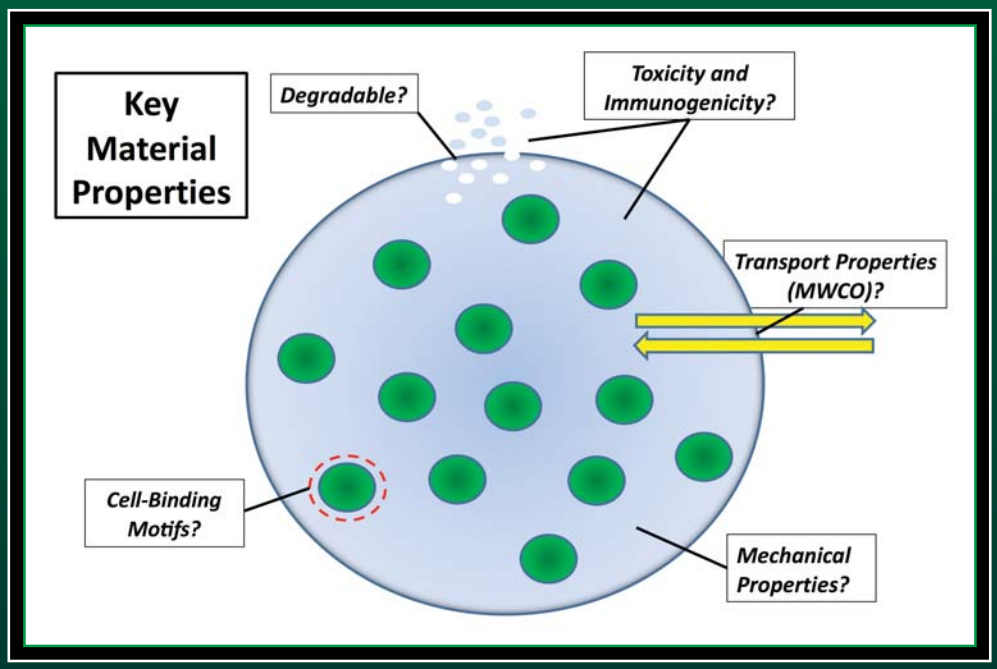
GREEN CHEMISTRY AND CHEMICAL ENGINEERING SERIES

Materials in BIOLOGY AND MEDICINE



Edited by
Sunggyu Lee
David Henthorn

CRC Press
Taylor & Francis Group

Lee | Henthorn
Materials in BIOLOGY AND MEDICINE
CRC Press

Materials in BIOLOGY AND MEDICINE

GREEN CHEMISTRY AND CHEMICAL ENGINEERING

Series Editor: Sunggyu Lee
Ohio University, Athens, Ohio, USA

Materials in Biology and Medicine
Sunggyu Lee and David Henthorn

Particle Technology and Applications
Sunggyu Lee and Kimberly H. Henthorn

Lithium-Ion Batteries: Advanced Materials and Technologies
Xianxia Yuan, Hansan Liu, and Jiujun Zhang

Carbon-Neutral Fuels and Energy Carriers
Nazim Z. Muradov and T. Nejat Veziroğlu

Oxide Semiconductors for Solar Energy Conversion: Titanium Dioxide
Janusz Nowotny

Magneto Luminous Chemical Vapor Deposition
Hirotsugu Yasuda

Nuclear Hydrogen Production Handbook
Xing L. Yan and Ryutaro Hino

Efficiency and Sustainability in the Energy and Chemical Industries: Scientific Principles and Case Studies, Second Edition
Krishnan Sankaranarayanan, Jakob de Swaan Arons, and Hedzer van der Kooi

Proton Exchange Membrane Fuel Cells: Contamination and Mitigation Strategies
Hui Li, Shanna Knights, Zheng Shi, John W. Van Zee, and Jiujun Zhang

Proton Exchange Membrane Fuel Cells: Materials Properties and Performance
David P. Wilkinson, Jiujun Zhang, Rob Hui, Jeffrey Fergus, and Xianguo Li

Solid Oxide Fuel Cells: Materials Properties and Performance
Jeffrey Fergus, Rob Hui, Xianguo Li, David P. Wilkinson, and Jiujun Zhang

Materials in BIOLOGY AND MEDICINE

Edited by
Sunggyu Lee
David Henthorn

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20120202

International Standard Book Number-13: 978-1-4398-8170-5 (eBook - PDF)

Contents

Green Chemistry and Chemical Engineering

Series Statement

The subjects and disciplines of chemistry and chemical engineering have encountered a new landmark in the way of thinking about, developing, and designing chemical products and processes. This revolutionary philosophy, termed "green chemistry and chemical engineering," focuses on the designs of products and processes that are conducive to reducing or eliminating the use and generation of hazardous substances. In dealing with hazardous or potentially hazardous substances, there may be some overlaps and interrelationships between environmental chemistry and green chemistry. While environmental chemistry is the chemistry of the natural environment and the pollutant chemicals in nature, green chemistry proactively aims to reduce and prevent pollution at its very source. In essence, the philosophies of green chemistry and chemical engineering tend to focus more on industrial application and practice rather than academic principles and phenomenological science. However, as both chemistry and chemical engineering philosophy, green chemistry and chemical engineering derive from and build upon organic chemistry, inorganic chemistry, polymer chemistry, fuel chemistry, biochemistry, analytical chemistry, physical chemistry, environmental chemistry, thermodynamics, chemical reaction engineering, transport phenomena, chemical process design, separation technology, automatic process control, and more. In short, green chemistry and chemical engineering are the rigorous use of chemistry and chemical engineering for pollution prevention and environmental protection.

