Advance Materials Series

ADVANCED HEALTHCARE MATERIALS

Edited By
Ashutosh Tiwari

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Advance Materials Series

The Advance Materials Series provides recent advancements of the fascinating field of advanced materials science and technology, particularly in the area of structure, synthesis and processing, characterization, advanced-state properties, and applications. The volumes will cover theoretical and experimental approaches of molecular device materials, biomimetic materials, hybrid-type composite materials, functionalized polymers, superamolecular systems, information- and energy-transfer materials, biobased and biodegradable or environmental friendly materials. Each volume will be devoted to one broad subject and the multidisciplinary aspects will be drawn out in full.

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Preface

Advanced healthcare materials are attracting strong interest in fundamental as well as applied medical science and technology. *Advanced Healthcare Materials* summarizes the current state of knowledge in the field of Advanced Materials for functional therapeutics, point-of-care diagnostics, translational materials and up-and-coming bioengineering devices. In this book we have highlighted the key features which enable the design of stimuli-responsive smart nanoparticles, novel biomaterials, and nano/micro devices for either diagnosis or therapy, or both, called theranostics. The latest advancements in healthcare materials and medical technology are also presented. In narrative outline, this volume of the Advanced Materials series includes fourteen chapters divided into four main areas: "Functional Therapeutics," "Point-of-Care Diagnostics," "Translational Materials" and "Up-and-Coming Bioengineering Devices."

The chapter "Stimuli-Responsive Smart Nanoparticles for Biomedical Application," describes the synthesis and engineering of stimuli-responsive polymeric nanosystems and their use in sensors, logic operations, biomedicine, tissue engineering and regenerative medicine, synthetic muscles, "smart" optical or microelectromechanical systems, membranes, electronics and self-cleaning surfaces. The chapter entitled "Diagnosis and Treatment of Cancer – Where We Are and Where We Have to Go!" is an overview of new methods and technology such as functional nanoparticles-based drug delivery and diagnostics systems for overcoming obstacles in cancer diagnosis and treatment. Also, exploratory fundamental and cutting-edge accounts of advanced materials including nanoparticles, nanopolymers, metal-organic frameworks and zeolites in drug delivery and diagnostics are presented in the chapter, "Advanced Materials for Biomedical Application and Drug Delivery." Another chapter, "Nanoparticles for Diagnosis and/or Treatment of Alzheimer's Disease," focuses on the nanotheranostic approach to Alzheimer's treatment.

The chapters "Novel Biomaterials for Human Health: Hemocompatible Polymeric Micro- and Nanoparticles and Their Application in Biosensor" and "The Contribution of Smart Materials and Advanced Clinical Diagnostic Micro-Devices on the Progress and Improvement of Human Health Care," cover the application of advanced healthcare materials for point-of-care diagnostics. The notable advantages and limitations of translational biomaterials are described in the chapters "Hierarchical Modeling of Elastic Behavior of Human Dental Tissue Based on Synchrotron Diffraction Characterization," "Biodegradable Porous Hydrogels," and "Hydrogels: Properties, Preparation, Characterization and Biomedical Applications in Tissue Engineering, Drug Delivery and Wound Care." Up-and-coming bioengineering devices are covered in the chapters entitled "Modified Natural Zeolites – Functional Characterization and Biomedical Application," "Supramolecular Hydrogels Based on Cyclodextrin Poly(Pseudo)Rotaxane for New and Emerging Biomedical Applications," "Polyhydroxyalkanoate-Based Biomaterials for Applications in Biomedical Engineering," "Biomimetic Molecularly Imprinted Polymers as Smart Materials and Future Perspective in Health Care," and "The Role of Immunoassays in Urine Drug Screening."

