

Synthesis of Nanomaterials



Editor:
Felipe López-Saucedo

Bentham Books

Frontiers in Nanomedicine

(Volume 3)

Synthesis of Nanomaterials

Edited by

Felipe López-Saucedo

Department of Radiation Chemistry and Radiochemistry

Institute of Nuclear Sciences

Universidad Nacional Autónoma de México

Mexico

Frontiers in Nanomedicine

(Volume 3)

Synthesis of Nanomaterials

Editor: Felipe López-Saucedo

ISSN (Online): 2405-9137

ISSN (Print): 2405-9129

ISBN (Online): 978-981-5136-92-0

ISBN (Print):978-981-5136-93-7

ISBN (Paperback): 978-981-5136-94-4

©2023, Bentham Books imprint.

Published by Bentham Science Publishers Pte. Ltd. Singapore. All Rights Reserved.

First published in 2023.

BENTHAM SCIENCE PUBLISHERS LTD.

End User License Agreement (for non-institutional, personal use)

This is an agreement between you and Bentham Science Publishers Ltd. Please read this License Agreement carefully before using the book/echapter/ejournal (“**Work**”). Your use of the Work constitutes your agreement to the terms and conditions set forth in this License Agreement. If you do not agree to these terms and conditions then you should not use the Work.

Bentham Science Publishers agrees to grant you a non-exclusive, non-transferable limited license to use the Work subject to and in accordance with the following terms and conditions. This License Agreement is for non-library, personal use only. For a library / institutional / multi user license in respect of the Work, please contact: permission@benthamscience.net.

Usage Rules:

1. All rights reserved: The Work is the subject of copyright and Bentham Science Publishers either owns the Work (and the copyright in it) or is licensed to distribute the Work. You shall not copy, reproduce, modify, remove, delete, augment, add to, publish, transmit, sell, resell, create derivative works from, or in any way exploit the Work or make the Work available for others to do any of the same, in any form or by any means, in whole or in part, in each case without the prior written permission of Bentham Science Publishers, unless stated otherwise in this License Agreement.
2. You may download a copy of the Work on one occasion to one personal computer (including tablet, laptop, desktop, or other such devices). You may make one back-up copy of the Work to avoid losing it.
3. The unauthorised use or distribution of copyrighted or other proprietary content is illegal and could subject you to liability for substantial money damages. You will be liable for any damage resulting from your misuse of the Work or any violation of this License Agreement, including any infringement by you of copyrights or proprietary rights.

Disclaimer:

Bentham Science Publishers does not guarantee that the information in the Work is error-free, or warrant that it will meet your requirements or that access to the Work will be uninterrupted or error-free. The Work is provided "as is" without warranty of any kind, either express or implied or statutory, including, without limitation, implied warranties of merchantability and fitness for a particular purpose. The entire risk as to the results and performance of the Work is assumed by you. No responsibility is assumed by Bentham Science Publishers, its staff, editors and/or authors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products instruction, advertisements or ideas contained in the Work.

Limitation of Liability:

In no event will Bentham Science Publishers, its staff, editors and/or authors, be liable for any damages, including, without limitation, special, incidental and/or consequential damages and/or damages for lost data and/or profits arising out of (whether directly or indirectly) the use or inability to use the Work. The entire liability of Bentham Science Publishers shall be limited to the amount actually paid by you for the Work.

General:

1. Any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims) will be governed by and construed in accordance with the laws of Singapore. Each party agrees that the courts of the state of Singapore shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims).
2. Your rights under this License Agreement will automatically terminate without notice and without the

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.

80 Robinson Road #02-00

Singapore 068898

Singapore

Email: subscriptions@benthamscience.net



CONTENTS

PREFACE	i
DEDICATION	ii
LIST OF CONTRIBUTORS	iii
CHAPTER 1 BIOMATERIALS APPLIED TO MEDICAL DEVICES AND PHARMACY	1
<i>Tri-Dung Ngo</i>	
INTRODUCTION	1
CLASSIFICATION	2
ADVANTAGES AND DISADVANTAGES OF BIOMATERIALS AND THEIR USES	5
REQUIREMENTS FOR BIOMATERIALS IN MEDICAL DEVICES AND PHARMACY	7
BIOMATERIALS' MANUFACTURING AND MARKET	8
Electrospinning	9
Additive Manufacturing	10
CONCLUSION	11
CONSENT FOR PUBLICATION	11
CONFLICT OF INTEREST	11
ACKNOWLEDGEMENT	11
REFERENCES	12
CHAPTER 2 MATERIAL SYNTHESIS, STRUCTURES AND CHARACTERIZATION	14
<i>Luis Alberto Camacho Cruz, Marlene Alejandra Velazco Medel, Luis Ramón Ortega Valdivinos, Angélica Cruz Gómez cpf Emilio Bucio</i>	
INTRODUCTION	14
POLYMERS RELEVANT TO MEDICAL APPLICATIONS	15
Natural Polymers	16
<i>Polysaccharides</i>	16
<i>Chitosan</i>	16
<i>Cellulose</i>	17
<i>Alginates</i>	17
<i>Hyaluronic Acid</i>	18
<i>Polypeptides</i>	18
<i>Collagen and Gelatin</i>	19
<i>Polyisoprene</i>	20
Synthetic Polymers	20
<i>Polyethylene Glycol</i>	21
<i>Poly(Lactic-co-Glycolic Acid)</i>	22
<i>Polysiloxanes</i>	22
<i>Polycaprolactone</i>	23
<i>Polyacrylic and Derivatives</i>	23
<i>Poly(Ether-Etherketone)</i>	24
<i>Polyurethane</i>	25
<i>Polyethylene</i>	25
<i>Polytetrafluoroethylene</i>	26
<i>Polyamides</i>	26
APPLICATIONS OF POLYMERS IN MEDICINE	27
Polymeric Drug Delivery Systems	27
<i>Stimuli-responsive Polymers for Drug Delivery</i>	28
Polymers for Tissue Engineering	33
<i>Hemocompatible Polymeric Materials</i>	33
<i>Tissue Engineering</i>	34
Polymeric Implants	35

<i>Absorbable Polymers</i>	36
<i>Non-absorbable Polymers</i>	37
Polymers in Cardiology	37
<i>Polymeric Cardiac Stents</i>	38
<i>Polymeric Tissue Substitutes</i>	39
Polymers in Ophthalmology	39
<i>Contact Lenses</i>	40
<i>Intraocular Implants</i>	40
Polymers in Nephology	41
<i>Use of Novel Materials for Catheters and Stents</i>	42
<i>Polymer Coating of Catheters and Stents</i>	43
Polymers in Dentistry	43
CONCLUSION	45
LIST OF ABBREVIATIONS	45
CONSENT FOR PUBLICATION	46
CONFLICT OF INTEREST	46
ACKNOWLEDGEMENTS	46
REFERENCES	46
CHAPTER 3 NANOENGINEERING FOR BIOMEDICAL DEVICES	60
<i>David Romero-Fierro, Moises Bustamante-Torres, Sophia Anchali and Emilio Bucio</i>	
INTRODUCTION	60
Brief Review of the Development of Biomaterials	60
FUNDAMENTALS OF NANOENGINEERING APPLIED TO BIOMEDICAL DEVICES	62
Nanomaterials	62
Nanomedicine	62
Biocompatibility	64
SYNTHESIS OF NANOMATERIALS APPLIED TO BIOMEDICINE	65
Polymeric Materials	65
<i>Emulsion Diffusion Method</i>	66
<i>Solvent Emulsion Evaporation Method</i>	66
<i>Double Emulsion Solvent Evaporation Method</i>	67
<i>Micro-emulsion Polymerization</i>	68
<i>Nanoprecipitation Method</i>	68
<i>Coacervation Method</i>	69
<i>Polymerization Method</i>	70
<i>Ionic Gelation Method</i>	70
<i>Nanoparticles from Supercritical Fluid</i>	70
<i>Molecular Self-assembling</i>	71
Iron Oxide Nanoparticles	72
<i>Co-precipitation Method</i>	72
<i>Thermal Decomposition</i>	74
<i>Microemulsion</i>	74
<i>Hydrothermal Synthesis</i>	75
<i>Sonochemical Synthesis</i>	75
Synthesis of Metallic Nanoparticles	76
<i>Top-down Methods</i>	77
<i>Bottom-up Methods</i>	78
<i>Liquid-state Synthesis Methods</i>	79
<i>Gas Phase Methods</i>	81

<i>Biological Method</i>	82
COMMON CHARACTERIZATION TECHNIQUES	82
Scanning Electron Microscopy	83
Transmission Electron Microscopy	83
Atomic Force Microscopy	83
UV-Vis Spectroscopy	84
X-ray-based Techniques	84
Dynamic Light Scattering	85
Zeta Potential	85
Aerodynamic Particles Sizer	85
APPLICATIONS OF NANOENGINEERING IN MEDICINE	86
Diagnosis	86
Disinfection	88
Nervous System	90
Implants and Tissue Engineering	91
Treatment of Skin Wounds	92
<i>Metal and Metal Oxide Nanomaterials</i>	93
<i>Non-metallic Nanomaterials</i>	93
Drug Delivery	94
Regenerative Medicine	95
<i>Organic and Polymeric Nanomaterials</i>	96
<i>Inorganic Nanomaterials</i>	97
ETHICS AND NANOENGINEERING	97
CONCLUSION	98
CONSENT FOR PUBLICATION	99
CONFLICT OF INTEREST	99
ACKNOWLEDGEMENTS	99
REFERENCES	99
CHAPTER 4 STIMULI-RESPONSIVE BIOMATERIALS WITH PHARMACOLOGICAL APPLICATIONS	111
<i>Julián Eduardo Sánchez-Velandia, David Valverde, Raul Porcar cpf Aída Luz Villa</i>	
INTRODUCTION	112
SYNTHESIS OF BIOPOLYMERS	115
Conventional Synthesis	116
Sequence-controlled Polymers	117
Electrospinning	122
Other Chemical Methodologies	125
APPLICATIONS	127
CONCLUSION	131
CONSENT FOR PUBLICATION	132
CONFLICT OF INTEREST	132
ACKNOWLEDGEMENTS	132
REFERENCES	132
CHAPTER 5 HYDROGELS AND NANOHYDROGELS	140
<i>Moises Bustamante-Torres, David Romero-Fierro, Bryan Chiguano-Tapia, Estefani Chichande-Proaño and Emilio Bucio</i>	
INTRODUCTION	141
HYDROGEL	142
Properties	143
CLASSIFICATION OF HYDROGELS	145

