

## Contents

### List of Contributors *xvii*

<b>1</b>	<b>Application of Nanocellulose for Controlled Drug Delivery</b>	<b>1</b>
	<i>Lalduhsanga Pachuau</i>	
1.1	Introduction	1
1.2	Biodegradability, Cytotoxicity, and Cellular Internalization of Nanocellulose	3
1.3	Nanocellulose in Nanoparticulate Drug Delivery	5
1.4	Nanocellulose in Microparticulate Drug Delivery	8
1.5	Nanocellulose in Tablet Formulations	10
1.6	Aerogel Systems	10
1.7	Hydrogels	11
1.8	Nanocellulose in Transdermal Drug Delivery	13
1.9	Conclusion	14
	References	14
<b>2</b>	<b>Bacterial Cellulose and Polyester Hydrogel Matrices in Biotechnology and Biomedicine: Current Status and Future Prospects</b>	<b>21</b>
	<i>Rajnikant Borkar, Sanghratna S. Waghmare, and Tanvir Arfin</i>	
2.1	Introduction	21
2.2	Chemical Structure of Cellulose	21
2.3	Types of Cellulose	21
2.4	Bacterial Cellulose	22
2.5	Chemical Structure of BC	22
2.6	History of BC	23
2.7	Biosynthesis of Bacterial Cellulose	23
2.8	Properties	23
2.8.1	Biocompatibility	25
2.8.1.1	<i>In Vitro</i> Biocompatibility	25
2.8.1.2	<i>In Vivo</i> Biocompatibility	26
2.8.2	Hemocompatibility	26
2.8.3	Mechanical Properties	27
2.8.4	Microporosity	27
2.8.5	Biodegradability	28

2.9	Present Status of BC	28
2.10	Applications	29
2.10.1	Drug Delivery	29
2.10.2	Antibacterial/Antimicrobial Studies	29
2.10.3	Biomedicine	30
2.10.4	Wound Dressing	30
2.10.5	Cardiovascular Implant	30
2.10.6	Cartilage Meniscus Implant	31
2.10.7	Bone Tissue Implant	31
2.10.8	Other Biomedical Applications	31
2.10.9	Artificial Cornea	32
2.10.10	Biotechnology	32
2.11	Future Prospects	33
2.12	Polyester Hydrogels	33
2.13	Chemical Structure of Hydrogels	33
2.14	Types of Hydrogels	34
2.15	Properties of Hydrogels	34
2.15.1	Swelling Properties	34
2.15.2	Biodegradability	35
2.15.3	Biocompatibility	36
2.16	Historical Background of Polyester Hydrogels	36
2.17	Recent Developments of Polyester Hydrogels	37
2.18	Applications of Polyester Hydrogels	38
2.18.1	Drug Delivery	38
2.18.2	Antibacterial/Antimicrobial Studies	38
2.18.3	Biomedicine	38
2.18.4	Biotechnology	39
2.18.5	Tissue Engineering	39
2.19	Future Prospects	39
	References	40
<b>3</b>	<b>Bacterial Nanocellulose Applications for Tissue Engineering</b>	<b>47</b>
	<i>Muhammed Lamin Sanyang, Naheed Saba, Mohammad Jawaid, Faruq Mohammad, and Mohd Sapuan Salit</i>	
3.1	Introduction	47
3.2	Cellulose	47
3.3	Nanocellulose and Its Types	50
3.3.1	Cellulose Nanocrystals (CNCs)	50
3.3.2	Cellulose Nanofibrils (CNFs)	52
3.3.3	Bacterial Cellulose (BC)	52
3.4	Isolation and Preparation of Bacterial Cellulose	53
3.5	BC Properties for Tissue Engineering Applications	54
3.5.1	Mechanical Properties of BC	54
3.5.2	Surface Biochemistry Properties	55
3.5.3	Biological Properties	56
3.5.3.1	Biocompatibility	56
3.5.3.2	Biodegradability <i>In Vivo</i>	57