This book has been written for a large readership including university students and researchers from diverse backgrounds such as chemistry, materials science, physics, pharmacy, medical science, and biomedical engineering. It can be used not only as a textbook for both undergraduate and graduate students, but also as a review and reference book for researchers in materials science, bioengineering, medical, pharmacy, biotechnology and nanotechnology. We hope the chapters of this book will provide readers with valuable insight into the important area of advanced healthcare materials, especially the cutting-edge technology in functional therapeutics, point-of-care diagnostics, translational materials and up-and-coming bioengineering devices. The interdisciplinary nature of the topics in this book will help young researchers and senior academicians. The main credit for this book goes to the contributors who have comprehensively written their updated chapters in the field of Advanced Healthcare Materials.

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Part 1

FUNCTIONAL THERAPEUTICS

1

Stimuli-Responsive Smart Nanoparticles for Biomedical Application

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Abstract
Biological systems consist largely of regulation systems; these natural feedback regulation systems are very important to stabilize such non-equilibrium systems like a living organism. One example is release of hormones from secretory cells, which is regulated by physiological cycles or by specific input signals. It is not surprising that regenerative medicine and drug delivery are also utilizing similar responsive strategies in a biomimetic fashion. During the last two decades, scientists have been trying to mimic nature in designing "smart" synthetic materials from various functional molecular building blocks that respond to stimuli such as temperature, pH, ionic strength, light, electric or magnetic field, chemical and biochemical stimuli in order to mediate molecular transport, shape changes, tune adhesion and wettability, or to induce signal transduction of (bio-)chemical or physical stimuli into mechanical, optical or electrical responses. Biomimetic approaches have been employed in the design, synthesis and engineering of stimuli-responsive polymeric systems, which undergo reversible abrupt phase transitions upon variation of a variable around a critical point and their use in a plethora of applications, including sensors, logic operations, biomedicine, tissue engineering and regenerative medicine, synthetic muscles, "smart" optical or microelectromechanical systems, membranes, electronics and self-cleaning surfaces has been explored.

Keywords: Biological systems, nanomedicine, nanoparticles, biomedical applications

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1.1 A Brief Overview of Nanotechnology

Nanotechnology has emerged in the last decades of the 20th century with the development of new enabling technologies for imaging, manipulating, and simulating matter at the atomic scale. The frontier of nanotechnology research and development encompasses a broad range of science and engineering activities directed toward understanding and creating improved materials, devices and systems that exploit the properties of matter that emerge at the nanoscale. The results promise benefits that will shift paradigms in biomedicine (e.g., imaging, diagnosis, treatment, and prevention); energy (e.g., conversion and storage); electronics (e.g., computing and displays); manufacturing; environmental remediation; and many other categories of products and applications.

Amongst leading scientists, there is growing awareness about the tremendous impact this field will have on society and the economy. It is forecasted to become possibly even more important than, for example, the invention of the steam engine or the discovery of penicillin.

The landmark lecture by eminent Nobel Laureate Richard Feynman in 1959 entitled "There's plenty of room at the bottom," brought life (to) the concept of nanotechnology, which has been influencing all the different fields of research involving hard core science such as chemistry, physics, and other applied fields of science, such as electronics, materials science and biomedical science, agrochemicals, medicine and pharmaceutical sciences etc. [1].

Nanotechnology and nanoscience are widely seen as having a great potential to bring benefits to many areas of research and applications. They are attracting increasing investments from governments and private sector businesses in many parts of the world. Concurrently, the application of nanoscience is raising new challenges in the safety, regulatory, and ethical domains that will require extensive debates on all levels.

The prefix nano is derived from the Greek word dwarf. One nanometer (nm) is equal to one-billionth of a meter, that is, 10^{-9} m. The term "nanotechnology" was first used in 1974, when Norio Taniguchi, a scientist at the University of Tokyo, Japan, referred to materials in nanometers.

At the nanometer scale, the physical, chemical and biological properties of nanomaterials are fundamentally different from those of individual atoms, molecules, and bulk materials. They differ significantly from other materials due to two major principal factors: the increased surface area and quantum effects. A larger surface area usually results in more reactive chemical properties and also affects the mechanical or electrical properties of the materials. At the nanoscale, quantum effects dominate the behaviors of a material, affecting its optical, electrical and magnetic properties. By exploiting these novel properties, the main purpose of research and development in nanotechnology is to understand and create materials, devices and systems with improved characteristics and performances [2].