The Pollution Prevention Act of 1990 in the United States established a national policy to prevent or reduce pollution at its source whenever feasible. And adhering to the spirit of this policy, the Environmental Protection Agency (EPA) launched its Green Chemistry Program to promote innovative chemical technologies that reduce or eliminate the use or generation of hazardous substances in the design, manufacture, and use of chemical products. The global efforts in green chemistry and chemical engineering have recently gained a substantial amount of support from the international community of science, engineering, academia, industry, and governments in all phases and aspects. Some of the successful examples and key technological developments include the use of supercritical carbon dioxide as green solvent in separation technologies, application of supercritical water oxidation for destruction of harmful substances, process integration with carbon dioxide sequestration steps, solvent-free synthesis of chemicals and polymeric materials, exploitation of biologically degradable materials, use of aqueous hydrogen peroxide for efficient oxidation, development of hydrogen proton exchange membrane (PEM) fuel cells for a variety of power generation needs, advanced biofuel productions, devulcanization of spent tire rubber, avoidance of the use of chemicals and processes causing generation of volatile organic compounds (VOCs), replacement of traditional petrochemical processes by microorganism-based bioengineering processes, replacement of chlorofluorocarbons (CFCs) with nonhazardous alternatives, advances in design of energy efficient

processes, use of clean alternative and renewable energy sources in manufacturing, and much more. This list, even though it is only a partial compilation, is undoubtedly growing exponentially.

This book series on Green Chemistry and Chemical Engineering by CRC Press/Taylor & Francis is designed to meet the new challenges of the twenty-first century in the chemistry and chemical engineering disciplines by publishing books and monographs based on cutting-edge research and development to effect reducing adverse impacts on the environment by chemical enterprise. To achieve this, the series will detail the development of alternative sustainable technologies that will minimize the hazard and maximize the efficiency of any chemical choice. The series aims at delivering readers in academia and industry with an authoritative information source in the field of green chemistry and chemical engineering. The publisher and its series editor are fully aware of the rapidly evolving nature of the subject and its long-lasting impact on the quality of human life in both the present and future. As such, the team is committed to making this series the most comprehensive and accurate literary source in the field of green chemistry and chemical engineering.

Sunggyu Lee

Preface

The history of human civilization is best understood by tracking the materials and remains thereof that humans have found, created, modified, processed, and used according to their specific life needs at different time periods and geographical regions. Therefore, the prevailing materials of choice of a given era often serve as its defining point, with the Stone Age, Bronze Age, and Steel Age being good examples. Historically, the process of transitioning from one type of principal structural material to another could take up to thousands of years; however, modern development of new materials is much faster paced and more multidirectional in its intended end uses. Some may refer to the current era as the Silicon Age, owing to the profound impact that silicon has had on the way we live and work; however, modern materials are far more diverse in their compositional and structural forms than a single substance and are greatly versatile in their desired applications and deliverable functionality. Although the list of modern materials is truly rapidly increasing, most materials may still be fitted into broader categories of metals, ceramics, semiconductors, polymers, biomaterials, composites, magnetic materials, and exotic materials. Remarkable advances in materials include biomaterials for artificial human body parts and organs, ceramics for bone and tooth replacement, biodegradable and biocompatible polymers, semiconductor materials, solar grade silicon, highly capable energy storage materials, reinforced structural materials, highly functional composites, high-performance alloys, ultra-high temperature-resistant materials, liquid crystals, aerogels, buckyballs and nanotubes, oil-producing microalgae, and much more.

The discipline of materials science and engineering is relatively new and may be defined as an applied and interdisciplinary field concerned with the relationship between the structure and properties of materials. Materials science and engineering is the field where scientists, engineers, and physicians of diverse backgrounds can work together for common targets and goals, thereby developing new materials, enhancing material properties, expanding the boundaries of applications, and devising new technologies of processing or manufacturing. This book is intended to provide the readers with a solid background, including recent successful examples, in the subfield of materials in biology and medicine. Principal foci of the book are placed on biomaterials and bioinspired materials, functional and responsive materials, controlling biology with materials, and development of devices and enabling technologies. All chapters were written by subject experts in a consistent and readable fashion by fully describing the relevant scientific background as well as thoroughly discussing the logical sequences of new development and applications. Although this book is intended for readers who have a background in college-level chemistry, biology, and physics, the value of this book may be more appreciated by graduate students working on diverse scientific and engineering problems involving materials in biology and medicine, researchers and inventors in related fields, and practicing engineers, scientists, and physicians in their chosen areas. It is the editors' wish that this book contribute to scientists, engineers, medical researchers, and industrialists in their technological thinking, tackling challenges in novel materials, carrying out new product and process development projects, and devising and inventing new methodologies in applying novel materials for life quality enhancement.

