Biomedical Materials for Multi-functional Applications

Deepa Suhag

Handbook of Biomaterials for Medical Applications, Volume 2

Applications

Springer

Biomedical Materials for Multi-functional Applications

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Preface

The field of biomaterials stands at the forefront of medical innovation, offering unprecedented possibilities for enhancing health care and improving patient outcomes. This handbook, *Biomaterials for Medical Applications*, provides a comprehensive exploration of the diverse applications and transformative potential of biomaterials across various medical disciplines.

At the core of this field is the use of advanced materials in artificial organs and biomedical devices, which have revolutionized the treatment of many conditions. The development of immunomodulatory biomaterials highlights the sophisticated interplay between these materials and the immune system, aiming to enhance therapeutic efficacy and minimize adverse reactions. In cardiovascular medicine, biomaterials are crucial for the development of life-saving devices such as stents and heart valves, which have significantly improved the prognosis for patients with heart disease.

The application of biomaterials extends to neurology, where they play a vital role in the creation of neural prosthetics and tissue engineering solutions, offering hope for patients with neurological disorders. In oncology, biomaterials are at the forefront of innovation, particularly in the realm of targeted drug delivery systems and cancer diagnostics, promising more precise and effective treatments.

Ophthalmology has benefited greatly from the integration of biomaterials in vision correction and ocular therapies, enhancing the quality of life for patients with visual impairments. Similarly, in dentistry, biomaterials are indispensable for restorative procedures and dental implants, ensuring better outcomes and patient satisfaction.

In the domain of skin and wound healing, biomaterials facilitate regenerative medicine and the treatment of burns, significantly improving healing times and outcomes. The handbook also presents case studies showcasing the real-world application of multifunctional therapeutics, demonstrating the practical benefits and successes of biomaterials in various medical scenarios.

Beyond the technical and clinical aspects, this handbook addresses the crucial regulatory and ethical considerations that govern the development and application of medical biomaterials, ensuring that advancements in this field are safe, effective, and ethically sound. Looking ahead, it also explores emerging trends and potential breakthroughs, offering insights into the future direction of biomaterials research and application.

With sections on abbreviations, a glossary of terms, and a curated list of resources for further reading, this handbook is designed to be an invaluable resource for researchers, clinicians, and students alike. It aims to educate, inspire, and support ongoing innovation in the field of biomaterials, ultimately contributing to the improvement of healthcare and patient outcomes worldwide.

Gurugram, India Dr. Deepa Suhag

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This book would not have been possible without the invaluable contributions of those who dedicated their expertise and time. I am particularly grateful to Ph.D. scholars Ms. Raksha Rathore and Ms. Ankita Yadav, whose tireless efforts have enriched the content of this monograph.

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Additionally, I owe a special note of gratitude to Swati Meherishi for her unwavering support and expert advice. Her contributions not only enhanced the scholarly rigor of this work but also made the publication process remarkably smooth.

Thank you all for your dedication and support, which have been vital in bringing this project to fruition.

Dr. Deepa Suhag

Contents

About the Author

Dr. Deepa Suhag is Assistant Professor in the Department of Nanotechnology, Amity University Haryana. She has published 17 research articles in major international and has filed six patents of which one has been granted by the Government of India. Patent titled "Method for preparation of highly fluorescent biocompatible Sulphur doped graphene quantum dots from affordable agro-industrial bio-waste cane molasses using hydrothermal synthesis for bioimaging application" was granted on 19.05.2022. Her research area spans from biomaterial engineering to wound healing and tissue regeneration. She currently has a combined research funding of 10 million from various funding Indian government agencies. Dr. Deepa Suhag's major collaborators are from CNCI Kolkata, AIIMS Delhi, IIT Delhi, TBRL Chandigarh, INST Mohali, RGCB Kerala, and Harvard University, USA.