1.2 Nanoparticulate Delivery Systems

The nanoparticulate system comprises of particles or droplets in the submicron range, i.e., below 1μm, in an aqueous suspension or emulsion, respectively. This small size of the inner phase gives such a system unique properties in terms of appearance and application. The particles are too small for sedimentation; they are held in suspension by the Brownian motion of the water molecules. They have a large overall surface area and their dispersions provide a high solid content at low viscosity.

Historically, the first nanoparticles proposed as carriers for therapeutic applications were made of gelatin and cross-linked albumin [3]. Use of proteins may stimulate the immune system, and to limit the toxicity of the cross-linking agents, nanoparticles made from synthetic polymers were developed. At first, the nanoparticles were made by emulsion polymerization of acrylamide and by dispersion polymerization of methylmethacrylate [4]. These nanoparticles were proposed as adjuvants for vaccines. Couvreur *et al.* [5] proposed to make nanoparticles by polymerization of monomers from the family of alkylcyanoacrylates already used in vivo as surgical glue. During the same period of time, Gurny *et al.* [6] proposed a method for nanoparticle synthesis from another biodegradable polymer consisting of poly(lactic acid) used as surgical sutures in humans. Based on these initial investigations, several groups improved and modified the original processes mainly by reducing the amount of surfactant and organic solvents. A breakthrough in the development of nanoparticles occurred in 1986 with the development of methods allowing the preparation of nanocapsules corresponding to particles displaying a core-shell structure with a liquid core surrounded by a polymer shell [7]. The nanoprecipitation technique was proposed as well as the first method of interfacial polymerization in inverse microemulsion [8]. In the succeeding years, the methods based on salting-out [9], emulsion–diffusion [10], and double emulsion [11] were described. Finally, during the last decade, new approaches were considered to develop nanoparticles made from natural origin such as polysaccharides [12]. These nanoparticles were developed for peptides and nucleic acid delivery. A further development was surface modification of nanoparticles to produce long circulating particles able to avoid the capture by the macrophages of the mononuclear phagocyte system after intravenous administration [13].

1.3 Delivery Systems

The specific delivery of active principles to the target site, organ, tissue, or unhealthy cells by carriers is one of the major challenges in bioactive delivery research. Many of the bioactive compounds have physicochemical characteristics that are not favorable to transit through the biological barriers that separate the administration site from the site of action. Some of the active compounds run up against enzymatic barriers, which lead to their degradation and fast metabolization. Therapeutically, distribution of such active molecules to the diseased target zones can therefore be difficult. Moreover, the accumulation of drugs in healthy tissues can cause unacceptable toxic effects, leading to the abandonment of treatment despite its effectiveness [14].

In order to overcome the above challenges an ideal delivery system must possesses basically two elements: the ability to transport loaded payload to the target site and control its release. The targeting will ensure high efficiency of loaded payload at the site of core interest and reduces any unwanted biological effects. Various delivery devices have been developed and an overview of each type of nanocarrier is given in the following section.

According to the process used for the preparation of nanoparticles, nanospheres or nanocapsules can be obtained. Nanospheres are homogeneous matrix systems in which the drug is dispersed throughout the particles. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a polymeric membrane [15].

1.3.1 Hydrogels

Hydrogels are three-dimensional networks composed of hydrophilic polymer chains. They have the ability to swell in water without dissolving. The type of cross-linking between the polymer chains can be chemical (covalent bonds) or physical (hydrogen bonds or hydrophobic interactions). The high water content in these materials makes them highly biocompatible. There are natural hydrogels such as DNA, proteins, or synthetic, e.g., poly(2-hydroxyethyl methacrylate), poly(N-isopropylacrylamide) or a biohybrid [16]. The release mechanism can be induced by temperature