271

9 Current State of the Potential Use of Chitosan as Pharmaceutical Excipient 275
  A. Raquel Madureira, Bruno Sarmento and Manuela Pintado
9.1 The World of Pharmaceutical Excipients 275
9.2 Chitosan 276
9.3 Activities Found for Chitosan 277
  9.3.1 Antimicrobial Activity 278
  9.3.2 Antioxidant Activity 279
  9.3.3 Anti-Inflammatory Activity 279
  9.3.4 Haemostatic Activity 279
  9.3.5 Antitumor Activity 280
  9.3.6 Hypocholesterolemic Activity 280
9.4 Properties of Chitosan 280
  9.4.1 Viscosity 280
  9.4.2 Biocytocompatibility 281
  9.4.3 Biodegradation 281
9.5 Applications as a Pharmaceutical Excipient 282
  9.5.1 Tablets 282
  9.5.2 Chitosan Microspheres/Nanoparticles 284
  9.5.3 Drug Delivery 284
  9.5.4 Tissue Engineering Agent 288
9.6 Conclusion 289
References 290
10 Modification of Gums: Synthesis Techniques and Pharmaceutical Benefits
Vikas Rana, Sunil Kamboj, Radhika Sharma and Kuldeep Singh

10.1 Introduction

10.2 Synthesis of Modified Gums
10.2.1 Gum Modification Using Chemical Reaction
   10.2.1.1 Carboxymethylation
   10.2.1.2 Carbamoylation
   10.2.1.3 Sulfation
   10.2.1.4 Phosphorylation
   10.2.1.5 Thiolation
   10.2.1.6 Gums Grafted with Acrylic Acid or Its Derivatives

10.2.2 Modification of Gums via Crosslinking Technique
   10.2.2.1 Crosslinking with Glutaraldehyde Group
   10.2.2.2 Phosphate Crosslinking of Natural Gums
   10.2.2.3 Crosslinking with Ions
   10.2.2.4 Crosslinking with Epichlorohydrin
   10.2.2.5 Mechanism of Crosslinking: Modification of Gums
   10.2.2.6 Crosslinker Interaction Chemistry

10.3 Characterization
   10.3.1 Spectral Attributes
      10.3.1.1 X-ray Powder Diffraction (XpRD)
      10.3.1.2 Nuclear Magnetic Resonance (NMR)
      10.3.1.3 Fourier Transform Infrared Spectroscopy (FTIR)
   10.3.2 Thermal Attributes
   10.3.3 Scanning Electron Microscopy (SEM)
   10.3.4 Rheology
   10.3.5 Average Molecular Weight

10.4 Pharmaceutical Applications of Modified Gums
   10.4.1 Tablet Formulations
   10.4.2 Mucoadhesion-Based Delivery System
   10.4.3 Colon-Specific Drug Delivery System
   10.4.4 Nanoparticles
   10.4.5 Microspheres
   10.4.6 Hydrogels

10.5 Conclusion and Future Prospective

Reference

11 Biomaterials for Functional Applications in the Oral Cavity via Contemporary Multidimensional Science
V. Tamara Perchyonok, Vanessa Reher, Nicolaas Basson and Sias Grobler