3.6	Tissue Engineering Applications	58
3.7	Conclusion and Future Research	61
	References	62
<b>4</b>	<b>Cellulose-Based Nanohydrogels for Tissue Engineering Applications</b>	<b>67</b>
	<i>Kalyani Prusty and Sarat K. Swain</i>	
4.1	Introduction	67
4.2	Preparation of Hydrogels/Cellulosic Hydrogels	69
4.3	Characterization of Hydrogels/Cellulosic Hydrogels	71
4.3.1	Fourier Transform Infrared Spectroscopy of Hydrogels/Cellulosic Hydrogels	71
4.3.2	Scanning Electron Microscopy of Hydrogels/Cellulosic Hydrogels	72
4.3.3	Nuclear Magnetic Resonance of Hydrogels	73
4.3.4	X-ray Diffraction (XRD) of Hydrogels	75
4.3.5	Transmission Electron Microscopy (TEM) of Hydrogels	76
4.4	Properties of Hydrogels	76
4.4.1	Swelling Properties of Hydrogels	76
4.4.2	Thermal Properties of Hydrogels	78
4.4.3	Rheological Properties of Hydrogels	79
4.4.4	Mechanical Properties of Hydrogels	80
4.5	Cellulose-Based Nanohydrogels for Tissue Engineering Applications	81
4.6	Concluding Remarks	84
	Acknowledgment	85
	References	85
<b>5</b>	<b>Chitosan-Mediated Layer-by-Layer Assembling Approach for the Fabrication of Biomedical Probes and Advancement of Nanomedicine</b>	<b>91</b>
	<i>Faruq Mohammad and Hamad A. Al-Lohedan</i>	
5.1	Introduction	91
5.2	Chitosan for Biofabrication	92
5.3	Derivatization of Chitosan	94
5.3.1	Derivatization by Direct Chemical Modification	94
5.3.2	Derivatization by Complex Formation	94
5.4	Chitosan-Mediated Biofabrication: Different Shapes and LBL Assembly	96
5.5	Chitosan-Mediated Assembly of Biomedical Probes and Devices	100
5.5.1	Biosensors	100
5.5.2	Biopharmaceuticals	102
5.5.3	Tissue Engineering Appliances	104
5.5.4	Implant Materials	106
5.5.5	Diagnostic Probes	107
5.5.6	Surgical Aids	108

5.6	Factors Influencing the Characteristics of Chitosan toward Biomedical Applications	109
5.6.1	Degree of Deacetylation (DD)	110
5.6.2	Degree of Quaternization (DQ)	111
5.6.3	Length and Type of Alkyl Chain	111
5.6.4	Solubility	112
5.6.5	pH	113
5.6.6	Molecular Weight (MW)	114
5.6.7	Substituent Charge	114
5.7	Summary and Conclusion	115
	Acknowledgments	115
	References	115
<b>6</b>	<b>Hydrogels Based on Nanocellulose and Chitosane: Preparation, Characterization, and Properties</b>	<b>125</b>
	<i>Meriem Fardiou, Abou el kacem Qaiss, and Rachid Bouhfid</i>	
6.1	Introduction	125
6.2	Polymeric Aerogels	126
6.2.1	Sol–Gel Process	126
6.2.1.1	Starch Gel by the Chemical Cross-linking Technique	126
6.2.1.2	Alginate Hydrogel by Ionic Interaction Technique	127
6.2.1.3	$\kappa$ -Carrageenan Hydrogel by Heating/Cooling Technique	127
6.2.1.4	Cellulose Hydrogel by the Hydrogen-Bonding Technique	129
6.2.2	Gel Drying	129
6.2.2.1	Ambient Pressure Drying	129
6.2.2.2	Freeze-Drying	129
6.2.2.3	Supercritical Drying	130
6.3	Chitosan and Functionalized Chitosan Hydrogels	131
6.3.1	Chitosan Biopolymer	131
6.3.2	Chemical and Physical Cross-linked Chitosan Hydrogel	131
6.3.2.1	Physical Gel	131
6.3.2.1.1	Ionically Cross-linked Chitosan Hydrogel	131
6.3.2.1.2	Polyelectrolyte Complexed Chitosan Hydrogels	132
6.3.2.2	Chemical Gels	132
6.3.3	Chitosan Hybrid Aerogels	133
6.4	Biopolymeric Aerogels in Biomedical Applications	134
	References	136
<b>7</b>	<b>Cellulose Nanocrystals and PEO/PET Hydrogel Material in Biotechnology and Biomedicine: Current Status and Future Prospects</b>	<b>139</b>
	<i>Shoeb Athar, Rani Bushra, and Tanvir Arfin</i>	
7.1	Introduction	139
7.2	Cellulose Nanocrystals	140
7.2.1	Cellulose	140
7.2.2	Cellulose Nanocrystals (CNCs)	141