Abbreviations

3D	Three-dimensional
AAVs	Adeno-associated viruses
ADM	Acellular dermal matrices
AI	Artificial intelligence
Al_2O_3	Aluminum oxide
AMD	Age-related macular degeneration
AMF	Alternating magnetic field
AMP	Antimicrobial peptide
ASTM	American society for testing and materials
ATP	Anti-tachycardia pacing
AuNPs	Gold nanoparticles
AV	Atrioventricular
BCIs	Brain-computer interfaces
BDNF	Brain-derived neurotrophic factor
BiVADs	Biventricular assist devices
BMP	Bone morphogenetic protein
BMS	Bare-metal stents
CABG	Coronary artery bypass grafts
CAD	Computer-aided design
CAM	Computer-aided manufacturing
CaO	Calcium oxide
CDRH	Center for devices and radiological health
CDSCO	Central drugs standard control organization
CIMT	Constraint-induced movement therapy
CNTs	Carbon nanotubes
Co-Cr	Cobalt-chromium
CRRT	Continuous renal replacement therapy
CT	Computed tomography
CTCs	Circulating tumor cells
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stents

DFUs	Diabetic foot ulcers
ECM	Extracellular matrix
ECMO	Extracorporeal membrane oxygenation
EGF	Epidermal growth factor
EHRs	Electronic health records
EMA	European Medicines Agency
ePTFE	Expanded polytetrafluoroethylene
ESCs	Embryonic stem cells
ESRD	End-stage renal disease
EtO	Ethylene oxide
FDA	Food and drug administration
FEA	Finite element analysis
FGF	Fibroblast growth factor
FRCs	Fiber-reinforced composites
GBR	Guided bone regeneration
GCP	Good clinical practice
GDDs	Glaucoma drainage devices
GDNF	Glial cell line-derived neurotrophic factor
GLP	Good laboratory practices
GMP	Good Manufacturing Practices
GTR	Guided tissue regeneration
HA	Hydroxyapatite
HBOT	Hyperbaric oxygen therapy
HDPE	High-density polyethylene
HIP	Hot isostatic pressing
IABP	Intra-aortic balloon pumps
ICDs	Implantable Cardioverter Defibrillators
ICUs	Intensive care units
IFNs	Interferons
IGF	Insulin-like growth factor
ILs	Interleukins
IMDRF	International medical device regulators forum
IOLs	Intraocular lenses
IOP	Intraocular pressure
iPSCs	Induced pluripotent stem cells
IRBs	Institutional review boards
ISO	International organization for standardization
IVDR	In vitro diagnostic medical devices regulation
JAK/STAT	Janus kinase/signal transducer and activator of transcription
KPro	Keratoprosthesis
LGN	Lateral geniculate nucleus
LVADs	Left ventricular assist devices
MDR	Medical devices regulations
ML	Machine learning
MMPs	Matrix metalloproteinases

MNPs	Magnetic nanoparticles
MRI	Magnetic resonance imaging
MSCs	Mesenchymal stem cells
MWA	Microwave ablation
Na_2O	Sodium oxide
NF-κB	Nuclear factor kappa B
NGF	Nerve growth factor
NIR	Near-infrared
NiTi	Nickel-titanium
NK	Natural killer
NLRs	NOD-like receptors
NMPA	National medical products administration
NPCs	Neural progenitor cells
NPWT	Negative pressure wound therapy
NSCs	Neural stem cells
OCT	Optical coherence tomography
P_2O_5	Phosphorus pentoxide
PCIs	Percutaneous coronary interventions
PCL	Polycaprolactone
PDGF	Platelet-derived growth factor
PDT	Photodynamic therapy
PE	Polyethylene
PEDOT	Poly(3,4-ethylenedioxythiophene)
PEEK	Polyether ether ketone
PEG	Polyethylene glycol
PEI	Polyethyleneimine
PEO	Poly (ethylene oxide)
PET	Positron emission tomography
PGA	Polyglycolic acid
PK	Penetrating keratoplasty
PLA	Polylactic acid
PLGA	Poly (lactic-co-glycolic acid)
PMA	Premarket approval
PMDA	Pharmaceuticals and Medical Devices Agency
PMMA	Polymethylmethacrylate
PRF	Platelet-rich fibrin
PRRs	Pattern recognition receptors
PTFE	Polytetrafluoroethylene
PTT	Photothermal therapy
PVA	Polyvinyl alcohol
PVC	Polyvinyl chloride
RFA	Radiofrequency ablation
RGCs	Retinal ganglion cells
RGD	Arginine-glycine-aspartate
RMGIs	Resin-modified glass ionomers