This book is published as a spin-off volume of the *Encyclopedia of Chemical Processing* and is based on encyclopedia entries recently published and soon to be published in the

current theme of materials in biology and medicine. This book is also published as a book in the Green Chemistry and Chemical Engineering book series.

Sunggyu Lee
Athens, Ohio

David B. Henthorn
St. Louis, Missouri

About the Editors

Dr. Sunggyu Lee earned both his Bachelor's and Master's degrees in chemical engineering from Seoul National University, Seoul, Korea, in 1974 and in 1976, respectively. He received his Ph.D. in chemical engineering from Case Western Reserve University, Cleveland, Ohio in 1980. He started his professorial career with The University of Akron in 1980 and was promoted to full professor in 1988. From 1988–1997, he served as Robert Iredell Professor and Chairman of chemical engineering as well as the Founding Director of the Process Research Center. From 1997–2005, he held positions of chairman and C. W. LaPierre Professor of chemical engineering at the University of Missouri. From 2006–10, he was with Missouri University of Science and Technology, where he established the Laboratory for Transportation Fuels and Polymer Processing. Since 2010, he has held positions as the Russ Ohio Research Scholar and professor of chemical and biomolecular engineering, Ohio University, Athens, Ohio. He has established the Sustainable Energy and Advanced Materials (SEAM) Laboratory as a stand-alone off-campus laboratory of excellence.

Dr. Lee has authored 7 books, 9 monographs, 9 book chapters, 144 refereed journal articles, and over 360 proceedings and conference papers. Titles of his published books include *Methanol Synthesis Technology*, *Oil Shale Technology*, *Alternative Fuels*, *Methane and Its Derivatives*, *Handbook of Environmental Technology*, and *Handbook of Alternative Fuel Technologies*. He is the editor of the *Encyclopedia of Chemical Processing* (5 volumes with 350 chapters), published in 2006. He has received 30 U.S. patents based on his inventions, mainly in the areas of clean alternative energy, functional polymers, and supercritical fluid technology. Most of his inventions are being commercially utilized. He has received and directed over 100 research grants/contracts from both industrial and governmental agencies totaling over $19M as principal investigator and co-principal investigator. His specialties are in the areas of alternative fuels, supercritical fluid technology, chemical process engineering and reactor design, polymer synthesis and processing. He has guided over 90 advanced degree students and 24 postdoctoral fellows as major advisor.

Dr. David B. Henthorn received his Bachelor's (1999) and Doctoral (2004) degrees in chemical engineering from Purdue University in West Lafayette, Indiana. For his doctoral work, Dr. Henthorn studied the formation of densely crosslinked hydrogel networks and their applicability as biomimetic materials under the direction of Professors Nicholas A. Peppas and Kinam Park. In 2004, he joined the Department of Chemical and Biological Engineering at Missouri University of Science and Technology (then the University of Missouri-Rolla) as an assistant professor. In 2010, he was awarded tenure and promoted to associate professor of chemical and biological engineering. In the fall of 2010, Dr. Henthorn moved to the Biomedical Engineering Department at Saint Louis University, where he is currently an associate professor.

Dr. Henthorn's research focuses on polymeric materials in biomaterials, biosensors, bioMEMS devices, and drug delivery devices. A strong proponent of involving students in research, Dr. Henthorn has worked with 21 undergraduate students in the last 7 years. Over that same period of time, he has supervised 8 graduate students.

Contributors

Shubhayu Basu
Department of Chemical and Biomolecular Engineering, The Ohio State University Columbus, Ohio, U.S.A.

Sujata K. Bhatia
Dupont Central Research and Development, Wilmington, Delaware, U.S.A.

Surita R. Bhatia
Department of Chemical Engineering, University of Massachusetts–Amherst, Amherst, Massachusetts, U.S.A.

James Blanchette
University of South Carolina, Columbia, South Carolina, U.S.A.

Frank Davis
Cranfield University, Silsoe, U.K.

Amy S. Determan
Department of Chemical and Biological Engineering, Iowa State University, Ames, Iowa, U.S.A.

Hugo S. Garcia
UNIDA, Instituto Tecnologico de Veracruz, Veracruz, Mexico

David B. Henthorn
Department of Biomedical Engineering, Saint Louis University, St. Louis, Missouri, U.S.A.

Séamus P. J. Higson
Cranfield University, Silsoe, U.K.