7.2.3	Why CNC?	142
7.2.3.1	Mechanical Properties	142
7.2.3.2	Surface Chemistry	142
7.2.3.3	Biocompatibility	142
7.2.3.4	<i>In vivo</i> Biodegradability	143
7.2.3.5	Toxicity	143
7.2.4	CNC in Biotechnology and Biomedicine	143
7.2.4.1	Biotechnology	143
7.2.4.1.1	Tissue Engineering	143
7.2.4.1.2	Enzyme or Protein Immobilization and Recognition	144
7.2.4.2	Biomedicine	146
7.2.4.2.1	Drug-Loaded System	146
7.2.4.2.2	Medical Implants	148
7.2.4.2.3	Cancer Targeting	150
7.2.4.2.4	Antimicrobial Nanomaterials	151
7.2.5	Future Prospects	153
7.3	Polyethylene Oxide (PEO)/Polyethylene Terephthalate (PET) Hydrogel	155
7.3.1	Hydrogel	155
7.3.2	Classification	156
7.3.3	Polyethylene Oxide (PEO)/Polyethylene Terephthalate (PET)	156
7.3.4	PEO/PET Hydrogel in Biotechnology and Biomedicine	157
7.3.4.1	Biotechnology	157
7.3.4.1.1	Tissue Engineering	157
7.3.4.1.2	Medical Devices and Biosensors	158
7.3.4.2	Biomedicine	159
7.3.4.2.1	Drug Delivery	159
7.3.4.2.2	Medical Implants	159
7.3.4.2.3	Wound Dressings	162
7.3.5	Future Prospects	162
7.4	Conclusion	163
	References	164

## **8 Conducting Polymer Hydrogels: Synthesis, Properties, and Applications for Biosensors** 175

*Yu Zhao*

8.1	Introduction	175
8.2	Synthesis and Processing of CPHs	177
8.2.1	Conventional Synthetic Methods for CPHs	177
8.2.2	Recently Developed Preparation Routes for CPHs	179
8.3	CPHs for Electrochemical Biosensors	182
8.3.1	Conducting Polymer-Based Biosensors	184
8.3.2	Hydrogel-Based Biosensors	187
8.3.3	Ionically Cross-linked Conducting Polymer Hydrogels and Their Applications in Biosensors	189

- 8.3.4 Doping Acid Cross-Linking as a Novel Method to Fabricate Conducting Polymer Hydrogels and Their Application in Biosensors 192
- 8.4 Conclusion 200
  - Acknowledgments 201
  - References 201