ROS	Reactive oxygen species
rTMS	Repetitive transcranial magnetic stimulation
SCI	Spinal cord injury
SEM	Scanning electron microscopy
SERS	Surface-enhanced Raman scattering
SiO_2	Silicon dioxide
siRNA	Small interfering RNA
SMAs	Shape memory alloys
TAHs	Total artificial hearts
TAVR	Transcatheter aortic valve replacement
TCP	Tricalcium phosphate
TEM	Transmission electron microscopy
TGA	Therapeutic goods administration
TGF-β	Transforming growth factor-beta
Ti-6Al-4V	Titanium-6 aluminum-4 vanadium
TIMPs	Tissue inhibitors of metalloproteinases
TLRs	Toll-like receptors
TME	Tumor microenvironment
TMJ	Temporomandibular joint
TNF-α	Tumor necrosis factor-alpha
UHMWPE	Ultra-high-molecular-weight polyethylene
VADs	Ventricular assist devices
VEGF	Vascular endothelial growth factor
YSZ	Yttria-stabilized zirconia
ZrO_2	Zirconium dioxide

Chapter 1
Introduction to Biomaterials

1.1 Introduction to Biomaterials

1.2 Defining Biomaterials

Biomaterials are distinctly engineered substances that are formulated to interact with biological systems for a variety of medical purposes, including diagnostic, therapeutic, and structural applications [1]. The scope of biomaterials is broad, encompassing both natural and synthetic materials that integrate with bodily tissues and systems. Their role is critical in medicine: they support, enhance, or completely replace damaged tissue or biological functions. Biomaterials are not just passive recipients in biological environments but actively interact with their surroundings, often tailoring responses that are pivotal in therapeutic outcomes.

1.3 Classification and Types of Biomaterials

Biomaterials are classified into several categories based on their composition and origin (Fig. 1.1):

- **Metals**: Used in load-bearing applications due to their high strength and toughness. Common metals include stainless steel, titanium alloys, and cobalt-chromium alloys [2]. They are widely used in orthopedic pins, screws, hip and knee replacements, and dental implants.
- **Ceramics**: These are primarily used for their wear resistance and strong compressive strength but lack in tensile strength. Bio-ceramics like alumina, zirconia, and bioactive glass are used in joint replacements and dental implants [3]. They are

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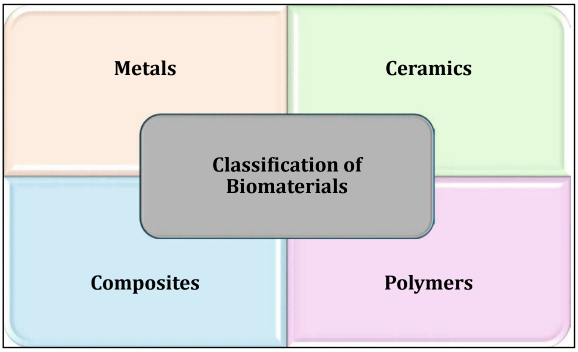

Fig. 1.1 Classification of biomaterials

favored in applications requiring high durability and resistance to wear in harsh body environments.

- **Polymers**: Organic-based biomaterials that include both natural (e.g., collagen, chitosan) and synthetic polymers (e.g., polyethylene, PMMA, PLA). Polymers are particularly useful in applications requiring flexibility such as in vascular grafts, sutures, and soft tissue replacements [4]. Their versatility allows for easy fabrication into complex shapes and textures.
- **Composites**: Combine two or more distinct materials that possess complementary properties. Composite biomaterials often involve a combination of ceramics and polymers, providing structural integrity while mimicking the natural tissue's mechanical and interface properties. They are frequently used in bone grafts, where their customized properties can be engineered to match those of the surrounding bone.

1.4 Historical Context and Evolution

The use of biomaterials is not new and dates back to antiquity. Ancient civilizations utilized various natural materials to repair and replace body functions. For example, the ancient Egyptians used sutures made from animal sinew to close wounds, and ancient Romans used gold for dental restorations. The development of biomaterials has closely followed the advancement of medicine and materials science through history.

In the twentieth century, the field of biomaterials began to formalize with the development of stainless steel and vitallium in dental and orthopedic applications. The late twentieth and early twenty-first centuries have seen rapid advances due to the integration of biotechnology and nanotechnology, leading to the development of more sophisticated materials like biodegradable polymers and composites that can actively participate in the healing process.