Charles G. Hill, Jr.
Department of Chemical and Biological Engineering University of Wisconsin–Madison, Madison, Wisconsin, U.S.A.

Kang Moo Huh
Department of Polymer Science and Engineering, Chungnam National University, Daejeon, South Korea

L. James Lee
Department of Chemical Engineering, The Ohio State University, Columbus, Ohio, U.S.A.

Sunggyu Lee
Department of Chemical and Biomolecular Engineering, Ohio University, Athens, Ohio, U.S.A.

Surya K. Mallapragada
Department of Chemical and Biological Engineering, Iowa State University, Ames, Iowa, U.S.A.

Balaji Narasimhan
Department of Chemical and Biological Engineering, Iowa State University, Ames, Iowa, U.S.A.

Cristina Otero
Departamento de Biocatálisis, Instituto de Catálisis y Petroleoquimica, CSIC, Campus Universidad Autonoma, Cantoblanco, Madrid, Spain

Jae Hyung Park
Department of Advanced Polymer and Fiber Materials, Kyung Hee University, Gyeonggi-do, South Korea

Kinam Park
Departments of Pharmaceutics and Biomedical Engineering, Purdue University, West Lafayette, Indiana, U.S.A.

Clayt Robinson
Department of Chemical and Biomolecular Engineering, The Ohio State University, Columbus, Ohio, U.S.A.

Gregory T. Rushton
Department of Chemistry and Biochemistry, Kennesaw State University, Kennesaw, Georgia, U.S.A.

Ken D. Shimizu
Department of Chemistry and Biochemistry, University of South Carolina, Columbia, South Carolina, U.S.A.

Maria P. Torres
Department of Chemical and Biological Engineering, Iowa State University, Ames, Iowa, U.S.A.

Chun Wang
Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, U.S.A.

Shang-Tian Yang
Department of Chemical and Biomolecular Engineering, The Ohio State University, Columbus, Ohio, U.S.A.

Hirotsugu Yasuda
Center for Surface Science and Plasma Technology, University of Missouri, Columbia, Missouri, U.S.A.

Mingli Ye
Departments of Pharmaceutics and Biomedical Engineering, Purdue University, West Lafayette, Indiana, U.S.A.

1

Introduction: Materials in Biology and Medicine

David B. Henthorn and Sunggyu Lee

CONTENTS

Discoveries in medicine, biotechnology, biology, and biochemistry are occurring at a rate previously unthinkable. The fields of genomics, proteomics, genetic engineering, computational chemistry, etc., have revolutionized our approach to unlocking the mysteries of living organisms and their responses to various stimuli. Development of new materials to complement these advance—whether to serve as replacement limbs, as structures to encourage tissue growth, as sensing elements to determine blood glucose levels, or as micr-scale vessels for determination of serum antibody level—has been equally rapid and diverse.

Materials

The study of biomaterials, materials used in biomedical applications with the designed intent to interact with the surrounding tissue, is one of the most diverse multidisciplinary endeavors, requiring the talents of scientists (biology, chemistry, physics, materials science), engineers (biomedical, chemical, mechanical, electrical, materials), and physicians. In Chapter 2 of this book, Bhatia and Bhatia describe the basic aspects of biomaterials, highlighting the essential property of biocompatibility. Myriad materials have been utilized over the years in medicine and biology, ranging from ceramics, metals, polymers, glasses, and composites. Later chapters highlight aspects of biomaterials research, moving from bulk materials to applications with cells and tissues, and ending with the fabrication of complex and integrated biodevices.

Polymer—long-chain molecules based on repeating monomeric unit—are some of the most versatile biomaterials in use—since the chemistry of the repeating units is so easily varied—leading to diverse physical, chemical, thermal, optical, and mechanical properties. Hydrophilic (water loving) materials are some of the most widely used in medicine and biology, owing to the fact that the physiological environment is largely based in water. Examples of hydrophilic polymer materials include poly(ethylene glycol) (PEG), poly(methacrylic

acid), poly(acrylic acid), poly(vinyl alcohol), and poly(2-hydroxyethylmethacrylate). Their uses range from soft contact lenses, burn and wound dressing, membranes for immobilization of proteins and other active biomolecules, drug delivery matrices, and absorbents. The solvation of these chains by water or physiological fluid is an area of intense study, and has led to unique biomedical applications for many materials.(PE) is one of the most widely applied material to increase biocompatibility, for instance. The ability of PEG to be solvated by water has made it an immensely useful coating for various hydrophobic surfaces. Protein deposition, platelet adhesion, and other undesirable processes are slowed through the masking of the surface with hydrophilic polymers, such as PEG.