11.1 Introduction

11.2 Free Radical Formation, Antioxidants and Relevance in Health
   11.2.1 Generation of Free Radicals in Living Systems
   11.2.2 Antioxidants
   11.2.3 Oxidative Stress
   11.2.4 Advantages of Free Radicals in the Cell
11.3  Oral Diseases: Oxidative Stress and the Role of Antioxidant Defenses in the Oral Cavity 369
11.3.1  Oral Mucosa and Design of Buccal Drug-Delivery Systems 370
11.4  Biomaterials and Intelligent Design of Functional Biomaterials 371
11.4.1  Hydrogels as Carrier Molecules 371
11.4.2  Chitosan Hydrogels as a Vehicle for Optimal Oral Drug-Delivery Systems 371
11.5  In-Vitro Developments of Free Radical Defense Mechanisms and Drug-Delivery Systems 372
11.6  Practical In-Vitro Applications of Chitosan-Based Functional Biomaterial Prototypes in Dentistry 375
11.6.1  Preventive Dentistry and Chitosan 375
11.6.2  Restorative Dentistry and Chitosan 377
11.6.2.1  Mechanistic Problems in Bonding to Dentin: Can it be overcome? 378
11.6.2.2  Development of Dentin Adhesives 379
11.6.2.3  Chitosan as a Bioadhesive Material 380
11.6.2.4  Chitosan and Derivatives as Bioactive Materials 381
11.6.2.5  Cytotoxic Effect of Chitosan Hydrogels 382
11.6.2.6  Antioxidant Containing Chitosan Hydrogels on Dentine Bond Strength: In-Vitro Approach 383
11.6.3  Antibiotics in Dentistry 390
11.6.3.1  A Brief Introduction 390
11.6.3.2  The Target: Microorganism 390
11.6.3.3  Functional Antibiotic/Antioxidant-Containing Chitosan Hydrogels 391
11.6.3.4  Insights into Performance of Antibiotic-Chitosan Gels as Effective Free Radical Defense Functional Material 396
11.6.4  Analgesics/Anti-Inflammatories in Dentistry 397
11.6.4.1  Pain and Antioxidants Control 397
11.6.4.2  Pain and Aspirin, Naproxen and Ibuprofen Containing Hydrogels: In-Vitro Studies 398
11.7  Conclusion 398
References 399

12  Role of Polymers in Ternary Drug Cyclodextrin Complexes 413
Renu Chadha, Madhu Bala, Parnika, Kunal Chadha and Maninder Karan
12.1  Introduction 413
12.2  Cyclodextrins (Cycloamyloses, Cyclomaltoses, Schardinger Dextrins) 414
12.2.1  Properties and Characteristics 414
12.2.2  Cyclodextrin Inclusion Complexes 415
12.3  Role of Biodegradable/Water-Soluble Polymers in Efficacy of Inclusion Complexes 416
12.3.1  Merits of Water-Soluble Polymers 417
12.3.2  Polymer-Cyclodextrin Interactions 418
13 Collagen-Based Materials for Pharmaceutical Applications 439
Daniela Pamfil, Manuela Tatiana Nistor and Cornelia Vasile

13.1 Introduction 439
13.2 Collagen Structure and Its Properties 440
  13.2.1 Structure 440
  13.2.2 Collagen Properties 440
13.3 Preparation Methods of Collagen-Based Biomaterials 443
  13.3.1 Blends Based on Collagen 444
  13.3.2 Chemical Analogous Modifications in Collagen Molecule 445
  13.3.3 Crosslinked Collagen-Based Structures 446
    13.3.3.1 Chemical Crosslinking of Collagen 446
    13.3.3.2 Collagen-Based Hydrogels 449
13.4 Pharmaceutical Applications of Collagen-Based Products 450
  13.4.1 Available Forms of Collagen-Based Materials in the Pharmaceutical Area 450
    13.4.1.1 Collagen Sponges for Wound Dressing 450
    13.4.1.2 Collagen-Based Hydrogels 452
    13.4.1.3 Nanoparticles/Nanospheres/Microspheres 452
    13.4.1.4 Liposome 452
    13.4.1.5 Collagen Membranes 452
  13.4.2 Collagen Wound Dressings 452
    13.4.2.1 Modifications in Collagen Structure for Wound Dressings Applications 454
    13.4.2.2 Drug Delivery Applied for Wound Dressings 454
  13.4.3 Collagen-Based Materials for Drug Delivery 455
13.5 Concluding Remarks and Future Perspectives 462
Acknowledgments 468
References 468

14 Natural Polysaccharides as Pharmaceutical Excipients 483
Nazire Deniz Yılmaz, Gülbanu Koyundereli Çilgi and Kenan Yılmaz

14.1 Introduction 483
14.2 Natural Polysaccharides 485
  14.2.1 Plant Polysaccharides 485
    14.2.1.1 Cellulose 485
    14.2.1.2 Hemicellulose 489
    14.2.1.3 Pectins 490
    14.2.1.4 Starches 492
14.2.1.5 Inulin 494
14.2.1.6 Gums and Mucilages 494
14.2.2 Seaweed Polysaccharides 502
14.2.2.1 Alginites 502
14.2.2.2 Carrageenans 503
14.2.2.3 Gum Agar 504
14.2.3 Microbial Polysaccharides 505
14.2.3.1 Xanthan Gum 505
14.2.3.2 Gellan Gum 507
14.2.3.3 Pullulan 508
14.2.4 Animal Polysaccharides 508
14.2.4.1 Chitin 508
14.2.4.2 Chitosan 509