Synthesis of Hydrogels	145
<i>Physical Cross-Linking</i>	145
<i>Chemical Cross-Linking</i>	146
<i>Interpenetrating Polymer Networks</i>	149
Types of Hydrogels	150
<i>Smart Hydrogels</i>	150
<i>Nanocomposite Hydrogels</i>	153
NANO GELS	153
Nanogel Functionalization	155
SYNTHESIS OF NANO GELS	155
Nanogels Synthesized using Polymer Cross-Linking	155
<i>Chemical Cross-Linking Based on Polyaddition Reactions</i>	155
<i>Cross-linking Induced by Irradiation</i>	157
Nanogels Synthesized by Cross-Linking Polymerization of Monomers	159
<i>Precipitation Polymerization</i>	159
HYDROGEL AND NANO GEL CHARACTERIZATION METHODS	163
Light Scattering	163
Gel Permeation Chromatography	164
Viscosimetry	164
Differential Scanning Calorimetry	165
Microscopy	165
Spectroscopies	166
Limit Swelling	167
APPLICATIONS	167
CONCLUSION	169
CONSENT FOR PUBLICATION	169
CONFLICT OF INTEREST	170
ACKNOWLEDGEMENTS	170
REFERENCES	170
CHAPTER 6 SELF-HEALING AND REGENERATIVE MATERIALS	183
<i>Lorena Duarte-Peña and Emilio Bucio</i>	
INTRODUCTION	183
HISTORY: SELF-HEALING MATERIALS OVER TIME	186
EXTRINSIC SELF-HEALING MATERIALS	186
Encapsulated Self-healing Systems	187
Vascular Network Self-healing Systems	189
INTRINSIC SELF-HEALING MATERIALS	190
Dynamic Covalent Bond-based Materials	190
<i>C=N Dynamic Covalent Bonds</i>	191
<i>Disulfide Bonds</i>	192
<i>C=C Dynamic Covalent Bonds</i>	194
<i>B-O Dynamic Covalent Bonds</i>	196
Non-covalent Interactions of Self-healing Materials	196
<i>Ionic Interactions-based Self-healing Materials</i>	197
<i>Van der Waals Forces-based Self-healing Materials</i>	197
<i>Host-Guest Interaction-based Self-healing Materials</i>	199
Combined Self-healing Systems	200
CONCLUSION	201
CONSENT FOR PUBLICATION	201
CONFLICT OF INTEREST	202

ACKNOWLEDGEMENTS	202
REFERENCES	202
CHAPTER 7 COMPUTATIONAL AND THEORETICAL TECHNIQUES IN BIOMEDICINE	207
<i>Saikat Mukherjee, Wayenbam Sobhachandra Singh and Sumita Banerjee</i>	
INTRODUCTION	207
Computational and Theoretical Techniques in Biomedicine	208
History of Computational Biomedicine	208
VIRTUAL PHYSIOLOGICAL HUMAN	208
OTHER EXAMPLES OF COMPUTATIONAL BIOMEDICINE	209
COMPUTATIONAL INTELLIGENCE AND ITS APPLICATIONS IN BIOMEDICINE ...	211
Role of Bioinformatics in Biomedicine	212
Computational Intelligence	212
<i>Algorithms Contributing to Computational Intelligence</i>	213
Computational Intelligence in Understanding Gene Expression	214
Computational Techniques in Analysis of DNA Microarray	214
Analysis of Protein Sequence Using Computational Intelligence	215
Gene Selection Using Computational Intelligence	215
Computational Intelligence in Protein Structure Prediction	215
Computational Tools in Human Genetics	215
CONCLUSION	216
LIST OF ABBREVIATIONS	217
CONSENT FOR PUBLICATION	217
CONFLICT OF INTEREST	217
ACKNOWLEDGEMENTS	217
REFERENCES	217
CHAPTER 8 MICROENCAPSULATION	222
<i>Anh Thuy Vu and Tuyen Chan Kha</i>	
INTRODUCTION	222
BIOACTIVE COMPOUNDS AS CORE MATERIALS	223
WALL MATERIALS	226
Alginate	227
Gum	228
Carrageenan	229
Chitosan	229
Starch	230
Cellulose	230
Pectin	231
Gelatin	232
Wax	233
Combination of Wall Materials	233
ENCAPSULATION TECHNIQUES	234
Preparation of Formulation	235
Encapsulation Method	236
<i>Physical Methods</i>	239
<i>Chemical Methods</i>	244
<i>Physicochemical Methods</i>	246
Release Rate and Release Mechanisms	248
Physical Characterization of Encapsulated Products	251
CONCLUSION	252
CONSENT FOR PUBLICATION	253

CONFLICT OF INTEREST	253
ACKNOWLEDGEMENT	253
REFERENCES	253
SUBJECT INDEX	27;

PREFACE

Frontiers in Nanomedicine Vol. 3, Synthesis of Nanomaterials is a multidisciplinary reference book that comprises some of the latest findings in nanomaterial design for biomedical applications. This volume includes introductory concepts and synthesis methods. Chapter 1 opens with the essentials of biomaterials and pharmacy. Chapter 2 is dedicated to synthesis and characterization, and chapter 3 on nanoengineering of biomaterials. Chapter 4 presents stimuli-responsive biomaterials, chapter 5 nanohydrogels, and chapter 6 self-healing and regenerative materials. While chapter 7 serves as a bridge for computational modeling applied to biomedicine. And chapter 8 covers microencapsulation techniques for drug delivery.

Advances in nanotechnology have been outstanding in the last decades; ergo, this technology will become more deeply entrenched in the lifestyle of the next generations since prolific fields such as nanoengineering, organic and inorganic synthesis, pharmacy, and computational modeling converge to achieve goals in healthcare sectors. Although nanomedicine is a broad and challenging field of the future, its progress already influences modern life. Thereby, concepts such as prevention, recovery, and rehabilitation materialize in the form of new drugs, sanitary disposables, or biomedical devices that are valuable in our daily life.

I hope you will find this book helpful in understanding the foundations and applications of nanomedicine.

Felipe López-Saucedo
Department of Radiation Chemistry and Radiochemistry
Institute of Nuclear Sciences
Universidad Nacional Autónoma de México
Mexico

DEDICATION

*Dedicated to the memory of our beloved Emilia Saucedo Chavez
The true master
I am thou, and thou art I*

List of Contributors

- Aída Luz Villa** Environmental Catalysis Research Group, University of Antioquia, Calle 70 N° 52-21, Medellín, Colombia
- Angélica Cruz Gómez** Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico
- Anh Thuy Vu** Faculty of Chemical Engineering and Food Technology, Nong Lam University, Ho Chi Minh City, Vietnam
- Bryan Chiguano-Tapia** Department of Chemistry, School of Chemical and Engineering, Yachay Tech University, Urcuqui City, Ecuador
- David Romero-Fierro** Department of Chemistry, School of Chemical and Applied Science, Yachay Tech University, Urcuqui City, Ecuador
Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, National Autonomous University of Mexico, Mexico City 04510, Mexico
- David Valverde** Research Laboratory in Sustainable Chemistry, Universidad Estatal a Distancia de Costa Rica, Heredia 40205, Costa Rica
- Emilio Bucio** Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico
- Estefani Chichande-Proaño** Department of Biology, Faculty of Biology, Universidad Central del Ecuador, Quito City 170402, Ecuador
- Julián Eduardo Sánchez-Velandia** Research Group on Sustainable and Supramolecular Chemistry, Department of Inorganic and Organic Chemistry, Jaume I University, Castellón de la Plana, Spain
- Lorena Duarte-Peña** Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico
- Luis Alberto Camacho Cruz** Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico
- Luis Ramón Ortega Valdovinos** Faculty of Chemistry, Universidad Nacional Autónoma de México, 04510, Mexico City, Mexico
- Marlene Alejandra Velazco Medel** Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico
- Moises Bustamante-Torres** Department of Biomedical Engineering, School of Biological and Applied Science, Yachay Tech University, Urcuqui City, Ecuador
Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, National Autonomous University of Mexico, Mexico City 04510, Mexico

iv

- Raul Porcar** Bioorganic Supramolecular Systems Group, Department of Organic and Bio-Organic Chemistry, Faculty of Sciences, UNED, Avenida de Esparta s/n, 28232 Las Rozas-Madrid, Spain
- Saikat Mukherjee** Department of Biochemistry, Manipur University, Imphal, Manipur, India
- Sophía Anchali** Department of Chemistry, School of Chemical and Applied Science, Yachay Tech University, Urcuqui City, Ecuador
- Sumita Banerjee** Department of Oral Pathology, Dental College, Regional Institute of Medical Sciences, Imphal, Manipur, India
- Tri-Dung Ngo** Bioindustrials Research and Development, InnoTech Alberta (Formerly Alberta Research Council (1921-2010) and Alberta Innovates Technology Futures (2010-2016)), 250 Karl Clark Road, Edmonton, Alberta, T6N 1E4, Canada
- Tuyen Chan Kha** Faculty of Chemical Engineering and Food Technology, Nong Lam University, Ho Chi Minh City, Vietnam
- Wayenbam Sobhachandra Singh** Department of Biochemistry, Manipur University, Imphal, Manipur, India

CHAPTER 1**Biomaterials Applied to Medical Devices and Pharmacy****Tri-Dung Ngo^{1,*}**

¹ *Bioindustrials Research and Development, InnoTech Alberta (Formerly Alberta Research Council (1921-2010) and Alberta Innovates Technology Futures (2010-2016)), 250 Karl Clark Road, Edmonton, Alberta, T6N 1E4, Canada*

Abstract: Biomaterials have been utilized in healthcare applications a number of times. Nowadays, subsequent evolution and the increase in the life expectancy of world's population have made biomaterials more attractive and versatile, and have increased their utility. Concerning the manufacturing of medical devices and pharmacy, the development of new biomaterials, new manufacturing methods and techniques has always been the researchers' focus. Recently, nanotechnology and nanomedicine have attracted a great deal of attention, which would further enhance the use of biomaterials in medical devices and pharmacy. In the development of medical devices and pharmacy, the selection of the proper material to be used is of utmost importance. This chapter aims to provide a review of the most used biomaterials. After an explanation of what biomaterials are and what defines them, a more in-depth approach to the major types of biomaterials is presented, such as metal, polymer, ceramic, and composites; also, the advantages and disadvantages of biomaterials, their main characteristics, and preferred applications in the area of medical devices and pharmacy are discussed.

Keywords: Biodegradable, Biomaterial, Ceramic, Composite, Drug delivery, Material, Medical devices, Medicine, Metal, Nanomedicine, Nanotechnology, Pharmacy, Polymer, Tissue, Treatment.