Cross-linking of these hydrophilic polymers, whether through chemical or physical means, leads to the creation of water-swellable three-dimensional networks known as hydrogels. Long used as a biomaterial due to their high water content, hydrogels are found in applications such as soft contact lenses, hemostatics and absorbents, drug delivery devices, immobilization matrices for enzymes, etc. The degree to which the network swells is dependent upon a number of factors, including the interaction strength between the chains and water, extent of cross-linking, presence of solvent during the cross-linking procedure, temperature, pressure, and concentration of ions. Superabsorbent hydrogels may consist of more than 99% water by weight. Their use as drug delivery matrices has been well-studied, with release rates of drugs showing both traditional diffusional behavior (Fickian) along with more complex (non-Fickian) behavior altered by solvation, chain relaxation, and crystal melting.

Fickian diffusion from these drug delivery matrices, with drug release rates evolving over time with the inverse square root of time ($t^{-1/2}$), has been a hurdle to those interested in designing systems that deliver in constant, pulsatile, or delayed rates. Attempts to control the release of active therapeutics from materials have taken a number of different approaches. A radically different approach to this problem employs materials where the rate of degradation is instead controlled. In this case, the matrix material is sufficiently hydrophobic to halt influx of physiological fluid, preventing solvation and drug from the bulk. Fabrication of such a device from hydrolyzable materials ensures drug release from the surface, allowing the designer to tailor the device's geometry to obtain the desired controlled release rate. Polyanhydrides are often formed from the polymerization of diacid monomers, with copolymerization commonlyused to achieve the desired material properties and ultimate degradation rates. By carefully choosing the repeating units of the polymer, hydrolysis of these materials *in vivo* results in the controlled release of the active agent along with monomeric species that are easily metabolized by the body.

Functional and Responsive Materials

For a long time, the search to improve biocompatibility centered on the physical and chemical tailoring of materials and their surfaces to lower protein adsorption, to boost hydrophilicity and wettability, and in general less likely to trigger a foreign-body response. This approach has trade-offs, as exemplified in the evolution of soft contact lenses. While traditional soft contact lenses, developed by Otto Wichterle in the 1960s, were comprised of a hydrogel based around the neutral monomer 2-hydroxyethylmethacrylate and were reasonably hydrophilic and water-swollen, incorporation of monomers that boosted swelling became advantageous. The resulting lenses, with their higher water content, not only

were more comfortable to wear but also had higher oxygen permeabilities and therefore lower propensity to trigger hypoxia. The monomers incorporated in this new generation of lenses—the same that are used in disposable diapers for their ability to absorb vast quantities of water—are, however, ionized in aqueous solution and more likely to trigger protein adsorption. The solution, therefore, was to suggest shorter lifetimes for the lenses and rely on improvements in the manufacturing process to maintain price parity. In the late 1980s, it was not uncommon for a single pair of soft contact lenses to be retained by a patient for a full year, with the patient employing various cleaning techniques, including weekly treatment with concentrated protease solutions, to maintain comfort. The introduction of contact lenses with higher water content increased comfort, but the charged materials required more frequent replacement, with monthly, weekly, and even daily replacement possible.

In the design of implantable devices and other applications with long-term use, scientists and engineers are not likely to have options such as these. Other functionalization techniques or utilization strategies must therefore be employed. In a series of seminal articles, leaders in the biomaterials field argued that the passive approach to biocompatibility—building in stealth-like properties that allow a material to hide from the foreign-body response—was not enough. Biomaterials, they argued, need to take an active role, participating in healing. A material, for instance, that resists adsorption of general serum proteins while recruiting specific, beneficial molecules and interacting with the local tissue has a much greater chance of successful integration. Knowledge, built over years of work on surface passivation, is used to create a foundation where no-specific interactions are minimized. Control of specific interactions is then added through the introduction of surface charges, peptidic oligomers, cell adhesion molecules/fragments, carbohydrates, etc.

An example of this approach is used in the technique of molecular imprinting. A hydrogel material, long used as a biomaterial because of its high water content, ability to mimic tissue properties, and passive nature, is tailored to add affinity for a specific target molecule or family of molecules. This affinity is typically imparted during material formation. A template molecule, either the interaction target or a close analog, is added in material formation, driving self-assembly of the monomers species. This assembly is then locked into the material during polymerization and cross-linking. Removal of the template molecule, typically through dialysis, yields analyte-specific binding sites inside the bulk of the normally passive hydrogel structure. In recent time, researchers have expanded this technique to focus on the creation of these binding sites on a material's surface, allowing for interaction with macromolecules and other species that are either too large or immobile to interact with the bulk of the hydrogel.

Molecularly imprinted polymers and other biomimetic materials illustrate the interest in creating synthetic materials for use in medicine, biology, and biotechnology. Natural materials, however, are still the gold standard in terms of signaling, molecular recognition, transport, and catalysis. Enzymes, for instance, have some of the greatest catalytic ability of any known molecular structures. While the specificity and turnover rate of an enzyme may be tailored through genetic engineering, biological organisms are still required for their production. As such, yields are low and expensive; time-consuming separation steps must be employed to capture the proteins in active form. Solid support materials, therefore, are frequently used when enzymatic action is utilized in a chemical or biological process. These support material—microparticles, gels, columns, etc—allow the enzymatic materials to be easily recaptured once the process is finished. The coupling of biologically active molecules, such as enzymes, with nanotechnology and nanomaterials is an exciting

field that combines the unique properties at the nanoscale (high surface-to-volume ratio, quantum effects, etc.) with the recognition and catalytic abilities of biomolecules.