1.5 Properties Essential for Medical Applications

The ideal properties of biomaterials depend largely on their intended function but typically include biocompatibility, mechanical strength, durability, and functionality specific to the biological environment:

- **Biocompatibility**: The ability of a material to perform with an appropriate host response in a specific application. This is critical because materials must not elicit a significant immune response which could lead to rejection and failure of the implant.
- **Mechanical Properties**: Depending on the application, materials must exhibit appropriate mechanical properties such as strength, elasticity, and fatigue resistance. For example, materials used in bone replacements must be strong and durable, whereas materials used in heart valves require flexibility and fatigue resistance [5].
- **Degradation**: The rate at which a material degrades within the body can be crucial, especially for temporary implants like sutures and tissue scaffolds. Controlled degradation that matches tissue growth is vital for materials that are designed to be absorbed by the body.

1.5.1 Biocompatibility

Biocompatibility is arguably the most critical property of biomaterials used in medical devices and implants. It describes the ability of a material to perform its desired function without eliciting any undesirable reactions from the body [6]. The ideal biomaterial should not cause inflammation, should be non-toxic, and should not trigger an immune system response. However, the degree and type of biocompatibility required can vary significantly depending on the intended application of the material—whether it will have transient contact with tissue, as with a catheter, or permanent implantation, as with joint replacements.

- **Host Response**: Understanding the host response involves studying the interaction between the biomaterial and the biological environment at the molecular, cellular, and tissue levels. This includes assessing protein adsorption, cell adhesion, cell proliferation and differentiation, immune response (both innate and adaptive), and the integration or rejection of the biomaterial.
- **Testing and Standards**: Rigorous testing standards are established to evaluate biocompatibility, including in vitro cytotoxicity tests, genotoxicity assays, and in vivo animal testing. Regulatory frameworks, like those provided by the FDA or ISO, guide these evaluations, ensuring that biomaterials are thoroughly vetted before clinical use.

1.5.2 Mechanical Properties

The mechanical properties of biomaterials are crucial for ensuring the reliability and durability of implants. Properties such as strength, elasticity, hardness, and fatigue resistance must be aligned with the mechanical demands of the body part [6] they are intended to replace or support.

- **Material Selection**: Materials are selected based on the mechanical stresses they will face in the human body. For instance, metals like titanium and stainless steel are used in load-bearing implants due to their high tensile strength and fatigue resistance, whereas polymers might be more suitable for less demanding applications like catheters or sutures.
- **Influence of Processing on Properties**: The manufacturing process can significantly affect the mechanical properties of biomaterials. For example, the microstructure of metallic implants can be tailored through processes like forging and annealing to enhance strength or ductility.

1.5.3 Degradation Characteristics

The degradation characteristics of a biomaterial determine its longevity and stability within the biological environment. Degradation should occur at a rate that matches the healing or regeneration of the surrounding tissues.

- **Biodegradable Materials**: These are designed to break down within the body over a controlled period. For example, polylactic acid (PLA) and polyglycolic acid (PGA) are used in sutures and tissue engineering scaffolds that degrade as the tissue heals. Factors influencing degradation: Environmental factors within the body such as pH, temperature, and the presence of enzymes can affect the degradation rate of biomaterials [7]. Understanding and controlling these factors is crucial to ensure that the material provides support without overstaying its welcome. Implications of degradation products: It's important that the products of degradation are non-toxic and can be safely absorbed or excreted by the body. Unintended consequences of degradation, such as inflammation caused by acidic degradation products, must be carefully managed.

  The properties of biomaterials are multifaceted and need to be tailored to their specific medical applications. Biocompatibility ensures that the material can function in harmony with the body, while mechanical properties must meet the physical demands of the application site. Bioactivity promotes integration with bodily tissues, and controlled degradation allows materials to support healing processes without causing harm. Each of these properties must be carefully balanced and optimized during the development of new biomaterials to ensure their safety, functionality, and efficacy in medical applications. This comprehensive approach to understanding and designing biomaterials is what ultimately enables innovations in medical technology and improves patient outcomes.