INTRODUCTION

Biomaterials are often defined as substances that have been engineered to interact with biological systems for medical and pharmaceutical purposes. The materials are utilized in many biomedical and pharmaceutical areas, such as the treatment, augmentation, reparation, or replacement of biological function, and in medical devices and pharmacy. Biomaterials also play an integral role in medicine today, such as restoring function and facilitating healing after an injury or disease.

* **Corresponding author Tri-Dung Ngo:** Bioindustrials Research and Development, InnoTech Alberta (Formerly Alberta Research Council (1921-2010) and Alberta Innovates Technology Futures (2010-2016)), 250 Karl Clark Road, Edmonton, Alberta, T6N 1E4, Canada; E-mail: tridung.ngo@innotechalberta.ca

Biodegradable materials have also revolutionized controlled drug delivery design and biomaterial applications for implants and tissue engineering. Pharmaceutical biomaterial is a connecting branch of pharmacy and biomaterial sciences that commonly deals with the strategies related to manipulating bio-originated or bio-applicable materials in a way that can be advantageous for patients in the treatment, diagnosis, or prevention of diseases [1, 2]. Examples of biomaterials utilized for various drug delivery systems and tissue replacement are shown in Fig. (1).

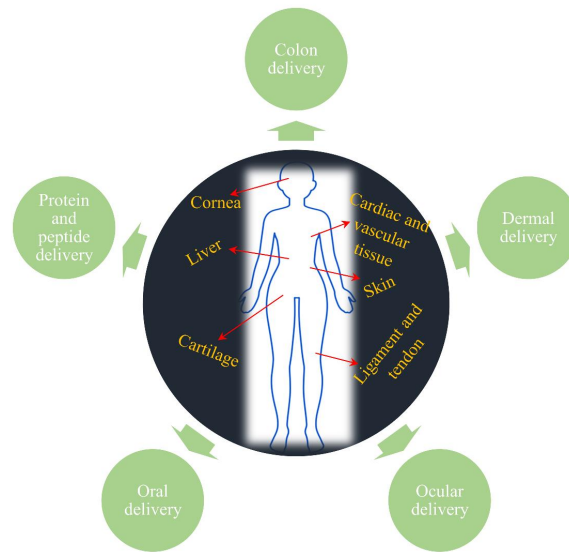


Fig. (1). Biomaterials for various drug delivery (white-green circle) and tissue replacement (orange) [2].

The biomaterial science field is about 50 years old. As biomaterials science has matured, it has taken on much more biological content, moving from an approach that emphasizes inertness to one that embraces biological activity. Researchers are also developing smart biomaterials that can respond biologically to environmental conditions by changing their biomechanical or drug-releasing properties.

CLASSIFICATION

Bioactive biomaterials have wide applications as medical devices and in drug delivery systems. Bioactive biomaterials can be natural (bovine bone mineral matrix, hyaluronic acid, collagen, gelatine, fibrin, agarose, alginate, chitosan, silk) or synthetic (ceramics, metals, polymers, hydrogels, and composites). Biomaterials can be derived either from nature or synthesized in the laboratory using a variety of chemical approaches. From the healthcare perspective, biomaterials can be divided into the following categories: (1) synthetic (metals,

polymers, ceramics, and composites); (2) naturally derived (animal and plant-derived); (3) semi-synthetic or hybrid materials.

Ceramics: Traditionally, ceramics have seen widescale use as restorative materials in dentistry. These include materials for crowns, cement, and dentures. Ceramics are defined as inorganic, non-metallic materials. The ceramic materials are hard, brittle, have great strength and stiffness, wear and corrosion resistance, and low density. Ceramics work well with compressive forces and are electrical and thermal insulators. They are used in dentistry, orthopaedic, some nondental biomedical applications and as medical sensors. Conversely, ceramics are also at risk of having cracks or other defects, and the use of ceramic biomaterials in other fields of biomedicine has not been as extensive, compared to metals and polymers. The poor fracture toughness of ceramics severely limits their use for load-bearing applications. Some ceramic materials are used for joint replacement and bone repair and augmentation [3 - 5]. Ceramic biomaterials are important in the biomedical field due to their chemical similarity to the bone, and are ideal for surgical implants due to their thermal and chemical inertness, and they have high strength, wear resistance, and durability. Ceramic biomaterials also stimulate bone growth and have low friction coefficients. They do not create strong biologically relevant interfaces with bones, but they do promote strong adhesions to bones. Ceramics are biocompatible materials, also known as bioceramics. In the 1950s, inert ceramic materials were found and used for structural bone replacement because of their biocompatibility and mechanical properties. In the 1980s, ceramic materials, like glass-ceramic, bioactive glasses, calcium sulphates and phosphates, were used as bone grafts or for the metallic implant's coatings because of their degradation behaviour [6]. There are different generations of bioceramic materials, and each of them includes some specific type of material as follows: 1) Alumina: aluminium oxide; 2) Zirconia: zirconium dioxide carbons; 3) Calcium phosphates: calcium sulphate, calcium phosphates and sulphates + zinc oxide, iron (III) oxide, calcium carbonate, hydroxyapatite, glasses, glass ceramics, and 4) Bioglass: porous bioactive and biodegradable ceramics, mesoporous materials, and organic-inorganic hybrids.

Metals: Metal materials have intrinsic properties, such as high strength, elasticity, mechanical reliability, good corrosion resistance, wear resistance and fatigue, toughness, and thermal and electrical conductivity. These properties make medical metal devices predominate over other materials. Metallic biomaterials have been used in implants spanning all areas of use in the human body. It is estimated that between 70 and 80% of implants are metallic. Metals are the most widely used for load-bearing implants. These range from simple wires and screws to fracture fixation plates and total joint prostheses (artificial joints) for hips, knees, shoulders, ankles, and so on. In addition to orthopedics, metallic implants

Material Synthesis, Structures and Characterization

Luis Alberto Camacho Cruz¹, Marlene Alejandra Velazco Medel¹, Luis Ramón Ortega Valdovinos², Angélica Cruz Gómez¹ and Emilio Bucio^{1,*}

¹ Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico

² Faculty of Chemistry, Universidad Nacional Autónoma de México, 04510, Mexico City, Mexico

Abstract: Polymers have been employed for the development of medical devices and implants as some of them are biocompatible. Synthetic procedures and extraction techniques have allowed the obtention of different polymers, classified in this chapter as synthetic and natural polymers. In the process of synthesis of the polymer, its properties can be modulated to obtain more flexible or thermostable materials, non-toxic or transparent, depending on the desired properties of the final product. A wide range of polymers have been used for the manufacturing of catheters, valves, tubes, and other medical devices; therefore, in this chapter, there is a brief description of some of them, their chemical structure and properties, and finally, their application in medicine is shown.

Keywords: Biocompatibility, Biomedical, Catheter, Drug delivery, Flexibility, Free-radical polymerization, Glass temperature, Hemocompatibility, Implants, Melting temperature, Polymerization, Structure, Tissue engineering.

INTRODUCTION

For the development of advanced healthcare techniques, many tangible medical tools are essential; for instance, materials for medical devices and for tissue emulation have always been an important part of healthcare. Therefore, when a suitable material or a set of materials have been discovered for certain applications in medicine, they tend to become invaluable. Polymers, in this sense, have dominated the medical scene because of their useful and versatile properties. Although these materials present many advantages in comparison to other

* **Corresponding Author Emilio Bucio:** Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico; E-mail: ebucio@nucleares.unam.mx

alternatives, many intrinsic properties of these materials are not completely compatible with the human body, and therefore, many developments have emerged due to this motivation.

Since many of the processes in human medicine are very complex, the advances in each area of medicine have typically focused on the adaptation of a cornucopia of polymeric alternatives to specific objectives for each organ or tissue. However, properties of the human body can often be emulated only by a handful of polymeric alternatives, so many areas share polymeric solutions between them. Having this in mind, this review focused on describing the properties and common synthetic pathways for some of the most used polymers in medicine, as well as briefly describing their uses in areas of medicine where polymers have been used frequently. It is important to note that this review is non-exhaustive since the number of applications of polymers in medicine is extensive; however, we focused on building a guide to the most used polymeric alternatives. In addition to this, it is important to mention that many advances that seem useful in a laboratory setting or even in *in vitro* testing often show many complications in a real-world setting, either because of the complexity of patient care or because of a lack of insight when designing the system; for example, not considering patient comfort and only looking for certain functionality. Therefore, the potential of a given implementation should be optimistic only when continuous testing has proven its safety and effectiveness.

POLYMERS RELEVANT TO MEDICAL APPLICATIONS

Polymers are macrostructures formed from repeating units called monomers (Fig. 1). These macromolecules, either natural or synthetic, show interesting properties, and thus are used in all aspects of human life. The synthesis or biosynthesis of these macromolecules consists of the linkage of monomers by the effect of an initiator; this initiator can be an enzyme, a free-radical initiator, or ionic compounds, among others. The chemical nature of the initiator and monomers will determine the reaction mechanism of the polymerization and the polymeric structure; for example, they can be obtained by ring-opening polymerization, condensation reactions, or metal-catalyzed reactions, among others. The polymerization techniques and procedures can be reviewed more deeply in books and reviews on polymer chemistry [1, 2]; in this chapter, we will focus on the chemical structure and properties of polymers used in medicine.

With respect to organic polymers, there are different classifications; one of the most accepted in this research line involves natural and synthetic polymers. On the one hand, natural polymers are obtained from natural sources; these are found in animals and plants, and most are intrinsically compatible with the human body;

this group involves polysaccharides, polynucleotides, and polypeptides. On the other hand, synthetic polymers are man-made polymers that are prepared through polymerization reactions. In the following sections, some of the most relevant examples in the medical field of natural and synthetic polymers are presented from a synthetic perspective.

Polymerization reaction

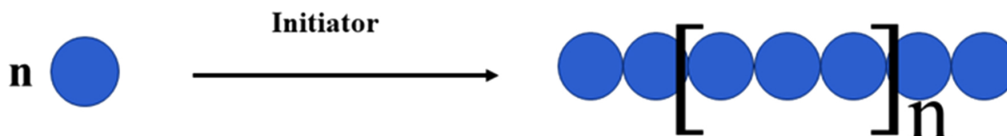


Fig. (1). Schematic representation of polymer synthesis.

Natural Polymers

Natural polymers are obtained from the cells of plants and animals and are naturally produced by biosynthetic pathways. Examples of these polymers include polysaccharides, polypeptides, and polynucleotides, which are advantageous in the medical field because of their high biocompatibility with human tissues and their ability to be bioabsorbable or biodegradable.