Nanomaterials such as carbon nanotubes, normally too hydrophobic to disperse well in the aqueous environment, have many desirable physical, mechanical, and optical properties. Researchers have therefore been interested in the modification of these nanomaterials for use in biomedical and biotechnological applications. First, modification must be done to improve the aqueous dispersibility of the nanotubes, allowing them to interact individually with cells, proteins, etc. This modification, however, is typically done in a manner that allows for simultaneous surface passivation and incorporation of elements to control specific interaction. For instance, hydrophilic polymer chains may be attached to or grown from the nanotube surface, aiding in dispersibility. Functional groups on these chains, e.g., carboxylate or epoxide groups, may serve as sites where adhesion molecules, antigens, antibodies, enzymes, DNA/RNA, etc., may be added. Surface functionalization techniques have been used to fabricate dispersible carbon nanotubes that circulate freely in aqueous media, interact with specific cells, and triggering internalization by targeted ones. These internalized, targeted nanomaterials may act as a vector to identify diseased cells and even to deliver therapeutic agents.

Controlling Biology with Materials

The growth of cells and tissues is inextricably linked with the support and substrate materials provided to them. In cell culture, surfaces covered with peptide oliogmers, cell adhesion molecules, fragments of extracellular matrices, etc., are used to promote growth. This idea of using engineered materials to grow cells in three dimensions has led to the field of tissue engineering. Scaffolds are used to promote and regulate cellular growth in geometric structures, with an ultimate goal of replacing diseased or damaged tissue. Tissue engineering scaffolds have been constructed from a variety of materials, including from both synthetic and naturally derived sources. Bioresorbable materials, such as the copolymer poly(lactic-co-glycolic acid), have found use as scaffolds for the repair of various tissues, with the rate of degradation carefully tuned to allow the tissue to be established before diminishment of mechanical and biochemical support. Other materials, such as bioactive glasses that resorb into hydroxyapatite (the main mineral component of bone), are utilized in the fabrication of scaffolds for hard tissue restoration. The efficient transport of nutrients to the tissue, and waste products away, remains one of the greatest problems facing researchers in the area of tissue engineering.

To protect cells from immune response, allowing for the transplantation of allogenic or xenogenic tissues, it is possible to encapsulate a group of cells in a matrix material that allows for biochemical transport. Transplantation of islet cells into type 1 diabetic patients, for the restoration of insulin production, is one of the most commonly researched applications of this technology. The encapsulating material must allow for transport of nutrients to the transplanted tissue, removal of waste products, and the relatively unhindered release of the therapeutic agent (e.g., insulin in islet cell encapsulation). The material, however, must work to hinder the immune response while retaining the integrity of the cellular aggregates. For example, the molecular size disparity between insulin and immunoglobulins allows researchers to tailor materials with molecular weight cutoffs that

allow for diffusion of the peptidic hormone out of the matrix while preventing inflow of antibodies, etc.

Devices

The idea that materials can be made to incorporate, utilize, or release bioactive agents is driving a revolution in implantable device design. Immobilized enzymes, antibodies, or nucleic acids could provide molecular recognition for the device, once implanted. Release of growth factors, cytokines, and other signaling molecules could help recruit desirable tissue growth in the local area of the device, instead of formation of a fibrous capsule and scar tissue. Surface-grafted cell adhesion molecules and biocompatible surfaces would help mask the presence of a device, the operation of which is becoming more complex over time due to improvements in miniaturization and fabrication techniques.

By adopting the fabrication techniques developed in the manufacture of integrated electrical circuits, researchers have been able to create therapeutic and diagnostic devices that operate on the micro- and even nanoscale. Early work in the area of microelectromechanical systems (MEMS) devices led to the development of now-ubiquitous commercial devices such as the accelerometer used in automobiles to trigger activation of airbags. Translation of this work into biomedicine and biotechnology (BioMEMS) has been done to provide for devices that separate, analyze, sense, and respond to various chemical and physiological signals. In addition to research in device creation, interest in BioMEMS has led to advances in materials. While silicon is the most traditional substrate material for integrated circuit manufacture, researchers in the BioMEMS field have pioneered the fabrication of devices using glasses, epoxies, and silicones. Rigid silicon devices with long fabrication times, for instance, are replaced by flexible, rapid-formingpoly(dimethyl siloxane) silicone rubber, allowing for rapid prototyping. In recent years, there has been a substantial push to lower material and fabrication costs, with new disposable devices being contemplated from paper, tape, etc.