14.3 Conclusion 510
Reference 510

15 Structure, Chemistry and Pharmaceutical Applications of Biodegradable Polymers 517

Mazhar Ul-Islam, Shaukat Khan, Muhammad Wajid Ullah and Joong Kon Park

15.1 Introduction 517
15.2 History of Polymers 518
15.3 Concept of Biodegradability 522
15.4 Biodegradable Polymers and Their Classification 522
15.4.1 Agropolymers 523
15.4.1.1 Starch-Based Polymers 523
15.4.1.2 Protein-Based Biodegradable Polymers 525
15.4.2 Biodegradable Polymers from Natural or Microbial Sources (Polyesters) 525
15.4.2.1 Microbial Polyesters 525
15.4.2.2 Bacterial Cellulose 525
15.4.2.3 Polyhydroxyalcanoates (PHAs) 526
15.4.2.4 Polylactic Acid (PLA) 526
15.4.3 Synthetic Biodegradable Polymers 528

15.5 Biocompatibility of Biodegradable Polymers 528
15.6 Biodegradable Polymers in Pharmaceutical Applications 530
15.6.1 Biodegradable Polymers in Drug Delivery 530
15.6.2 Limitations of Conventional Drug-Delivery Systems 530
15.6.3 Advantages of Using Biodegradable Polymers in Drug Delivery 531
15.6.4 Factors Affecting the Degradation of Polymers 531
15.6.5 Mechanisms of Action of Drug Release from Biodegradable Polymers 532

15.7 Development of Various Biodegradable Polymer Systems for Drug Delivery 532
15.7.1 Microparticles 533
15.7.2 Emulsions 534
15.7.3 Liposomes 534
15.7.4 Micelles 534
15.7.5 Injectibles 534
15.7.6 Elastomers 535
15.7.7 Hydrogels 535
15.8 Future Prospects 535
Acknowledgment  536
Reference 536

16 Preparation and Properties of Biopolymers: A Critical Review 541
Selvaraj Mohana Roopan, T. V. Surendra and G. Madhumitha
16.1 Introduction 541
16.2 Nature of Biopolymers 543
16.2.1 Life Cycle Assessment of Biopolymers 543
16.2.2 Life Cycle Assessment as a Method for Quantifying Environmental Impacts 543
16.3 Common Biopolymers 544
16.4 Biopolymers in Drug Development 545
16.4.1 Cellulose and Its Derivatives 546
16.4.2 Starch 546
16.4.3 Hemicellulose 547
16.4.4 Pectin 547
16.5 Biobased Polymers Production 548
16.5.1 Polylactic Acid 548
16.5.2 Polyhydroxy Alkanoates 549
16.5.3 Polybutylene Succinate 550
16.5.4 Biopolyethylene 550
16.6 Properties of Biopolymers 551
16.6.1 Physical Properties 551
16.6.2 Mechanical Properties 552
16.6.3 Specific Mechanical Properties 552
16.6.4 Fiber Mechanical Properties 553
16.6 Conclusion and Remarks 553
Acknowledgement  553
Reference 553

17 Engineering Biodegradable Polymers to Control Their Degradation and Optimize Their Use as Delivery and Theranostic Systems 557
Ilaria Armentano, Loredana Latterini, Nicoletta Rescignano, Luigi Tarpani, Elena Fortunati and Josè Maria Kenny
17.1 Introduction 557
17.2 Nanotechnology 559
17.3 Nanostructured Biodegradable Polymers 560
17.3.1 Biopolymeric Nanoparticles 560
17.3.2 BioPolymeric Hybrid Nanoparticles 561
  17.3.2.1 Magnetic Nanoshell 562
  17.3.2.2 Metal Nanoshell 563
17.3.3 Bionanocomposites 563
17.4 Design Strategies for Fluorescent Biodegradable Polymeric Systems 566
  17.4.1 Fluorescence Spectroscopy 566
  17.4.2 Generation and Detection of Fluorescence Signals on Nanostructured Polymers 567
  17.4.3 Fluorescence Imaging Methods 568
17.5 Conclusions and Perspectives 570
Reference 570