1.6 Looking Ahead: Innovations and Future Directions

The future of biomaterials is a promising frontier filled with potential innovations aimed at enhancing patient care (Fig. 1.2). Advances in genetic engineering, nanotechnology, and materials science are leading to the next generation of biomaterials that are smart, capable of adapting to their environment, and even delivering therapeutic agents precisely where needed. Emerging trends include the development of materials that can mimic the mechanical and chemical properties of natural tissues, smart materials that respond to physiological conditions, and the use of stem cells in conjunction with biomaterial scaffolds to enhance regenerative strategies.

These advancements herald a new era where materials science converges with biology, creating opportunities that were once thought impossible [8]. As researchers continue to innovate and understand the interactions between biomaterials and biological systems better, the future holds a promise of revolutionary changes to medical treatments and improved patient outcomes.

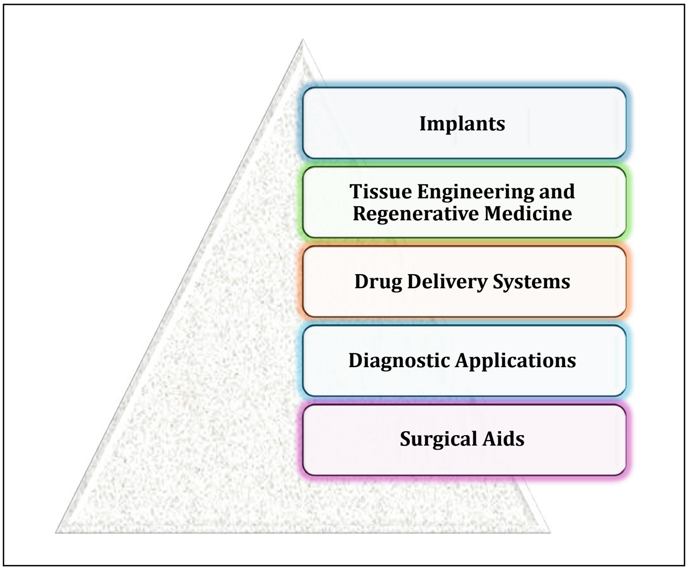

Fig. 1.2 Role and applications of biomaterials in medicine

1.7 Role and Applications of Biomaterials in Medicine

1.7.1 Implants

- **Orthopedic Implants**: Biomaterials are integral to orthopedic applications, such as joint replacements (hip, knee, shoulder) and bone plates. Metals like titanium and stainless steel, ceramics like alumina and zirconia, and polymers such as ultra-high-molecular-weight polyethylene (UHMWPE) are commonly used due to their strength, durability, and biocompatibility. These materials must withstand the mechanical loads of daily activities and mimic the function of natural bone.
- **Dental Implants**: In dental applications, biomaterials are used for crowns, bridges, and implant fixtures that integrate with the jawbone. Titanium is a popular choice for the fixtures due to its excellent biocompatibility and strength, while ceramics are preferred for visible parts of the implant due to their esthetic qualities and compatibility with gum tissues.
- **Cardiovascular Devices**: Biomaterials are used in heart valves, stents, and pacemaker leads. Materials used in these applications must be exceptionally biocompatible and offer minimal thrombogenicity (tendency to cause blood clots). Flexible polymers, stainless steel, and cobalt-chromium alloys are common, as they can endure the dynamic environment of the cardiovascular system.

1.7.2 Tissue Engineering and Regenerative Medicine

Biomaterials provide scaffolds that support the growth and differentiation of cells, guiding the formation of new functional tissues for regenerative medicine [9]. These scaffolds are designed to mimic the extracellular matrix, providing not only structural support but also biological cues that direct cells in tissue formation.

- **Scaffold Design**: The design of these scaffolds requires careful consideration of pore size, degradation rate, and mechanical properties to ensure they mimic the natural cell environment. Materials like collagen, gelatin, and synthetic polymers are often used.
- **Applications**: Applications include skin regeneration for burn victims, bone and cartilage repair, and even organ bio-fabrication. Innovations like 3D bioprinting have expanded the possibilities in this field, allowing for the precise placement of cells and scaffold materials to create complex tissue structures.

1.7.3 Drug Delivery Systems

Biomaterials revolutionize drug delivery by facilitating controlled release profiles and targeted delivery. This enhances therapeutic efficacy and minimizes side effects.