Polysaccharides

Chitosan, alginate, hyaluronic acid (HA), and cellulose are some of the most abundant polysaccharides obtained from nature and exploited for medical applications. Even when these polymers are abundant, experimenting with them is not trivial because of non-convenience, such as their low solubility in most solvents due to their supramolecular structure leading to high crystallinity. Therefore, special synthetic conditions have been employed to manipulate this kind of polymers [3, 4]. A brief description of the most common polymers is presented below, as well as their application in the medical field [4 - 6].

Chitosan

Chitosan is a positively charged polymer that prevents microbial growth because of interactions between the bacterial cell wall and the polymer [7]. This synergy between chitosan and bacteria is conditional to the hydrophilicity of the cell wall, which is why chitosan is non-toxic to human cells [8]. Chitosan's ability to adhere to surfaces is one of its major features; this property of mucoadhesive is represented in the polymer chitosan/HA/sodium tripolyphosphate synthesized to encapsulate antibiotics for the treatment of bacterial keratitis [9, 10] (Table 1).

Nanoengineering for Biomedical Devices

David Romero-Fierro^{1,3,*}, Moises Bustamante-Torres^{2,3}, Sophía Anchalí¹ and Emilio Bucio^{3,*}

¹ Department of Chemistry, School of Chemical and Applied Science, Yachay Tech University, Urcuqui City, Ecuador

² Department of Biomedical Engineering, School of Biological and Applied Science, Yachay Tech University, Urcuqui City, Ecuador

³ Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, National Autonomous University of Mexico, Mexico City 04510, Mexico

Abstract: Nanomedicine aims to control, repair, or comprehensively improve all human biological systems, working from a molecular level with engineering devices and nanostructures to achieve medical benefits. This science has had a greater development in recent years, thanks to the great technological advances achieved in developed countries, which is due to the large investment that is made due to the promising incursion of nanotechnology in the diagnosis and treatment of various diseases. This chapter covers this topic from a technical point of view that involves the synthesis of materials and the development of techniques with their respective biomedical application. In addition, the ethical issues related to its application and the actions that have been taken to regulate it are detailed.

Keywords: Applications, Biocompatibility, Biomedical devices, Characterization techniques, Composites, Diagnosis, Disinfection, Drug delivery, Implants, Nanomedicine, Nanoparticles, Nanotechnology, Polymers, Regenerative medicine, Regulations, Synthesis, Technology, Therapy, Toxicity, Treatments.

INTRODUCTION

Brief Review of the Development of Biomaterials

The term biomaterial designates the materials or combination of materials of natural or synthetic origin (polymers, ceramics, metals) used to make systems intended to interact with the biological environment.

* **Corresponding authors David Romero-Fierro and Emilio Bucio:** Department of Chemistry, School of Chemical and Applied Science, Yachay Tech University, Urcuqui City, Ecuador, Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, National Autonomous University of Mexico, Mexico City, Mexico; E-mail: david.romero@yachaytech.edu.ec

In the beginning, were used to make useful devices in the area of medicine and pharmacy, but today, they are also used as supports for cell cultures, in devices for handling proteins in the laboratory, and in the near future, we may find them as a component of biochips (silica + cells) embedded in computers.

Although we can find documented antecedents of the application of different materials in the implementation of therapeutic or surgical techniques before the Christian era, systematic and planned research in the area emerged after the Second World War. In the 1950s, there was a significant increase in the number of cases of empirical adaptation of conventional materials in medical applications, with the majority participation of surgeons motivated by the existence of millions of war-disabled and encouraged by the discovery of antibiotics. The formation of multidisciplinary working groups was a determining factor in the vertiginous evolution observed in this field.

Thus, in 1974, the Society for Biomaterials of the United States was founded, and in 1978, the first World Congress of Biomaterials was held. Since then, evolution has been observed from the search for materials initially considered inert towards what is now called biocompatible with a limited useful life. The advancement of knowledge in general (in biology, chemistry, physics, and electronics), the recognition of the importance of the phenomena that take place at the device-biological environment interface, and the growing interest in having high-performance biocompatible systems gave rise to the differentiation of two fields, biomaterial science and engineering, which bring together researchers and professionals from many disciplines.

From the sustained growth of this area, a great challenge has been raised, which consists of achieving the second generation of materials and devices that are advanced in the structural and functional aspects and that can interact in a controlled way with the biological environment. The materials of the future will be designed based on the requirements of each application as part of active devices in the physiological sense and correctors of pathologies for extended periods. The results of the numerous ongoing projects in tissue engineering, microsystems, and nanotechnologies will contribute significantly to the achievement of this goal.

It should be noted that most of the commercial biomaterials used today were not designed for medical use. That is why, in contact with the organism, they provoke a non-specific response, activation of a wide variety of biological processes, and exhibit very slow kinetics.

Cellular responses are also conditioned by the topography of the material and by the mechanical stimulation to which they are subjected. The biomaterials science

area attempts to elucidate the interaction phenomena that take place between a given material and the biological environment, thus building a database that will be very useful for the design of advanced medical instruments and implants. In the near future, the design of specific cell receptor-bearing surfaces will provide devices capable of exerting precise control of biological reactions.

The process of going from idea to device on the market takes an average of ten years. The rapid advancement of science has now led to the design of sophisticated biomedical materials and devices, which has caused a great gap in the level of knowledge of those who design and research in this field, both manufacturers and users.

The degree of sophistication observed in the field of biomaterial formulation, surface modification techniques, tissue engineering, development of hybrid systems, and technology of medical devices, will require the implementation of multidisciplinary projects for the identification and analysis of variables significant in each case.

FUNDAMENTALS OF NANOENGINEERING APPLIED TO BIOMEDICAL DEVICES

Nanomaterials

A nanomaterial, as defined in 2011 by the European Commission Recommendation, is a natural, accidental, or manufactured material that contains particles where one or more external dimensions are in the size range of 1 to 100 nm, *i.e.*, nanoparticles (NPs) (Fig. 1), and often have properties specific to the size, properties that the material with larger sizes does not have [1].

Advances in nanoscale characterization techniques, such as microscopy, allow us to understand and manipulate matter on such small scales that a few years ago, it was unimaginable [2]. Since then, although there is still controversy over the correct definition of nanomaterials, there has been an exponential growth of nanotechnological products on the market, including different areas, such as biomedical applications, which is known as nanomedicine.

Nanomedicine

Nanomedicine is the application of nanotechnology in health. As defined by the European Science Foundation, nanomedicine uses nanosized tools for the diagnosis, prevention, and treatment of diseases and to gain a greater understanding of the complex underlying pathophysiology of the disease. The last

Stimuli-responsive Biomaterials with Pharmacological Applications

Julián Eduardo Sánchez-Velandia^{1,*}, David Valverde², Raul Porcar³ and Aída Luz Villa⁴

¹ Research Group on Sustainable and Supramolecular Chemistry, Department of Inorganic and Organic Chemistry, Jaume I University, Castellón de la Plana, Spain

² Research Laboratory in Sustainable Chemistry, Universidad Estatal a Distancia de Costa Rica, Heredia 40205, Costa Rica

³ Bioorganic Supramolecular Systems Group, Department of Organic and Bio-Organic Chemistry, Faculty of Sciences, UNED, Avenida de Esparta s/n, 28232 Las Rozas-Madrid, Spain

⁴ Environmental Catalysis Research Group, University of Antioquia, Calle 70 N° 52-21, Medellín, Colombia

Abstract: Natural and synthetic biomaterials are useful for different biological and industrial applications, and their impact, as well as the interest (in both academy and industry) in those materials, have grown up in the last few years. This chapter presents some advances in the synthesis of biopolymers and related materials using different synthetic and non-synthetic strategies (from conventional chemical synthesis using click reactions and more sophisticated ones, such as electrospinning) and their applications in the field of medicine and biology. For the treatment of diseases and tissue engineering, we describe several biomaterials prepared by different extraction methodologies from natural sources (*e.g.*, chitosan and collagen) and their benefits as biodegradability, circular economy, and recycling. Several synthetic approximations for the preparation of biopolymers and their potential in several applications are discussed based on the available information about synthesis, application, and biodegradability. As several approaches are currently applied for the synthesis of biomaterials with different applications, in the second and last sections, we discuss some of these strategies considering the green chemistry principles. In many cases, an appropriate building and synthesis of biopolymers could optimize chemical and physical properties, such as solubility, viscosity, adhesiveness, degradability, and *in vivo* response. In this chapter, also the conditions of synthesis of monomers will be discussed, focusing on some advanced and green strategies for replacing toxic solvents (and even complexes) that are used and make the process of obtaining green materials difficult according to the desired target biopolymers. Finally, some applications related to pharmacology and tissue engineering will be presented.

* Corresponding author Julián Eduardo Sánchez-Velandia: Research Group on Sustainable and Supramolecular Chemistry, Department of Inorganic and Organic Chemistry, Jaume I University, Castellón de la Plana, Spain; E-mail: velandia@uji.es

Keywords: Biodegradability, Biomaterials, Biopolymers, Chitosan, Click reaction, Collagen, Drug delivery, Electrospinning, Green chemistry, Hydrogels, Implants, Pharmacology, Tissue engineering.

INTRODUCTION

The treatment of different diseases and the recovery of parts of living systems (tissue engineering (TE), cellular adhesion) have given to scientists the revolutionary tools to evaluate and promote the use of several branches of chemistry and biology. Then, biotechnology and biomedical sciences, especially drug delivery, have been widely explored because of their importance in human lives [1, 2]. The central role of polymers would be the development of functional biomaterials (polymers derived/extracted from living organisms) [3], which could be responsive to desired physiological properties [4]. In this way, biomaterials have attracted increased attention as new matter for the surface, construction [5], and different applications, including TE, recovery of body parts (after injury or disease), drug delivery, as biosensors, molecular probes, and nanoparticles. For example, among biomaterials used for these applications, chitosan has become a good candidate for TE having several outstanding properties related to biodegradability, biocompatibility and antimicrobial activity [6]. The ideal biomaterial is one that is considered inert rather than one that dynamically interacts with cellular behavior, increasing different levels of sophistication towards managing complex physical and biological properties; in addition, it also should be biocompatible [7]. In connection with the green chemistry principles, the design of chemical products, and more specifically, the development and advances in green polymers (biopolymers materials) chemistry (Fig. 1) [8] are still an exciting topic that is of interest to scientists because of the potential economic benefits, mitigation of disposal problems, biodegradability, circular economy, recycling, and their numerous applications in medical and also in industrial areas [9, 10].