Index 577
At present, the world is facing serious problems related to environmental pollution and the preservation of the ecological system. A large portion of these problems have been attributed to nondegradable polymeric materials. Currently, various petrochemical and pharmaceutical industries are producing distinct synthetic polymers; after use, these materials are wasted, and this leads to environmental toxicity because of the nondegradable nature of these polymers. Despite their vital use in almost every field of life, nondegradable polymeric materials play a sound role in enhancing environmental and ecological disorders. The biggest challenge is the disposal of nondegradable polymer materials that are adversely affecting wild and marine life. Major hurdles are faced in the disposal of the long-lived materials employed in, for example, packaging, catering, engineering and medical applications, and this has resulted in the disturbance of the ecological system.

Biodegradable polymer materials are considered an important alternative and a possible solution to resolve these problems. Biodegradable materials are produced biologically (through microorganisms) as well as through chemical synthetic protocols. Over the last few decades, considerable interest has been devoted to biodegradable polymers because of the prominent role their use can play in addressing the serious environmental problems posed by nondegradable materials. These biodegradable polymers, especially those derived from natural resources, are rapidly replacing synthetic polymers. Biodegradable polymers are biomaterials intended to degrade in-vivo, either by enzymatic, microbial or chemical process, and produce biocompatible and/or nontoxic byproducts which are metabolized and converted into simpler compounds. Microorganisms and enzymes easily decompose these degradable materials into carbon dioxide, methane, water, inorganic compounds and biomass. These compounds are then redistributed via elemental cycles, including the carbon, nitrogen and sulphur cycles, followed by excretion by normal physiological pathways. Because of the advantage of being converted into nontoxic products within the biological system, these polymers have gained much attention from researchers.

Currently, an increasing number of applications have been developed in which biomaterials, including biodegradable polymers, can effectively offer a replacement for common synthetic nondegradable materials for pharmaceutical applications. In medical fields biodegradable polymers have been used in a number of applications, including controlled and targeted drug delivery. Biodegradable and biocompatible polysaccharides of different origin, including fungal origin, such as cell wall polysaccharides (e.g., chitin, chitosan, glucans, mannans) and extracellular polysaccharides (EPS) (e.g., pullulan, scleroglucan), have also been widely studied and proposed for a wide range of applications. Due to their properties, such polysaccharides have attracted increasing interest for pharmaceutical and biomedical applications, including in immunology and drug delivery systems. Many polysaccharides of different origins are currently being investigated for such uses in in-vitro, in-vivo and
clinical trials. Moreover, there are already several commercial polysaccharides available, although most of them are marketed as natural products and their clinical use is still not widespread. Biodegradable polymeric systems as drug carriers are being envisioned as an appropriate tool for temporal and spatial controlled drug delivery. The targeted delivery of drugs has been made possible by confining drugs inside biodegradable nontoxic capsules by numerous techniques. These approaches are demonstrated to be particularly effective in the treatment of cancer cells.

Unfortunately, despite impressive features and incontestable importance, the high production costs and inferior physico-mechanical properties of certain biodegradable polymers in comparison to other polymers are still obstacles for their widespread applications in industries and needs to be addressed. Thus, dedicated efforts are still required for replacing various items of common usage with biodegradable materials, and the main future concern will be regarding the materials used for pharmaceutical applications. In medicine, where function is more important than cost—biobased materials have already been used in a few crucial applications. Scientists in collaboration with pharmaceutical industries are extensively developing different types of biodegradable pharmaceutical materials. This third volume of Handbook of Polymers for Pharmaceutical Technologies is primarily focused on the biodegradable pharmaceutical polymers and deals with their different physiochemical, processing and application aspects. 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 biodegradable pharmaceutical polymers. The prime topics extensively described herein include: bioactive polysaccharides of vegetable and microbial origins: an overview; chitosan: an emanating polymeric carrier for drug delivery; fungi as sources of polysaccharides for pharmaceutical and biomedical applications; environmentally responsive chitosan-based nanocarriers (CBNS); biomass-derived and biomass-inspired polymers in pharmaceutical applications; current state on the potential use of chitosan as pharmaceutical excipient modification of cyclodextrin for improvement of complexation and formulation properties; modification of gums: synthesis techniques and pharmaceutical benefits of cellulosic, ethylene oxide and acrylic-based polymers in assembled module technology: structured biodegradable polymers for drug delivery; biomaterials for functional applications in the oral cavity via contemporary multidimensional science; role of polymers in ternary drug cyclodextrin complexes; collagen-based materials for pharmaceutical applications; and natural polysaccharides as pharmaceutical excipients.