## **9 Nanocellulose and Nanogels as Modern Drug Delivery Systems 209**

*Misu Moscovici, Cristina Hlevca, Angela Casarica, and Ramona-Daniela Pavaloiu*

- 9.1 Introduction 209
- 9.2 Nanoparticles as Drug Delivery Systems 210
  - 9.2.1 State of the Art 210
  - 9.2.2 Challenges 212
- 9.3 Nanocelluloses 212
  - 9.3.1 Nanocellulose Structure, Preparation, and Properties 212
  - 9.3.2 Nanocellulose as Drug Delivery Carrier 215
    - 9.3.2.1 Nanocellulose Drug Formulations for Topical Administration 215
      - 9.3.2.1.1 Topical Application of Nanocomposites with Local Effect 215
      - 9.3.2.1.2 Nanocellulose in Transdermal Drug Delivery Systems 217
    - 9.3.2.2 Nanocellulose Formulations for Internal (Into-the-Body) Administration 219
      - 9.3.2.2.1 Nanocellulose in Tablet Compression and Coating 221
      - 9.3.2.2.2 Nanocellulose in Implants for Local Therapy 222
      - 9.3.2.2.3 Biocompatibility and Toxicology 223
- 9.4 Nanogels 223
  - 9.4.1 Definition 223
  - 9.4.2 Characteristics 223
    - 9.4.2.1 Swelling 223
    - 9.4.2.2 Biocompatibility and Biodegradability 227
    - 9.4.2.3 Drug Loading 227
    - 9.4.2.4 Drug Release 229
  - 9.4.3 Stimuli-Responsive Nanogels 229
  - 9.4.4 Targetability 232
  - 9.4.5 Toxicity 234
  - 9.4.6 Easy Synthesis of Nanogels 234
  - 9.4.7 Nanogel Applications in Drug Delivery 236
    - 9.4.7.1 Nanogel Delivery Systems for Cancer Therapy 236
      - 9.4.7.1.1 Nanogels Carriers of More Than a Single Drug 240
      - 9.4.7.2 Nanogels for Drug Delivery across Biological Barriers 242
      - 9.4.7.3 Nanogels in Vaccine Delivery 247
      - 9.4.7.4 Nanogels in Anti-inflammatory Drug Delivery 248
      - 9.4.7.5 Nanogels in Treatment of Autoimmune Diseases 249
- 9.5 Conclusions and Outlook 250
  - References 254

- 10 Recent Advances on Inhibitors of Apoptosis Proteins (IAP) Particularly with Reference to Patents 271**  
*Riyaz Syed, Prema L. Mallipeddi, Syed Mohammed Ali Hussaini, Rahul V. Patel, A. Prasanth Saraswati, and Ahmed Kamal*
- 10.1 Introduction 271
- 10.1.1 Inhibitor of Apoptosis Proteins 271
- 10.1.2 IAPs and Cancer 273
- 10.1.2.1 XIAP 273
- 10.1.2.2 cIAPs 273
- 10.1.3 Mechanism of Action and Development of Smac Mimetics 273
- 10.1.3.1 Prudence Section 274
- 10.2 Patent Assessments 275
- 10.2.1 Fused Pyrrolidine as IAP Inhibitors 275
- 10.2.2 Fused Pyrazinone Derivatives 276
- 10.2.3 Indoles and Azaindoles 277
- 10.2.4 Dimeric Indoles 279
- 10.3 Other Heterocyclics as IAPs 279
- 10.3.1 Diazepine and Diazocine Derivatives as IAP Antagonists 281
- 10.3.2 Triazole-Containing Macrocycles as IAPs 281
- 10.3.3 Isoquinoline-Based IAP Antagonists 281
- 10.3.4 Dimeric and Pseudodimeric Peptidomimetics as IAPs 284
- 10.3.5 Pyrrolidine-Containing IAP Antagonists 285
- 10.3.6 Miscellaneous Structures as IAPs 286
- 10.4 Conclusion and Perspectives 288
- Acknowledgments 290
- References 290
- 11 Nanohydrogels: History, Development, and Applications in Drug Delivery 297**  
*Muhammad Akram and Razaqat Hussain*
- 11.1 Introduction 297
- 11.2 History 297
- 11.2.1 First-Generation Hydrogels 298
- 11.2.2 Second-Generation Hydrogels 298
- 11.2.2.1 pH-Sensitive Hydrogels 298
- 11.2.2.2 Temperature-Responsive Hydrogels 300
- 11.2.3 Third-Generation Hydrogels 300
- 11.3 Classification of Hydrogels Based on the Type of Cross-Link Junctions 301
- 11.3.1 Physical Network-Based Hydrogels 302
- 11.3.2 Chemical Network-Based Hydrogels 303
- 11.3.3 Hydrogels Based on Ionic Interaction 304
- 11.3.4 Enzyme-Based Cross-Linking Hydrogels 304
- 11.3.5 Photosensitive Functional Group-Based Cross-Linked Hydrogels 305
- 11.4 Classification of Hydrogels Based on Properties 305
- 11.5 Classification of Interpenetrating Network Hydrogels 307