There are several ways to produce biopolymers (concerning typical synthetic polymers: poly(hydroxyethyl methacrylate), poly(lactic-*co*-glycolic) acid (PLGA), poly(vinyl alcohol), and poly(ethylene glycol)) in order to make them useful for several applications; biopolymers can be isolated from natural sources (plants, algae, and hyaluronic acid extracted from umbilical cords of newborn children) or can be obtained by *in vitro* synthesis with enzymes and using fermentative production (*e.g.*, polysaccharides) [11]. An example of an application of this kind of biopolymers (biomaterials) is in TE (supplement or simply replace damaged or diseased tissue with different synthetic biopolymers or biomaterial [12]), which widely requires the use of physical, chemical, biological

and engineering processes to study the effect on the behavior of cells (and their interaction with immunologic cells, like macrophages) [13, 14]. On the other hand, biomaterials with biodegradability properties could be used as a temporary scaffold for tissue regeneration, gene therapy (transplantation to correct genetic disorders), controlled drug delivery, bio-nanotechnology, and fiber-forming polymers [15]. Thus, a correct characterization of bio-active materials (polymers) requires an interdisciplinary approach to connect these properties with their clinical applications. In general, the polymer type influences the structure and properties of the resulting biomaterials caused by several chemical interactions (covalent, ionic, van der Waals, London).

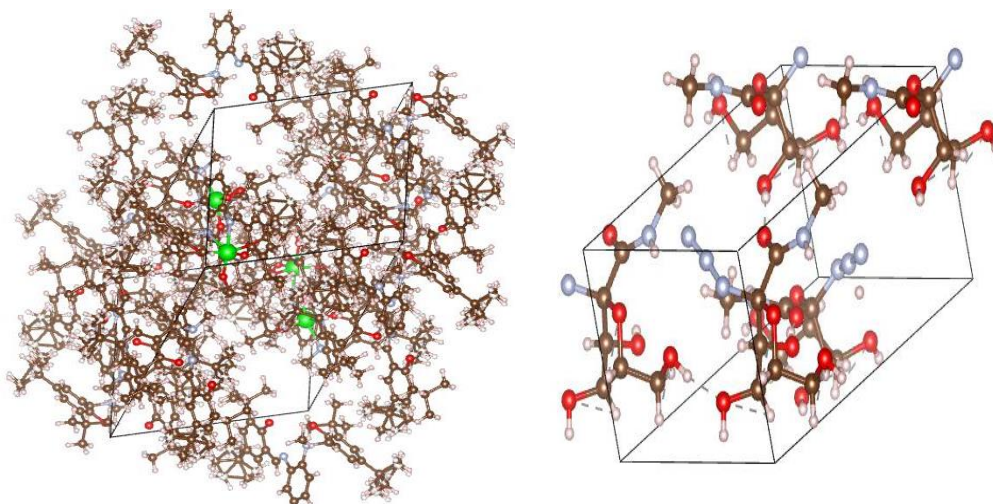


Fig. (1). Examples of biopolymers based on **a)** zirconium and aluminum salen initiators and **b)** tetrahydrofuran amino acids. Figure were modified in VESTA software [16] and downloaded from studies published earlier [17, 18].

Among existing biopolymers (synthetic and natural), lignin (which can be extracted from the cell wall, together with glucose, cellulose and hemicellulose; (Fig. 2)), after cellulose, is the second with exceptional properties as biopolymer [10]. This polymer is biocompatible, cheap, environmentally friendly, and easily accessible [19]. In addition, lignin can be used as a molecule to further replace fuels and also presents antimicrobial and anticancer properties [20]. On the other hand, lignocellulose, which is the most abundant renewable macromolecule on earth, is the source of many polymers widely used as starting materials or as building blocks of hydrogels [21]. It has been found that several of these materials have antimicrobial properties because of their structure that contains polyphenolic compounds.

Hydrogels and Nanohydrogels

Moises Bustamante-Torres^{1,2,*}, David Romero-Fierro^{2,3}, Bryan Chiguanotapia³, Estefani Chichande-Proaño⁴ and Emilio Bucio²

¹ Department of Biomedical Engineering, School of Biological and Engineering, Yachay Tech University, Urcuqui City, Ecuador

² Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, National Autonomous University of Mexico, Mexico City 04510, Mexico

³ Department of Chemistry, School of Chemical and Engineering, Yachay Tech University, Urcuqui City, Ecuador

⁴ Department of Biology, Faculty of Biology, Universidad Central del Ecuador, Quito City 170402, Ecuador

Abstract: Hydrogels and nanogels are exciting and promising materials for many applications due to their versatile features, such as interacting and absorbing a significant amount of water and other solvents, excellent mechanical properties, and adhesiveness. These materials are obtained based on the nature of the raw materials (natural or synthetic) and the synthesis route. There are many ways to synthesize hydrogels and nanogels; however, these routes can be classified as physical or chemical. Physical synthesis forms a reversible cross-linking. In contrast, chemical synthesis can generate a stable, rigid, and irreversible polymeric structure. Nowadays, the term “smart hydrogel” has gained significant attention due to its response to external factors, such as pH, temperature, light, electricity, and magnetic, and even an internal approach as substrate. Besides, the characteristics and properties of these polymeric matrices can be enhanced through the synergic relationship with nanoparticles. The inner and outer structure and the behavior of these materials can be studied through characterization techniques, such as light scattering, gel permeation chromatography, viscometry, thermal analysis, spectroscopies, microscopies, and swelling.

Keywords: Applications, Characterization, Hydrogels, Nanogels, Polymeric Matrix, Synthesis.

* **Corresponding author Moises Bustamante-Torres:** Department of Biomedical Engineering, School of Biological and Engineering, Yachay Tech University, Urcuqui City, Ecuador and Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, National Autonomous University of Mexico, Mexico City, Mexico; E-mail: moises.bustamante@yachaytech.edu.ec

INTRODUCTION

Hydrogels and nanogels are three-dimensional polymer networks with a great capacity to uptake water and other solvents due to their hydrophilic conformation. Hydrogels are usually prepared from polar monomers. Their starting materials can be divided into natural polymer hydrogels, synthetic polymer hydrogels, and combinations of the two classes [1]. In the past two decades, natural hydrogels have been gradually replaced by synthetic hydrogels with long service life, high water absorption capacity, and high gel strength [1].

Even though natural polymers have good bioactive properties, they are found to have low mechanical properties. Therefore, the use of synthetic polymers, because of their excellent mechanical strength and well-defined structure, can be modified to improve biocompatibility and biodegradability [2 - 5]. The first hydrogel synthesized was based on poly-2-hydroxyethyl methacrylate in the 1950s for its potential biomedical applications [6, 7]. Water-soluble polymers, such as poly(acrylic acid) (PAAc), poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), poly(ethylene glycol), polyacrylamide (PAM), and some polysaccharides, are the most common systems used to form hydrogels [8].

Some hydrogels present a stimuli-responsive approach where external stimuli can control the swelling. The majority of stimuli-responsive hydrogels are created using conventional (traditional) methods of synthesis of a relatively small number of synthetic polymers, especially methacrylate derivatives and their copolymers [9]. Other hydrogels have emerged with click chemistry employing physical interactions, such as metal coordination complex formations and stereo complex formations [10].

Nanogels are considered a three-dimensional hydrogel material at the nanoscale size range. They are formed through cross-linked swellable polymer networks with a high capacity to uptake and hold water without dissolving it into the aqueous medium. They can trap bioactive compounds inside their nanoscale core. Nanogels have been obtained by covalent cross-linking of the hydrophilic or hydrophobic polymer chains in these polymer micelles either at the core or shell [11].

As hydrogels and nanogels are subjected to polymeric cross-linking, there are different ways to synthesize them. Physical and chemical cross-linked can be an approach to obtaining a material with specific properties. However, the nature of the polymeric chains also plays an essential role in the final properties of the material. The increasing demand for biocompatible, biodegradable, environmentally friendly, and low-cost products led to replacing synthetic polymers with natural ones [12]. Likewise, the hydrogels obtained can be

characterized by different techniques, such as gel permeation chromatography, viscosimetry, differential scanning calorimetry (DSC), microscopy, spectroscopy, limit swelling, *etc.*, to study determining properties, such as mechanical, swelling, porosity, *etc.* Fig. (1) illustrates a representation of the structure of hydrogel and nanogel.

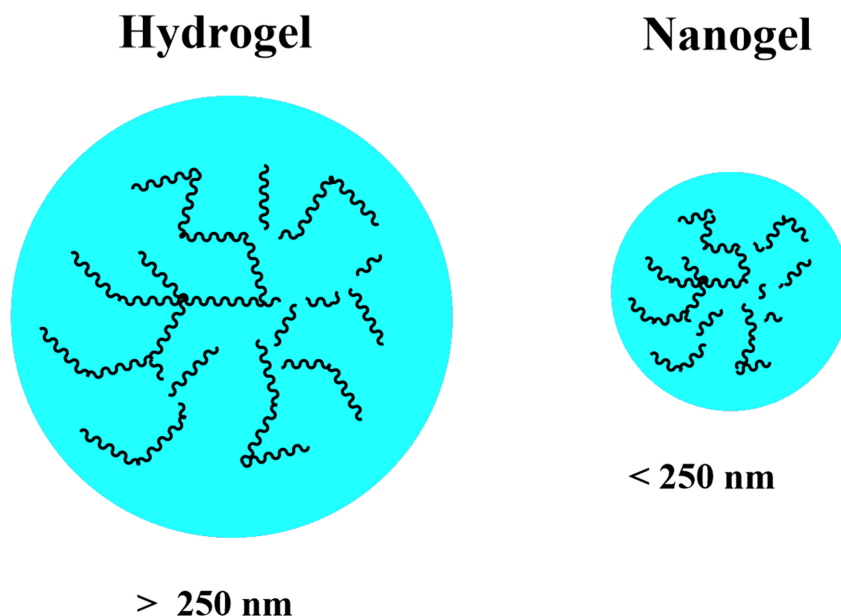


Fig. (1). Schematic representations of hydrogel and nanogel.

Natural biopolymers in the form of hydrogel are better than synthetic polymers in several aspects. The main feature is their biocompatibility with physiological environments and their abundance in nature, homogeneity, and environmental sensitivity. Over the last few years, the study on wounding care using natural polymers has played an important role. In literature, several wound dressing materials are reported, such as cellulose, chitosan, agar, *etc.* Recent reports have indicated that the addition of mineral clay into the hydrogel matrix improves the mechanical, thermal, and barrier properties of nanocomposite hydrogels as the stiffness of the material increases. Furthermore, adding mineral clays to the nanocomposite hydrogels enhances biocompatibility, increases the reactivity of the surface, and shows better rheological behavior [13].