We would like to thank Martin Scrivener of Scrivener Publishing for the invaluable help in the organization of the editing process. We would also like to thank our parents for their continuous encouragement and support.

Vijay Kumar Thakur, Ph.D.
Washington State University - U.S.A.

Manju Kumari Thakur, M.Sc., M.Phil., Ph.D.
Himachal Pradesh University, Shimla, India

June 2015
About the Editors

Vijay Kumar Thakur, Ph.D.

Email: drvijaythakur@gmail.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.
Bioactive Polysaccharides of Vegetable and Microbial Origins: An Overview

Giuseppina Tommonaro*,1, Annarita Poli1, Paola Di Donato1,2, Gennaro Roberto Abbamondi, Ilaria Finore1 and Barbara Nicolaus1

1National Council of Research of Italy, Institute of Biomolecular Chemistry, Pozzuoli (NA), Italy
2University of Napoli “Parthenope,” Department of Sciences and Technologies, Napoli, Italy

Abstract
Natural products play a dominant role in the discovery of leads to develop drugs for the treatment of human diseases. In recent years, some bioactive polysaccharides isolated from natural sources have attracted much attention in the field of biochemistry and pharmacology because of their biological activities as anticarcinogenic, anti-inflammatory, immunostimulating, antioxidant agents, etc. The high potential for some of these compounds suggested that they could be developed as drugs. This chapter presents the most relevant findings on the latest research concerning bioactive polysaccharides isolated from vegetables and microbial sources.

Keywords: Exopolysaccharides, antioxidant, anti-inflammatory, bioplastic, microbial source, plants

1.1 Introduction
The bioactive compounds that are synthesized in nature, in order to protect a living organism, have been selected from a wide variety of possibilities until reaching optimal activity after several hundreds of million years. The high potential for some of these products suggested that they could play a dominant role in the discovery of lead compounds for the development of drugs for the treatment of human disease. Recently, some bioactive polysaccharides isolated from natural sources have attracted much attention in the field of biochemistry and pharmacology: polysaccharides or their glycoconjugates were shown to exhibit multiple biological activities, including anticarcinogenic, anticoagulant, immunostimulating, antioxidant, etc.

Nowadays, the increased demand for the exploration and use of natural sources for white biotechnology processes has led to a renewed interest in biopolymers, in particular, in polysaccharides both of vegetable and microbial origins. Polysaccharides are naturally occurring polymers of aldoses and/or ketoses connected together through glycosidic linkages. They are essential constituents of all

*Corresponding author: gtommonaro@icb.cnr.it
living organisms and are associated with a variety of vital functions which sustain life. These biopolymers possess complex structures because there are many types of inter-sugar linkages involving different monosaccharide residues. In addition, they can form secondary structures which depend on the conformation of component sugars, molecular weight, inter- and intrachain hydrogen bondings. On the basis of structural criteria, it is possible to distinguish homoglycans and heteroglycans, if they are made up by the same type or by two or more types of monomer units; linear and branched polymers, with different degrees of branching; neutral or charged (cationic or anionic). Moreover, on the basis of their biological role, polysaccharide from vegetables can also be distinguished in structural elements, such as cellulose and xylans, and in energy-reserve polysaccharides such as starch and fructans. In the case of polysaccharides produced by microorganisms, they can be classified into three main groups according to their location in the cell: cytosolic polysaccharides, which provide a carbon and energy source for the cells; polysaccharides that make up the cell walls, including peptidoglycans, teichoic acids and lipopolysaccharides, and polysaccharides that are exuded into the extracellular environment in the form of capsules or slime, known as exopolysaccharides (EPSs). Since the latter are completely excreted into the environment, they can be easily collected by cell culture media precipitation by cold ethanol after removal of cells [1]. The elucidation of the polysaccharide structures are very important to clarify the physicochemical and biological properties of these biopolymers and to attribute, and in some cases predict, their biotechnological applications. Several chemical and physical techniques are used to determine the primary structure of these molecules: chemical degradation and derivatization, combined with chromatographic methods and mass spectrometry analysis, are used to determine the sugar composition, their absolute configuration and the presence and the position of possible substituents [2].