2

Biomaterials

Sujata K. Bhatia and Surita R. Bhatia

CONTENTS

Introduction

Biomaterials science is a multidisciplinary endeavor incorporating chemical engineering, medicine, biology, chemistry, materials science, bioengineering, and biomechanics. The past few years have witnessed an explosion in the field of biomaterials, with an expansion of both the compositions and the applications of medical implant materials. As the prevalence of chronic diseases such as diabetes, cardiovascular disease, and neurodegenerative disease increases, there will be an even greater need for innovative biomaterials. This chapter reviews the current status of the field of biomaterials, and highlights new developments in biomaterials. The chapter will provide an overview of medical applications of biomaterials, and will describe current classes of biomaterials, including metals, ceramics and glasses, and polymeric materials. The chapter will then discuss the next generation of biomaterials, including surface-modified biomaterials, smart biomaterials, bioactive materials, biomimetic materials, patterned biomaterials, and tissue engineering and regenerative medicine.

Definitions

A commonly used definition of a biomaterial, endorsed by a consensus of biomaterials experts, is "a nonviable material used in a medical device, intended to interact with biological systems."[1] An essential characteristic of biomaterials is biocompatibility, defined as "the ability of a material to perform with an appropriate host response in a specific application."[1] The goal of biomaterials science is to create medical implant materials with optimal mechanical performance and stability, as well as optimal biocompatibility.

Overview of Biomaterials Applications

Biomaterials are used in diverse clinical applications. Table 2.1 lists several examples of applications of biomaterials in medicine.[2] Note that metals, ceramics, polymers, glasses, carbons, and composite materials are listed.

TABLE 2.1

Examples of Clinical Applications of Biomaterials

Application	Types of Materials
Orthopedic	
Joint replacements (hip, knee)	Titanium, Ti–Al–V alloy, stainless steel, polyethylene
Bone plate for fracture fixation	Stainless steel, cobalt–chromium alloy
Bone cement	Poly(methyl methacrylate)
Bony defect repair	Hydroxyapatite
Artificial tendon and ligament	Teflon™, Dacron™
Cardiovascular	
Blood vessel prosthesis	Dacron™, Teflon™, polyurethane
Heart valve	Reprocessed tissue, stainless steel, carbon
Catheter	Silicone rubber, Teflon, polyurethane
Pacemaker	Polyurethane, silicone rubber, platinum electrodes
Ophthalmologic	
Intraocular lens	Poly(methyl methacrylate)
Contact lens	Silicone-acrylate, hydrogel
Corneal bandage	Collagen, hydrogel
Dental	
Dental implant for tooth fixation	Titanium, alumina, calcium phosphate
Neurologic	
Cochlear implant	Platinum electrode
General surgery	
Skin repair template	Silicone–collagen composite
Sutures	Silk, nylon, poly(glycolide-*co*-lactide)
Adhesives and sealants	Cyanoacrylate, fibrin
Organ replacement	
Heart–lung machine	Silicone rubber
Artificial kidney (hemodialyzer)	Cellulose, polyacrylonitrile
Artificial heart	Polyurethane

(Adapted from Ratner, Hoffman, Schoen, and Lemons.[2])

Types of Biomaterials

Metals

Metals and alloys have long been used in surgical and dental applications where materials with high strength are required. Metals are excellent for providing specific mechanical properties, including strength and ductility; however, corrosion of metallic implants in biological environments remains a concern. Corrosion not only limits device lifetime but also causes release of toxic metal ions that are often carcinogenic or mutagenic.[3,4] Thus, much of the current research focuses on minimizing and reducing corrosion of metallic biomaterials. Blackwood has recently reviewed common types of corrosion encountered in metal implants in vivo, as well as physiological parameters relevant to corrosion.[3] For surgical implants, relevant parameters are chloride content, pH, and dissolved oxygen levels in blood.[3] In vitro tests of corrosion resistance are typically performed in aqueous solutions containing 0.9% NaCl, with a pitting resistance number greater than 26 desirable for implanted materials.[3] Differences between in vitro and in vivo response are often attributed to dissolved oxygen content, sulfur-containing amino acids present in blood, and pathological changes associated with implantation such as generation of hydrogen peroxide and lowered pH (as low as 4) at the implant site.[3] Corrosion is an even greater concern in dental applications, because of the high acidity and chloride ion levels in many foods. Additionally, the corrosiveness of saliva is highly dependent on oral hygiene.[3] Thus, while reasonable in vitro models for saliva are available, it is difficult to predict in vivo corrosive resistance of dental materials.