HYDROGEL

Hydrogels are made up of cross-linked polymeric chains. They are water-swollen three-dimensional networks based on hydrophilic polymer chains [14]. The

Self-healing and Regenerative Materials

Lorena Duarte-Peña^{1,*} and Emilio Bucio¹

¹ Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico

Abstract: Self-healing systems have a high capacity for regeneration, managing to regain their functionality after suffering structural damage. This characteristic provides the materials with high durability and security in their use. Living organisms are the ideal self-healing systems, which is why they have served as inspiration for the development of these materials. Self-healing synthetic systems also show biomimetic characteristics and are widely studied as biomaterials. Different ceramic, metallic and polymeric materials can show self-healing capacity, although the polymeric self-healing systems have versatility, adaptability, and ease of synthesis. This chapter describes the general aspects, properties, and classification of polymeric self-healing materials, focusing on extrinsic and intrinsic self-healing materials. The self-healing behavior of extrinsic materials depends on microcapsules and vascular structures that act as healing agents' delivery systems. The self-healing behavior of intrinsic materials is governed by the presence of a dynamic crosslinking based on dynamic covalent bonds or non-covalent intermolecular interactions. In addition, examples of current developments in this field are shown.

Keywords: Biomaterials, Covalent bonds, Dynamics, Hydrogels, Intermolecular forces, Non-covalent interactions, Polymeric networks, Regenerative, Self-healing.

INTRODUCTION

One of the most astonishing characteristics of living organisms is the regenerative capacity of tissues, which have containment, regeneration, and repair damage mechanisms; there are even the systems that provide constant renewal, like the skin. This ability to respond spontaneously to structural damage has served as inspiration for the synthesis of self-healing materials. Self-healing materials can recover all or a large part of their initial properties after undergoing structural damage or deterioration caused by exposure to environmental and application

* Corresponding author Lorena Duarte-Peña: Department of Radiation Chemistry and Radiochemistry, Institute of Nuclear Sciences, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico; E-mail: lorena.du.pe@gmail.com

conditions (changes in temperature, radiation, corrosive substances, chemical attacks, *etc.*), prolonging their useful life [1]. These materials have a wide range of applications ranging from the construction sector to biotechnology. However, in recent years, their use in biomaterials manufacturing has increased since self-healing properties allow the preservation of medical devices in aggressive environments, such as the biological. Besides, due to their biomimetic characteristics, these materials can be used for the synthesis of tissues and the manufacture of high-performance and durable prostheses.

According to the definition, both self-recovery and self-healing refer to the ability of a material to recover its mechanical and rheological properties after undergoing damage, so they are usually used as synonymous. However, it is worth noting that self-healing additionally refers to a structural repair of the material, that is, recovery of its original shape [2]. Self-healing properties may mainly be present in ceramic, metallic, or polymeric materials. Ceramics are inert materials that usually have high hardness and compression resistance and low thermal and electrical conductivity. These characteristics are related to strong ionic and covalent bonds in ceramics' inorganic structure. Despite their compression resistance, ceramics are fragile and tend to crack, which limits their application; this problem could be overcome with self-healing ceramics [3]. Generally, ceramic materials are repaired by diffusion processes, but using this mechanism to give self-healing properties is difficult since temperatures above 1000 °C are required to overcome the internal force of the material and restructure it [4]. An alternative method consists of healing agents, which respond to surface cracks formation and stop the propagation, dispersed in the matrix [5]. Healing agents can be directly dispersed in the matrix or encapsulated in polymers [6, 7].

On the other hand, three main methods of self-healing in metallic solids are known. The first is intrinsic solid-state healing, which occurs in metals and alloys that automatically recover when heating at a temperature lower than the material melting point but higher than the service temperature, without external self-healing agents. The second is the extrinsic liquid-assisted method, which uses lower melting temperature metals or alloys as healing agents for higher melting point metal matrices. When the healing agent is heated, it flows to fill the crack and seal the damage while it solidifies; weld is an example of this system [8]. The third method is used to heal severe damage and is based on shape memory alloys; it is called the extrinsic shape memory alloy-assisted method [9].

For both ceramic and metallic materials, it is common to use self-healing polymeric coatings to protect and increase the life of devices. Polymeric materials are the most variable and efficient self-healing materials due to their versatility, mobility, and the facility for chemical modification of their polymeric structures.

In addition, self-healing polymer properties can be adapted to the application, which allows their wide use in the biomedical and biotechnological fields [10]. The ideal self-healing materials are multifunctional polymers that meet the mechanical requirements of the application, also being biodegradable and prepared from materials available with low energy methods.

Due to the versatility of polymeric structures, self-healing can be carried out using different approaches, classifying into two types of self-healing materials: extrinsic or irreversible and intrinsic or reversible, which in turn can present two behaviors, autonomous or non-autonomous. In autonomous materials, self-healing takes place simultaneously after damage, while non-autonomous materials require to be activated by an external stimulus. Extrinsic self-healing materials are based on healing agents incorporated into polymeric matrices through encapsulated or microchannels, which act in response to damage. On the other hand, intrinsic self-healing materials have dynamic bonds that break and recover when materials undergo damage [11].

In polymeric materials, the crosslinking interactions determine the mechanical properties of the material. Networks that depend on dynamic interactions tend to have low mechanical resistance and are soft, making handling difficult. Thus, there must be a balance between the self-healing capacity and mechanical properties; in addition, factors such as healing time, overall material performance, and the extent of the damage must be considered [1]. Depending on the use, materials may exhibit loss of local or global functionality. In the first case, the properties of a section of the material are degraded, but the complete piece maintains its behavior, and in the second case, the general properties of the material decrease in comparison to the original (before subjecting it to loads and operating environments) [12].

The self-healing capacity of a material can be measured by changes in the properties of the material when subjected to structural damage. Qualitatively, the self-healing capacity can be observed by the macroscopic method in which the material is divided into equal parts, which are dyed with different colorants and cut, then the parts are put in contact under conditions that stimulate healing, and finally, the degree of restoration of the material is observed [13]. Quantitatively, the change in the physical properties of the material is measured during each healing cycle. Depending on the property to be measured, different techniques can be used. The dynamic mechanical analysis allows the study of the viscoelastic properties (storage and loss modulus), shear storage modulus, and coefficient of thermal expansion [14]. The differential scanning calorimetry (DSC) measures the glass-transition temperature (T_g) of the matrix and active agents and monitors the healing and curing processes. The thermogravimetric analysis (TGA) determines

CHAPTER 7

Computational and Theoretical Techniques in Biomedicine

Saikat Mukherjee^{1,*}, Wayenbam Sobhachandra Singh¹ and Sumita Banerjee²

¹ Department of Biochemistry, Manipur University, Imphal, Manipur, India

² Department of Oral Pathology, Dental College, Regional Institute of Medical Sciences, Imphal, Manipur, India

Abstract: Biomedicine research has gained momentum for the development of various computational and theoretical techniques. Researchers working in biomedicine and bioinformatics depend on computational intelligence and its widespread applications. New algorithms have been described that enable computational simulations and mathematical modelling in coordination with analytical methods to comprehensively study biological systems. Many algorithms, such as Artificial Neural Networks (ANNs), Rough Sets (RS), Fuzzy Sets (FS), Particle Swarm Optimization (PSO), Evolutionary Algorithm (EA), *etc.*, allow reliable and accurate analysis of vast data sets in biomedicine. Computational techniques analyse gene expression data obtained from microarray experiments, predict protein-protein interactions, model the human body in disease conditions, such as Alzheimer's disease or cancer, follow the progression of the diseases, classify tumours, analyse which genotype responds to certain drugs, *etc.* Multiscale modelling of the human body in various disease conditions is a topic of interest in this context. Relevantly, the "Virtual Human" project has initiated the study of human organs and systems in disease conditions based on computational modelling. Therefore, many computational and theoretical techniques have been developed for intelligent information processing to lead an expansion in biomedicine research.

Keywords: Artificial neural networks, Computational intelligence, Computational techniques, DNA microarray, Evolutionary algorithms, Fuzzy logic, Fuzzy sets, Genetic algorithm, Particle swarm optimization, Virtual human project, Tumour classification.

INTRODUCTION

Computational bioscience and biomedicine consist of contributions from various sciences, such as computational genomics, mathematics, system biology, bioinformatics, and public health informatics. Many algorithms have continuously

* Corresponding author Saikat Mukherjee: Department of Biochemistry, Manipur University, Imphal, Manipur, India; Phone: +918787490855; Email: mukherjeesaikat333@gmail.com

been generated to deal with vast biological and biomedical data. This has resulted in developing algorithms for machine learning and analysis of functional information with applications ranging from analysis of gene expression data, single sequence data, molecular detection of pathogens, modelling of multiscale biomedical systems, reconstruction of biological networks to detection of genetic factors contributing to the disease, resulting in a revolution in biology.

Computational and Theoretical Techniques in Biomedicine

Computational biomedicine combines biological observation and computer modelling. It involves computer-based tools and approaches to simulate and model the human body in a disease condition. Various branches of science, such as epidemiology, pathology, and population health, are involved in computational biomedicine. Computational biomedicine gets support from simulation and modelling studies involving computer science and mathematics. It can reliably and precisely choose candidate compounds for drugs through *in silico* trials, which otherwise are generated through intensive laboratory processes [1].

History of Computational Biomedicine

In 2000, the first draft of the human genome sequence was published. The molecular and genetic information enables us to understand the whole biology of a human. There are complex interactions between molecules and networks in physiological and biochemical processes. Complex interactions between genetic and environmental factors cause diseases. It has been observed that environmental factors influence the behaviour of genes, as described by Denis Noble in the book titled “The Music of Life” [2, 3]. The first computer-based model of cardio physiology was developed in 1960 by Noble [4], who has been recognized as one of the fathers of integrated system biology. In Europe, Information and Communication Technology has broad applications in research. Therefore, the discipline of Information and Communication Technology receives a good amount of funding in research areas involving applications of integrative systems biology to medicine. In addition, European Union funds international collaborations involving cross-disciplinary research in biological sciences [5]. Such cross-disciplinary research involves the participation of clinicians, computational biologists, and other industrial scientists and entrepreneurs.