Since polysaccharides are biodegradable materials expressing biocompatibility, they could act as versatile tools for applications in biomedical fields such as drug delivery, tissue engineering, bioadhesives, prostheses and medical devices [3–7]. These polymers present several derivable groups on molecular chains that make polysaccharides a good substrate for chemical modification, such as acetylation, sulphation, silanation or oxidation, producing many kinds of polysaccharide derivatives with additional and different properties and bioactivities. The carboxymethyl pullulan conjugated with heparin represents an example of chemical modification for tissue engineering applications. Moreover, considering the presence of hydrophobic moieties in the chain of polysaccharide, the formation of self-assembled micelles can be possible, making natural EPSs like pullulan, dextran, levan or bacterial cellulose ideal candidates for drug solubility and stability [6,8,9].

Bacterial polysaccharides present a real potential in cell therapy and tissue engineering with the advantage, over the polysaccharides from eukaryotes, that they can be totally produced under controlled conditions in bioreactors. Polysaccharides synthesized by microorganisms suggest unique properties and advantages in their exploration and are an attractive alternative of plant, algal and synthetic polysaccharides. They represent a fast renewable resource that could partially compensate the restricted mass of plant polysaccharides. Their production is a matter of days, while plants’ life cycles last for months or years, being that the production cycle is usually
seasonal. Microbial polysaccharides are produced by a wide variety of microorganisms from both eukaryotic and prokaryotic groups, including cyanobacteria [10], lactic acid bacteria [11,12], and halophilic bacteria [13–16]. Other microorganisms such as yeast [17] and marine microalga [18,19] have been studied for EPS synthesis. The market price also depends on the infrastructures required for production, which can include bioreactors and maintaining asepsis [20]. The inherent costs of large-scale fermenters are significantly higher in comparison with chemical extraction processes for plant polysaccharides. Recently, the use of cheaper raw materials like agricultural waste or dairy waste has helped to reduce the cost of fermentative production [21–23].

The overall objective of this chapter is to provide information on these important biopolymers regarding applications in the field of medical industries for their pharmacological activities, including anticarcinogenic, anticoagulant, immunostimulating and antioxidant.

1.2 Anticarcinogenic Polysaccharides

Cancer is a leading cause of death in industrialized countries [24]. Although the mortality share has decreased in the last years, owing to the efforts that have been made in the search for new anticancer drugs and earlier detection, most cancers remain incurable. Chemoprevention represents a strategy used to decrease the incidence of cancer diseases in humans by inhibition of initiation step and spread of carcinogenesis and by improvement of lifestyle [25,26]. Many factors are involved in increasing the risk of cancer, including diet, exposure to radiation, environmental pollutants and tobacco use [27]. Cancer, a malignant neoplasm, is a kind of disease resulting from several causes [28]. Among these, mutations and epigenetic alterations of cancer genes promote the malignant transformation of cancer progenitor cells by disrupting key processes involved in normal growth control and tissue homeostasis [29].

Natural products play a dominant role in the discovery of lead compounds for the development of drugs to treat human diseases, including cancer, because of the variety of their chemical structures and biological activities [30]. Among natural products, polysaccharides also find their application as antitumor compounds (Table 1.1).

1.2.1 Microbial Sources

An active polysaccharide, named marinactan, was purified from the marine bacterium *Flavobacterium uliginosum*. Marinactan, a heteroglycan consisting of glucose, mannose and fucose (7:2:1 molar ratio), showed 70–90% inhibition of the growth of solid sarcome 180 in mice. Complete regression of the tumor was observed in some treated mice. Moreover, marinactan prolonged the survival period of mice bearing ascites sarcoma180 [31]. Previous papers described the antitumor activity of polysaccharides isolated from other microorganisms such as, for example, the β-(1→3)-D-glucan, produced by *Alcaligenes fecaels* var. *myxogenes* that showed a remarkable antitumor effect against sarcoma 180 solid tumor, with doses of 5 to 50 mg/Kg i.p. given once a day for 10 days [32]. Schizophyllan, a polymer isolated from
Table 1.1  Anticarcinogenic polysaccharides.