Most metallic biomaterials fall into one of four categories: stainless steels, titanium and titanium-based alloys, cobalt–chromium alloys, and amalgams.[3] Additionally, research is under way on a number of next-generation metallic biomaterials, including rare earth materials and shape-memory alloys. Of the stainless steels, type 304 had been used previously in medical applications, but problems with localized corrosion and tumor formation were sometimes reported.[3] Type 316L SS is currently the most widely used in biomedical applications.[5] This is an iron–chromium–nickel alloy with a low carbon content, where chromium provides corrosion resistance. The resistance to pitting corrosion can be improved if nitrogen additions are made.[3] More recently, additional corrosion-resistant stainless steels have been developed, including 316LVM grade with a typical composition of 18Cr14Ni3Mo. For dental materials, which must be extremely corrosion resistant, ultraclean high nitrogen austenitic stainless steels are recommended, such as 21Cr10Ni3Mo0.3Nb0.4N.[3] Finally, mixing different grades of stainless steels is not recommended, as this can lead to galvanic corrosion and failure. In general, stainless steels display better mechanical and formability properties but worse corrosion resistance than titanium-based alloys. Release of chromium presents a concern, although the levels of chromium are lower in stainless steels than in cobalt–chromium alloys.[3]

Titanium displays excellent biocompatibility and corrosion resistance; however, it does not have the high strength necessary for several biomedical applications.[3,5] The most popular material for load-bearing orthopedic applications is Ti6Al4V, a dual-phase alloy comprising an Al-stabilized η-phase and a V-stabilized β-phase.[5] Other alloys in use for medical applications include Ti2.5Al2.5Fe, Ti6Al7Nb, and Ti50Ta.[3,5] While all these alloys exhibit a higher tensile strength than titanium, their corrosion resistance is not as high.[3] They also display poor shear strength and thus should not be used for applications such as screws.[3]

Common cobalt–chromium alloys include CoCrMo, used in dentistry and artificial joint applications, and CoCrNiMo, used as a part of replacements for heavily loaded joints because of its very high tensile strength.[3] Other cobalt–chrome biomaterials include CoCrWNi, MP35N, and ASTM F1058 (40Co12Cr15Ni7Mo).[3,5] In all these materials, chromium is present at fairly high levels. Thus, the release of chromium upon corrosion is a concern, as chromium is a carcinogen.[3]

Amalgams are typically used in dental applications and are multiphase alloys. Silver–tin amalgam carries a risk of mercury release through corrosion of the Sn_7Hg γ2 phase.[3] Newer high copper amalgams reduce the risk of mercury release, as preferential corrosion of the η′ phase, Cu_6Sn_5, typically occurs.[3] However, release of mercury can still occur even in these materials. Older silver–tin amalgams are based on a silver–tin alloy, while high copper amalgams are based on either a silver–copper–tin alloy or a mixture of silver–tin and silver–copper alloys.[3]

Next-generation metallic biomaterials include porous titanium alloys and porous CoCrMo with elastic moduli that more closely mimic that of human bone; nickel–titanium alloys with shape-memory properties for dental braces and medical staples; rare earth magnets such as the NdFeB family for dental fixatives; and titanium alloys or stainless steel coated with hydroxyapatite for improved bioactivity for bone replacement.[3,5,6] The corrosion resistance, biocompatibility, and mechanical properties of many of these materials still must be optimized; for example, the toxicity and carcinogenic nature of nickel released from NiTi alloys is a concern.[3]

Ceramics and Glasses

Many ceramic materials possess improved biocompatibility as compared to metals, and corrosion is typically not an issue. Ceramics often have high strength but display brittleness, poor crack resistance, and low ductility.[7] Several ceramic materials are bioinert, bioactive (forming bonds with the surrounding tissue such as bone), or bioresorbable (as in the case of some porous ceramics).[7]

Arguably, the most important ceramic biomaterial is hydroxyapatite (HAP), $Ca_{10}(PO_4)_6(OH)_2$, a synthetic analog of bone mineral.[7] Natural bone is a composite comprising small crystalline HAP platelets bonded to collagen.[7] Synthetic hydroxyapatite is known to be bioactive, forming a strong bond with adjacent bone tissue and inducing bone growth along the interface (termed osteoconduction).[6] Hydroxyapatite and its derivatives are used most often in orthopedic and dental applications, for applications such as repair of bone defects and tooth root implants.[7] As mentioned above, HAP powders and coatings are also sometimes used in conjunction with metallic implants to induce adhesion with the surrounding tissue and to promote bioactivity.[6] Solid HAP is very robust in physiological environments and can remain in the body for 5–7 yr, while porous HAP can be resorbed by the body after approximately 1 yr.[7] Over 30 yr of research and clinical practice suggest that HAP and its related compounds are generally nontoxic and produce little or no inflammation or foreign body response. There have been some unfavorable biological reactions reported with porous HAP; these have been attributed to irritation from sharp edges of the implant and micromovement of the implant.[7]

Materials derived from HAP include Mg-HAP, which has been investigated for bone restoration in osteochondrosis; carbonate-HAP, with potential applications in the deposition of calcium and in some root canal fillings; silver-HAP, of interest for infected bone defects; and fluorine-HAP, of interest in the treatment of tooth defects and as coatings for metallic biomaterials.[7] Closely related materials include tricalcium phosphate, $Ca_3(PO_4)_2$,