VIRTUAL PHYSIOLOGICAL HUMAN

Computational biomedicine is also called virtual physiological human (VPH) in Europe. European Union supports the integrative system biology research framework 7 program, also known as The VPH initiative [6], which has provided Euro 200 million in funding. The initiatives gained momentum when International

Physiome Project was set up in 2001 by the International Union of Physiological Societies [7]. It aims to develop integrated computational models of the organs and systems of the human body and analyze their structure and function in health and disease conditions. The project aims at integration into a “Virtual Human.” In VPH, diseases in human organs and systems are studied based on computational models at several spatial and temporal scales. As a part of this VPH scheme, VPH Network of Excellence was set up as an initiative to support VPH-funded researchers as well as training, collecting, and disseminating computational tools, research dissemination, and networking. In the VPH annual conference in Brussels in 2012, the research papers described various models related to modelling the cardiovascular system [8]. The VPH initiatives comprised projects related to the multiscale modelling of human physiology and pathology. Moreover, VPH addresses projects that deal with the multi-scale modelling of human physiology and pathology. VPH research is devoted to modelling the immune system, respiratory system, central nervous system, and musculoskeletal system. Some VPH research initiatives also support research projects dedicated to oncology. Cardiac physiology has been modelled since Noble’s simulations of the movement of ions into and out of heart cells involving four differential equations [4]. Similarly, Noble’s group, in collaboration with Peter Hunter from VPH, collaborated and developed a multiscale model of the human ventricle for testing candidate drugs for side effects on the heart. Nowadays, various research groups are attempting to develop patient-specific models of a complete cardiovascular physiome.

OTHER EXAMPLES OF COMPUTATIONAL BIOMEDICINE

In the computational biomedicine conference held in 2019 in London, funded by European Commission, many new research projects were discussed. Molecular biology has been a success for over the last 60 years, along with modern approaches to drug discovery and the design of molecular medicine. Considering this, various examples have demonstrated its successful application [1, 9, 10]. Wan *et al.* described a combination of hit-to-lead and lead-discovery methods applied to the scientifically and pharmaceutically important class of G-protein coupled receptors to demonstrate how initial lead compounds of diverse natures can be selected and then can be refined [11]. In addition, Konig and Riniker used molecular mechanics to investigate the discrepancies between classical and forcefield-based protein calculations. However, they reported enhanced accuracy of classical parameterization in carefully tuned force fields. Computational molecular simulation also plays a direct role in clinical medicine, examining which drug a genotype or genetic variant can respond to. Sequencing of the tuberculosis genome of infected individuals enabled Philip Fowler to report free energy estimation could be used to treat bacterial or viral infections. The time

Microencapsulation

Anh Thuy Vu¹ and Tuyen Chan Kha^{1,*}

¹ Faculty of Chemical Engineering and Food Technology, Nong Lam University, Ho Chi Minh City, Vietnam

Abstract: It is well-known that bioactive compounds have many positive advantages for human health. The extension of their shelf life and their applications in the food and pharmaceutical sectors are important issues. Microencapsulation is one of the proven methods to protect bioactive compounds and enable various applications. In this chapter, microencapsulation technology, including the important steps of understanding the physicochemical properties of the bioactive compounds, selection of suitable encapsulation, and microencapsulation methods, is presented. Understanding of physicochemical properties of bioactive compounds and wall materials is the first important step. There are a variety of microencapsulation methods that can be selected to encapsulate the bioactive compounds, depending on the application purpose of the resultant microencapsulated product. In addition, the release rate and release mechanism of microencapsulated particles also play an important role, determined by the selection of wall materials and microencapsulation methods. Finally, methods to evaluate the physicochemical stability of the solution before microencapsulation and the characterization of the microencapsulated particles are also presented. Several examples of successful encapsulation technology and recommendations for further studies of the bioactive compounds are also reported throughout the chapter.

Keywords: Bioactive compound, Microcapsule release mechanism, Microencapsulation, Release rate.

INTRODUCTION

It is well-known that bioactive compounds play an important role in human health. A huge number of studies show that bioactive compounds have many positive effects on the treatment of diseases, such as cancer, inflammation, cardiovascular disease, *etc.* However, these compounds are usually unstable and very easily degrade under environmental conditions, such as temperature, light, air, humidity, *etc.* Therefore, this limits the application of these compounds in food and pharmaceutical products. In order to overcome this drawback, one of the effective techniques is to encapsulate those bioactive compounds to prevent

* Corresponding author Tuyen C. Kha: Faculty of Chemical Engineering and Food Technology, Nong Lam University, Ho Chi Minh City, Vietnam; Email: khachantuyen@hcmuaf.edu.vn

exposure to environmental conditions and simultaneously enable various applications in different fields.

Encapsulation is a technique where the material of interest (mainly bioactive compounds) is enveloped by at least one layer of wall material. The material of interest for encapsulation is referred to as the core material, whereas the wall material is also known as the encapsulating agent, capsule, membrane, carrier, and shell [1]. The core material can be in solid, liquid, or gaseous form [2]. The encapsulated products can be produced in different forms, such as simple (one layer of wall material with one core material), multi-wall (more than one layer of wall materials with one core material), and multi-core (one layer of wall material with more than one core material) [2].

One of the main purposes of encapsulation in food is to mask the taste and odor of the core material [3]. Other advantages of this technique include the sensitive core material can be protected from environmental conditions (*e.g.*, heat, moisture, light, and air); the procedure for handling the core material is easier (*e.g.*, converting a liquid or gas into a solid form); the reaction of bioactive compounds in the mixture can be separated; and the release rate of core material from wall material can be controlled by the right stimulus (temperature, irradiation, pH, or osmotic shock) at a certain time [4]. The number of encapsulated food or pharmaceutical products has significantly increased in the past decade. Recently, a wide range of core materials have been encapsulated by different types of wall material and produced by various encapsulation techniques based on the desired applications.

It is well-known that two important factors contributing to the efficiency of encapsulation are the properties of the wall material and the encapsulation technique. Therefore, these two factors must be taken into consideration in order to produce a desired encapsulated product. This chapter addresses the characterization of the core and wall of materials, as well as the principles of the encapsulation techniques and the release mechanisms. In addition, analytical measurement methods are also presented to evaluate the physicochemical stability of the initial preparation solution before encapsulation and the resultant encapsulated products.

BIOACTIVE COMPOUNDS AS CORE MATERIALS

Today, when human living standards are increasing, the need to eat is no longer a full meal but a diet having a nutritious, healthy, and therapeutic effect. Many studies show the positive effects of biological compounds from natural ingredients on common diseases, such as type II diabetes, obesity, osteoporosis, cardiovascular disease, and cancer. Therefore, the development of products from

bioactive compounds is of great significance in the food and pharmaceutical industries. However, bioactive compounds are often unstable and easily degraded under environmental conditions, so preserving these compounds by appropriate methods, such as microencapsulation, is preferable (described in the following section).

In the microencapsulation method, understanding the physicochemical properties of bioactive compounds (also known as core materials) is one of the most important criteria. The core materials should not react with the wall materials and be released under the desired conditions. Currently, there are many published studies on extracting bioactive compounds from various agricultural and aquatic raw materials, and food waste. Until now, there have been many ways proposed to classify bioactive compounds based on material sources, functional properties, or molecular structures. The process of understanding physicochemical properties and classification of bioactive compounds according to physicochemical properties is presented in Fig. (1). Different extraction methods could be used to extract bioactive compounds from different sources, including plants, animals, and seafood. Selection of the appropriate extraction method plays an important role in obtaining the highest content of the desired bioactive compound and the lowest content of the undesired compound. Conventional and novel extraction methods of bioactive compounds have been reviewed in the published literature, including advantages, disadvantages, mechanisms, and optimal extraction conditions [5, 6]. As compared to the conventional extraction method, it is reported that various bioactive components can be extracted by novel methods, including microwave-assisted extraction, ultrasound-assisted extraction, and supercritical carbon dioxide extraction. The main advantages of those methods are being more environmentally friendly, reduced extraction time, increased oil yield, high quality, and chemically solvent-free. Potentially understanding the advantages and drawbacks of different extraction methods can pave way for opportunities to combine different extraction methods to overcome the limitations and retain the advantages. Several combined extraction techniques, including ultrasound with microwave, have been successfully applied to extract bioactive compounds in foods [7]. For example, Lianfu and Zelong [8] successfully extracted lycopene from tomatoes using a combination of ultrasound and microwave. The results confirmed that the shorter extraction time, higher yield of lycopene, and less amount of solvent used were obtained in this combined extraction method compared to the ultrasound-assisted extraction.

It is well-known that bioactive compounds play an important role in human health. Many studies report that human health benefits are related to the chemical structure of the compounds. Several physical and chemical properties of common bioactive compounds are presented in Table 1. Based on those properties, an

SUBJECT INDEX

A

Acid 2, 10, 16, 18, 19, 20, 21, 22, 27, 29, 31, 32, 44, 45, 68, 74, 75, 76, 80, 81, 82, 87, 89, 90, 92, 112, 118, 121, 126, 128, 147, 149, 151, 154, 156, 157, 192, 196, 200, 201, 226, 229, 230, 231, 246, 247

acetic 121, 126

amine-carboxylic 147

ascorbic 121

boric 196

boronic 31, 32, 196

carboxylic 27, 29, 118, 126, 149, 156, 157, 246

citric 128

dicarboxylic 230

dihydrolipoic 87

ellagic 247

formic 80

glucuronic 19, 229

glutamic 89

hyaluronic 2, 16, 18, 92, 112, 154

hydrobromic 201

hydrocaffeic 192

hydrochloric 81

lactic-co-glycolic 21, 22

mannuronic 18

mercaptopoacetic 87

methacrylic 44, 151

nitric 246

oleic 74, 75, 76

phenolic 82

phenylboronic 32, 196

polyacrylic 20, 200

polygalacturonic 231

polylactic 10, 22, 68, 90, 128, 154

sulfonic 149

Alzheimer's disease 90, 207, 211, 216

Antibacterial activity 230

Antifungal agent 44

Antimicrobial activity 43, 89, 93, 112, 118, 126

Artificial neural networks (ANNs) 207, 212, 213, 214, 215

Aspergillus fumigatus 88

Atomic force microscopy (AFM) 83, 84, 125, 166

Autocatalysis 250

B

Bacillus subtilis 89

Bacterial cellulose (BC) 128, 191

Bioactive 3, 6, 123, 124, 128

 factors 128

 glasses 3, 6, 123, 124

Biopolymers 111, 112, 113, 114, 115, 116, 117, 122, 124, 125, 130, 131, 230, 231, 232

 amide-based 117

 anionic 230

C

Cancer 210, 215

 colon 215

 lung 210

Cardiovascular 4, 6

 devices 6

 surgery 4

Central nervous system (CNS) 90, 91, 209, 215

Chemical 74, 79, 155

 cross-linking of preformed polymers 155

 decomposition 74

 vapor deposition method 79

Chitosanase 30

Coacervation method 69, 70, 234, 247, 250

Collagen production 93

Computational 213, 214, 216

 intelligence techniques 213

 simulation techniques 216

techniques in analysis of DNA microarray
214
Cross-linking polymerization 159
Cryodesiccation 242
CVD process 79
Cyanobacteria 82