<table>
<thead>
<tr>
<th>Polysaccharide</th>
<th>Source</th>
<th>Model of study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marinactan</td>
<td><em>Flavobacterium uliginosum</em></td>
<td>solid sarcome 180 in mice</td>
<td>[31]</td>
</tr>
<tr>
<td>(1→3)-β-D-glucan</td>
<td><em>Alcaligenes fecalis var.</em> myxogenes</td>
<td>solid sarcoma 180 <em>in-vitro</em></td>
<td>[32]</td>
</tr>
<tr>
<td>Schizophyllan</td>
<td><em>Schizophyllum commune</em></td>
<td>sarcoma-37, sarcoma-180, Ehrlich carcinoma, and Yoshida sarcoma <em>in-vivo</em></td>
<td>[33]</td>
</tr>
<tr>
<td>Serratimannan and Serratigen</td>
<td><em>Serratia marcescens</em></td>
<td>solid sarcoma-180 in mice</td>
<td>[34]</td>
</tr>
<tr>
<td>Xanthan gum (XG)</td>
<td><em>Xanthomonas campestris pv.</em></td>
<td>B16K® melanoma cells <em>in-vivo</em></td>
<td>[35]</td>
</tr>
<tr>
<td>c-EPS galactan</td>
<td><em>Lactobacillus plantarum</em> 70810</td>
<td>HepG-2 (moderate), BGC-823 and HT-29 human cancer cell lines <em>in-vitro</em></td>
<td>[36]</td>
</tr>
<tr>
<td>r-EPS1 and r-EPS2</td>
<td><em>Lactobacillus plantarum</em></td>
<td>human tumor cell lines Caco-2, BGC-823 and HT-29 <em>in-vitro</em></td>
<td>[37]</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Polysaccharide</th>
<th>Source</th>
<th>Model of study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vegetable sources</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APS</td>
<td><em>Aloe barbadensis Miller</em></td>
<td>inhibition of B[a]P binding to DNA in mouse liver cells, <em>in-vitro</em>; reduction of oxidative DNA damage; inhibition phorbl myristic acetate (PMA)-induced ornithine decarboxylase activity in Balb/3T3 cells and PMA-induced tyrosine kinase activity in human leukemic cells, <em>in-vitro</em></td>
<td>[38]</td>
</tr>
<tr>
<td>LPS</td>
<td><em>Lentinus edodes</em></td>
<td>moderate inhibition of 8-OH-dG formation; moderate induction of GST; moderate inhibition of TK activity, moderate inhibition of superoxide anion formation</td>
<td></td>
</tr>
<tr>
<td>GPS</td>
<td><em>Ganoderma lucidum</em></td>
<td>induction of glutathione S-transferase <em>in-vitro</em></td>
<td></td>
</tr>
<tr>
<td>CPS</td>
<td><em>Coriolus versicolor</em></td>
<td>reduction of oxidative DNA damage <em>in-vitro</em></td>
<td></td>
</tr>
<tr>
<td>TSPS</td>
<td><em>Camelia sinensis</em> (tea)</td>
<td>K562 cells (human myelogenous leukemia) <em>in-vivo</em></td>
<td>[40]</td>
</tr>
<tr>
<td>Glycan</td>
<td><em>Camelia sinensis</em> (green tea)</td>
<td>SKOV-3 cells (human adenocarcinoma), hepatocellular carcinoma <em>in-vivo</em></td>
<td>[41]</td>
</tr>
<tr>
<td>Se-GTPs</td>
<td>Ziyang green tea</td>
<td>human MCF-7 breast cancer cells <em>in-vitro</em></td>
<td>[42]</td>
</tr>
<tr>
<td>LBP-1</td>
<td><em>Lili Bulbus</em></td>
<td>Lewis lung carcinoma in mice</td>
<td>[43]</td>
</tr>
<tr>
<td>F1 and F2 (Acidic polysaccharide fractions)</td>
<td><em>Cymbopogon citrates</em> (lemongrass)</td>
<td>human cancer cell lines Siha (cervix carcinoma) and LNCap (prostate carcinoma) <em>in-vitro</em></td>
<td>[44]</td>
</tr>
<tr>
<td>CP-1</td>
<td><em>Coix lachryma-jobi L.</em></td>
<td>A549 cells (human non-small cell lung cancer) <em>in-vitro</em></td>
<td>[45]</td>
</tr>
<tr>
<td>POL-P3b</td>
<td><em>Portulaca oleracea</em></td>
<td>HeLa cells and U14-bearing mice</td>
<td>[46]</td>
</tr>
</tbody>
</table>
the culture filtrate of *Schizophyllum commune*, was chemically characterized and showed to be formed by repeating units composed of three or four β-(1→3)-linked D-glucopyranose residues to one of which is attached, through β-(1→6)-linkage, a side chain consisting of a single β-D-glucopyranose residue. It was tested against four kinds of transplantable tumors in both ascites and solid forms. The most significant results were obtained with 0.5–10 mg/kg doses of schizophyllan on all the subcutaneously implanted tumors, i.e., sarcoma-37, sarcoma-180, Ehrlich carcinoma, and Yoshida sarcoma, accompanied by complete regressions. The treatment failed to inhibit the growth of ascites tumors or to induce prolongation of life span, with the exception of ascites sarcoma-180, moreover no inhibitory effect was observed also on Friend virus disease and spontaneous mammary carcinoma arising in Swiss mice. The mechanism of this action was considered to be host-mediated on the basis of lack of effect in *in-vitro* contact test [33]. A lipopolysaccharide (serratigen) and a polysaccharide (serratimannan), isolated from *Serratia marcescens*, red strain No. 51, were assayed for their antitumor activity against solid tumor of sarcoma-180 using ICR mice. Serratimannan showed 63% tumor inhibition and serratigen 38%, at a dose of 150 mg/kg [34].