11.5.1	Homopolymeric Hydrogels	307
11.5.2	Copolymeric Hydrogel	307
11.5.3	Semi-interpenetrating Hydrogels	308
11.5.4	Interpenetrating Hydrogels	308
11.6	Classification Based on Source	309
11.7	Properties of Hydrogels	309
11.7.1	Swelling Properties	309
11.7.2	Elasticity of Hydrogels	310
11.7.3	Porosity and Permeation of Hydrogels	311
11.7.4	Mechanical Properties of Hydrogels	312
11.7.5	Biocompatibility of Hydrogels	312
11.7.6	Inhomogeneity of Hydrogels	312
11.8	Nanohydrogels and Their Applications	313
11.8.1	Polysaccharide-Based Nanohydrogels	314
11.8.1.1	Hyaluronic Acid-Based Nanohydrogels in Drug Delivery	315
11.8.1.2	Chitosan-Based Nanohydrogels in Drug Delivery	316
11.8.1.3	Alginate-Based Nanohydrogels in Drug Delivery	317
11.8.1.4	Pectin-Based Nanohydrogels in Drug Delivery	317
11.8.1.5	Dextran-Based Nanohydrogels in Drug Delivery	317
11.8.1.6	Cellulose-Based Nanohydrogels in Drug Delivery	317
11.9	Conclusion	319
	References	319

## **12 Nanofibrillated Cellulose and Copoly(amino acid) Hydrogel Matrices in Biotechnology and Biomedicine** 331

*Azhar U. Khan, Nazia Malik, and Tanvir Arfin*

12.1	History and Background of Celluloses	331
12.2	Structure of Cellulose	331
12.2.1	Characterization of Cellulose	332
12.2.2	Crystalline and Amorphous Regions	332
12.3	Nanocelluloses	333
12.3.1	Nanofibrillar Cellulose (NFC)	333
12.3.2	Production of NFC	334
12.3.2.1	Surface Modification of Nanofibrillated Cellulose	334
12.3.2.2	Coupling Agent	334
12.3.2.3	TEMPO-Mediated Oxidation Pretreatment	335
12.3.2.4	Other Chemical Methods	335
12.3.3	Biomedical Applications of NFC	336
12.3.3.1	Immunoassays and Diagnostics	336
12.3.3.2	Three-Dimensional (3D) Cell Cultures	337
12.3.3.3	Replacement of the Nucleus Pulposus	337
12.3.3.4	Controlled Drug Delivery	338
12.3.3.5	Wound Healing	338
12.3.4	Biotechnology Applications of NFC	339
12.3.4.1	Genetically Engineered Fusion	339
12.3.4.2	Immobilization–Stabilization	339
12.3.4.3	Cartilage Tissue Engineering	340



12.4	Hydrogels	340
12.4.1	Role of Swelling in Hydrogels	340
12.4.1.1	Sol–Gel Transition in Hydrogels	341
12.4.1.2	Classification of Hydrogel Products	341
12.4.1.3	Hydrogel Technical Features	341
12.4.2	Preparation of Poly(amino acids)	342
12.4.3	Biomedical Application of Hydrogels	344
12.4.3.1	Treatment of Hepatoma	344
12.4.3.2	Drug Delivery	345
12.4.3.3	Anticancer Drug	345
12.4.4	Biotechnology Applications of Hydrogels	346
12.4.4.1	Genetic Engineering	346
12.4.4.2	Amyloidogenicity Code	346
12.4.4.3	Antibodies	346
12.5	Conclusion	347
	References	347
	<b>Index</b>	<b>353</b>