D

Debye induction forces 198
Decomposition 26, 44, 79, 71, 80, 124
 organic 71
 byproducts 26
Diels-Alder reactions 147, 148, 186, 195
Digital fabrication techniques 10
Diseases 1, 2, 11, 39, 40, 41, 60, 62, 86, 90,
 95, 112, 207, 208, 209, 210, 215, 216,
 222, 223
 cardiovascular 11, 222, 223
 genetic 86
 metabolic 216
 neural 95
 neurological 216
 ocular 39, 40, 95
 orphan 210
 retinal 41
DLS technique 164
DNA 86, 87, 116, 207, 210, 214
 based nanomachines 86
 microarrays 207, 214
 nanomotors 86
 unhybridized 87
Drugs 63, 66, 239
 oil encapsulating lipophilic 66
 therapeutic 63
 toxic 239
Dynamic(s) 83, 85, 129, 163, 164, 167, 183
 crosslinking 183
 light scattering (DLS) 83, 85, 163, 164
 spatiotemporal 129
Dynamic covalent bond 190
 formation 190
 reactions 190

E

Electron microscopy 83, 166, 251, 235
 techniques 83
 transmission 83, 166, 251

Electron spin resonance spectroscopy 166
Electrospinning 9, 10, 35, 111, 112, 122, 123,
 124, 125, 126, 131
 process 9, 10
 systems 122
 technique 9, 123
Electrostatic 9, 30, 85
 force 9
 repulsion 30, 85
ELISA and PCR methods 87
Emerging functional biomaterials 130
Emulsification ionic gelation process 70
Emulsifying 231, 232, 242
 agent 232, 242
 starches 242
Emulsion 26, 66, 68, 162, 189
 diffusion method 66
 photopolymerization 162
 polymerization 68, 162
 technique 26
 water-in-oil-in-water 189
Emulsion system 169
 oil-water 169
Environmental scanning electron 251
 microscopy (ESEM) 251
Enzymatic degradation processes 250
Escherichia coli 88
ESEM technique 251

F

Factors, brain-derived neurotrophic 96
Fatigue 3, 4, 5, 35
Fatty acid 228, 233, 243, 248
 polyunsaturated 243
FDA-approved synthetic polymers 128
Fluoropyrimidine RNA aptamers 95
Food
 and drug administration (FDA) 63, 71, 94,
 115, 210, 224
 processing 71
 waste 224
Forces 34, 85, 122, 192, 196
 adhesive 192
 electric 122
 electromagnetic 196
 electromotive 85
 hydrophilichydrophobic 34

G

- Gel permeation chromatography (GPC) 140, 142, 163, 164
- Gene therapy 113
- Growth 16, 159, 210
 - microbial 16
 - process 159
 - vascular 210

H

- Healing 183, 184, 185, 186, 187, 189, 190, 201
 - activation processes 187
 - agents 183, 184, 185, 186, 187, 189, 190
 - microencapsulated 201
- High 67, 77, 167
 - energy ball milling technique 77
 - pressure emulsification-solvent evaporation process 67
 - resolution NMR spectroscopy 167
- Human immunodeficiency virus (HIV) 87
- Hydrogel nanocomposite systems 153
- Hydrophobic 22, 23, 24, 25, 28, 32, 68, 72, 126, 130, 158, 236, 245, 247
 - chains 126
 - coating polymer 68
 - effect 130
- Hydrothermal 72, 75, 80
 - process 75, 80
 - synthesis 72, 75
- Hydroxyapatite-chitosan-gelatine 7

I

- Industries 224, 228, 230, 231, 232, 236, 239, 240, 243, 247
 - dairy 232
 - food and pharmaceutical 224, 228, 230, 231, 236, 239, 240, 243, 247
- Infections 28, 41, 43, 88, 93
 - bacterial 41
 - burn 93
 - fungal wound 93
 - urinary tract 41, 43
- Interpenetrating polymer networks (IPNs) 149, 161
- Ischemic stroke 90

K

- Klebsiella pneumoniae* 88
- Knee arthroplasty 7

L

- Lower critical solution temperature (LCST) 28, 29, 151, 159, 165

M

- Machine learning 208
- Macromolecular architectures 126
- Macromolecule coupling 155
- Magnetic 31, 74, 92, 169
 - mesoporous silica NPs 92
 - nanocomposites 169
 - nanoparticles 31
 - nanostructures 74
- Mechanical properties 3, 5, 34, 35, 128, 143, 144, 185, 186, 189, 190, 192, 193, 200, 201
- Metallic 3, 4, 21, 24, 37, 65, 76, 90, 183, 184, 199
 - aluminum 199
 - biomaterials 3, 4
 - nanoparticles 21, 76
 - traditional 24, 37
- Methods 71, 74, 75, 79, 80, 185, 246, 248
 - emulsification-evaporation 247
 - enzymatic 246
 - facile 71
 - hot-injection 74
 - hydrothermal 75, 80
 - liposome 248
 - macroscopic 185
 - sol-gel 79, 80
- Microemulsion 74, 87
 - method 74
 - polymerization process 87
- Microencapsulation 222, 224, 236, 252, 253
 - methods 222, 224, 236, 252
 - technique 253
 - technology 222
- Mobility, electrophoretic 164

N

Nanobiosensor 87
Nanobiotechnology 65
Nanocomposite hydrogels 94, 142, 153
Nanomaterials 93, 97
 chitosan-based 93
 inorganic 93, 97
Nanopore biosensor technology 87
Nanosensors 87, 90
 electrochemical 90
Nanostructured DNA biosensors 86
Nerve 92, 96
 functions 92
 tissue regeneration 92, 96
Nervous system 86, 90
Neural 19, 213, 215, 216
 networks 213, 215, 216
 tissues 19
Neurodegenerative disorders treatment 90
Neuro-molecular relationships 216
Neurons 213
 artificial 213
NPs 66, 94, 95
 and nanocapsules for applications 66
 applications 95
 based drug-release 94
 coating 94
Nuclear magnetic resonance (NMR) 167, 252

O

Oil(s) 69, 74, 169, 227, 238, 241, 243, 244,
 245, 247, 248
 flavor 247
 functional 245
 recovery methods 169
Orthopedic(s) 3, 25, 35, 36, 96
 surgery 35, 36
 therapy 96
Osteoporosis 223

P

Pathways 82, 124, 149, 215
 green chemistry 124
 green synthetic 149
 metabolic 82
 metastasis 215

PCR methods 87
Photoreaction 152
Photothermal molecule release 121
Physical vapor deposition method 78
Polylactic acid nanocomposite 89
Polymerase chain reaction (PCR) 86
Polymerization 15, 16, 68, 70, 116, 159, 160,
 161, 163, 169, 244
 pathways 116
 process 159, 160, 163, 244
 reactions 16, 68, 70, 161
 techniques 15, 159
Polymer(s) 16, 17, 24, 26, 29, 32, 38, 44, 113,
 125, 147, 151, 156, 167, 198
 crosslinked 32
 deacetylated 17
 dental 44
 drug-releasing 38
 dry 167
 electrospun 125
 fiber-forming 113
 fluorocarbon 26
 pH-sensitive 29, 151
 polyacrylic 24
 synthesis 16, 147, 156
 systems 198
Polysaccharide derivatives 35
Portobello mushrooms spores (PMS) 88
Post-polymerization modification 155
Pressure, osmotic 30, 250
Principal component analysis (PCA) 214
Probabilistic neural networks (PNN) 215
Protein(s) 18, 19, 20, 130, 131, 156, 157, 215,
 227, 228, 229, 230, 231, 240, 245
 plant-based 232
 protein docking interactions 212
Pseudomonas aeruginosa 88

R

Radiation 84, 88, 147, 158, 163, 166, 184
 electromagnetic 163, 166
 energy 147, 158
Radical polymerization 24, 157
Random Brownian motion 163
Recombinant human collagen (RHC) 125
Resource description framework (RDF) 216
Ritter reaction 27
Robotic instrumentation techniques 216

S

Salmonella enteritidis 88
Scaffolds, collagen-based 126
Self 197, 214
 healing polymeric biomaterials 197
 organizing tree algorithm (SOTA) 214
Sol 69, 76, 79, 124, 141, 248
 gel method 79
 gel process 79, 124
Sonication 69, 76, 161, 248
Sonochemical synthesis method 76
Sonochemistry 75
Spinal cord injury therapies 95
Spray drying 239, 240
 conditions 239
 process 239, 240
 system 240
Staphylococcus 89
 epidermidis 89
 haemolyticus 89
Stents 38, 41, 42
 cardiac 38
 drug-eluting 38
 urinary 41, 42
Sulfonated polystyrenes 31, 152
Support vector machines (SVM) 215
Synthesis 72, 75, 76, 77, 81, 118, 228
 mechanochemical 77
 microbial 228
 multifunctional polyamides 118
 solvothermal 81
 sonochemical 72, 75, 76

T

Thermal 201, 226
 diffusion processes 201
 stability 226
Transglutaminase 246
Translation 117, 211
 ribosomal 117
Transmembrane transport 131
Tumour growth 210
 malignant 210

U

Urinary 41, 42, 43

catheters 41, 42, 43
devices 41, 42
 medical device 42
UV/Vis spectroscopy 84

V

Vascular network self-healing systems 189
Virtual physiological human (VPH) 208, 209,
 210
Viscoelastic properties 185

W

Wound 18, 93, 128, 148
 regeneration 93
 repair 18, 128, 148

X

X-ray 83, 84, 251, 252
 absorption 251
 based techniques 84
 diffraction (XRD) 83, 84, 252
 methods 84
 micro-computed tomography 251

Z

ZnO morphology 93



Felipe López-Saucedo

Dr. Felipe López Saucedo earned his PhD from the National Autonomous University of Mexico (UNAM) at the Institute of Nuclear Sciences in the field of biopolymers and biomedical devices in 2018. He did BSc in chemistry from Faculty of Chemistry UNAM, and submitted thesis in organic synthesis (2011). He did MSc in chemistry from the Institute of Chemistry UNAM, and submitted thesis in homogeneous catalysis in 2014. DGAPA-UNAM has a postdoctoral position in organometallics at the Institute of Chemistry UNAM (2018-2020). CONACyT-UAEMEX postdoctoral position in biotechnology research (2021-2023). He is a coauthor of 21 research articles and 11 book chapters since 2016. He published two books in the book series entitled 'Frontiers in Nanomedicine'.