Recently it has been reported the antitumor activity through Toll-like receptor 4 (TLR-4) of xanthan gum (XG), a complex polysaccharide produced by plant-pathogenic bacterium *Xanthomonas campestris* pv. Results showed that *in-vitro* culture with XG induced interleukin-12 (IL-12p40) and tumor necrosis factor-alpha (TNF-α) production from murine macrophages J744.1 and RAW264.7. Moreover, XG stimulated macrophages in a MyD88 mice-dependent manner and was mainly recognized by TLR-4. Oral administration of XG significantly retarded tumor growth and prolonged survival of the mice inoculated subcutaneously with B16Kb melanoma cells. The *in-vivo* antitumor effects of XG were also dependent on TLR-4, likewise in C3/HeJ mice, which lack TLR-4 signaling, where XG exhibited no effect on the growth of syngeneic bladder tumor, MBT-2. Results suggested that oral administration of XG could be beneficial against cancer diseases [35].

Bacteria can produce exopolysaccharides, secreting them in the surrounding medium (released exopolysaccharides, r-EPS) or they can be attached to the bacterial surface (cell-bond exopolysaccharides, c-EPS). A c-EPS was isolated from the supernatant of *Lactobacillus plantarum* 70810. The chemical characterization revealed that it was a galactan containing a backbone of a-D-(1→6)-linked galactosyl, β-D-(1→4)-linked galactosyl, β-D-(1→2,3)-linked galactosyl residues and a tail end of β-D-(1→6)-linked galactosyl residues. The c-EPS was assayed for its inhibitory effect on the proliferation of HepG-2, BGC-823 and HT-29 human cancer cell lines. Results indicated moderate antitumor activity against HepG-2 cells (56.34±1.07% of inhibition, 600 mg/mL), whereas a significant inhibitory effect was observed on BCG-823 and HT-29 (61.57±2.07% and 88.34±1.97%, respectively) [36]. Wang *et al.* also reported the isolation and bioactivity of two exopolysaccharides (r-EPS1 and r-EPS2) released from *Lactobacillus plantarum* 70810. Results showed that both r-EPSs exhibited antiproliferative effects against the human tumor cell lines Caco-2, BGC-823 and HT-29. The r-EPS2 possessed higher growth inhibition effects on the cancer cell lines used than r-EPS1. The reason could be due to the presence of sulfated group and beta glycosidic bond composition in r-EPS2 [37].