



Edited by

ECATERINA ANDRONESCU

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# NANOSTRUCTURES FOR DRUG DELIVERY

NANOSTRUCTURES IN  
THERAPEUTIC MEDICINE SERIES

**Nanostructures in Therapeutic Medicine Series**

# Nanostructures for Drug Delivery

Edited by

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# Foreword of the Series

Material science and engineering at the nanoscale has brought revolutionary advances to the biomedical sciences, overturning many of the traditionally known approaches. Nanotechnology has driven many of the most successful innovative technologies, and the impressive record of accomplishments in the field make nanostructures promising candidates for medical therapy applications. The advantages that nanomaterials have already provided to therapeutics, such as targeted and controlled delivery, wide accessibility, high specificity, low side effects, improved efficiency, and impressive versatility are currently considered key elements in designing personalized medicine approaches for prophylaxis, diagnosis, and therapy.

Therapeutic nanostructures can be greatly diverse, and their unique properties have led to the development of highly specialized biosensors, more efficient drug delivery vehicles, and controlled release targeting systems to fight severe or incurable diseases, such as cancer, infections, and cardiovascular disease.

In view of the astounding progress made in the field of therapeutic nanotechnology and its rapidly progressing expansion, this book aims to collect in one place all the recent and most innovative aspects of nanomaterials in both current and future therapy. The series is organized into five volumes, covering the main areas that are relevant for the design and implementation of nanostructures in medical therapies.

The first volume, *Nanostructures for Novel Therapy: Synthesis, Characterization, and Applications*, describes methods to obtain and characterize nanosystems, emphasizing their biomedical applications. Special attention is paid in this volume to modern synthesis methods to reduce side effects and limit the toxicity of nanomaterials in biomedical applications. Numerous examples of nanostructures designed for therapy, as well as the most efficient synthesis and characterization routes for these materials, are clearly described and critically analyzed.

The second volume, entitled *Nanostructures for Drug Delivery*, covers one of the most widely utilized and investigated applications of nanomaterials in the biomedical field, namely, drug delivery. Designing nanostructures to specifically and safely carry therapeutic agents to their final destination is an intriguing approach to future targeted therapies. This approach could provide a treatment for previously incurable diseases, as well as reducing the side effects of current drugs. Many highly active drugs are severely limited by side effects related to their unspecific sites of action. This volume introduces the readers to the amazing field of nanomedicine by discussing the versatility and variety of nanovehicles for drug delivery and targeting. Moreover, readers will find numerous examples and will learn about the currently used or investigational drug delivery agents for therapy, prophylaxis, and diagnosis.

Volume 3, *Nanostructures for Antimicrobial Therapy*, highlights the impressive progress made by nanotechnology in the design of novel antimicrobial approaches. Since microbial resistance to antibiotics is a real and increasingly worrying issue across all countries, the development of more efficient antimicrobial agents to provide control of future infections is at a high priority. Antimicrobial nanosystems have proved to be remarkably efficient against drug-resistant microorganisms, plus they are able to fight biofilm-associated infections and can control the social behavior of microbial communities. Nanostructures can also reduce microbial virulence factors and reduce pathogenesis mechanisms, offering a promising alternative for future therapy.

Volume 4, entitled *Nanostructures for Cancer Therapy*, covers the applications of nanomedicine in cancer diagnosis and treatment. The use of nanoparticles for cancer therapy is not in itself a new approach, but numerous recent advances have been made in this area. The aim of this volume is to cover the most interesting new approaches in the management of this deadly disease. Nanosized drugs are currently believed to represent the most efficient approach in cancer chemotherapy, and this volume provides coverage of the latest and most novel findings, while also discussing possible improvements in more established types of nanosystems that can increase the efficiency of cancer therapy.

The final volume of this series, entitled *Nanostructures for Oral Medicine*, covers the progress made in applications of nanotechnology in treating various diseases of the oral cavity as well as progress in nanotechnology applications in dentistry. Readers can learn about the most efficient modern materials used to treat or to prevent widely encountered oral diseases such as gingivitis, periodontitis, caries, and dental plaque. Moreover, restorative dentistry also now makes wide use of nanomaterials.

Overall, this book series provides a state-of-the-art compendium of knowledge, and a crystal ball for seeing into the future of biomedical nanotechnology and nanomedicine. It has appeal for researchers, clinicians, engineers, pharmacologists, pharmacists, oncologists, infectious disease experts, and dentists. In addition, interested general readers will discover the impact, current progress, and future applications of nanotechnology in therapeutics and diagnosis. Taken together, nanoscale approaches will improve the efficiency of personalized medicine for better management of diseases in the 21st century.

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# Preface

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## ABOUT THE SERIES (VOLUMES I–V)

In our permanently changing world, novel therapeutics are constantly required to manage health and well-being of population. Although numerous diseases are currently considered incurable, massive progress made in biomedicine but also in associated fields, such as chemistry, physics, engineering, pharmacology and materials science, offers a new light to the therapeutics domain. In this context, most physicists and researchers believe that a personalized and adequate treatment may significantly improve the outcome of severe diseases and ensure a faster healing. Nanotechnology offers great perspectives for personalized medicine because nanostructured therapeutics proved their efficiency and amazing impact in improving therapy, prophylaxis, and diagnosis. The emerging field of nanosized materials has numerous applications in the biomedical field, especially in therapy. This series of five volumes came out by the need of learning about recent progress of the science of nanostructured materials to improve current therapy and lead to the next level. The books offer an interesting and updated perspective regarding applications of nanomaterials in therapy of most investigated and difficult-to-treat diseases, such as cancer and severe infections. The presentation approach of each chapter contained in those five volumes is clear and easy to understand by most readers and of a great interest for biomedical specialists, researchers, and engineers. The series is organized in an attractive manner for students and academics on the field, starting with a volume dealing with synthesis, characterization, and main applications of nanostructures, emphasizing on their impact in therapy. Next volume reveals the most recent progress made on a very investigated field, considered a key element in personalized medicine and future therapy, namely nanostructured drug delivery systems. Their impact in antimicrobial therapy is also widely discussed, and suggestive examples are given and explained. Moreover, a whole volume is dedicated to the management of the disease of the century—cancer—revealing the huge value added by the utilization of nanosystems in the therapy of this deadly disease. Important aspects related to improved diagnosis and prophylaxis are highlighted. In the last volume, the progress and novel applications of nanotechnology in oral medicine is dissected. The field of oral diseases represents an interesting and a priority field because both physicists and researchers believe that they can be prevented and treated more easily with targeting systems and nanofunctional prosthetics. All chapters are clearly illustrated to highlight most important or difficult-to-understand aspects, and suggestive examples are often enumerated in organized tables, which are explained and discussed. Overall, the series contains very recent but accessible and very interesting information regarding the progress of nanostructures in therapeutics and gives a novel perspective about future therapy of severe diseases.

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## ABOUT VOLUME II

The second volume of the series *Therapeutic Nanostructures* is entitled *Nanostructures for Drug Delivery*. This volume reveals the main types of nanosized drug delivery systems, dissecting their main advantages and drawbacks in the therapy of severe and difficult-to-treat diseases. Nanosized carriers are commented in all stages of their preparation and use, starting with suitable synthesis methods, appropriate characterization, and functionalization, and ending with their application in drug delivery and therapy. A special attention is given to green nanotechnology which enables the production of natural, biocompatible and less toxic nanosystems which may be efficiently used in delivering pharmacological agents. Numerous properties of such drug delivery systems are highly appreciated for future therapy, namely longtime circulation in the bloodstream, target specificity, stimuli responsively, possibility of intracellular delivery, contrast functionality, and increased stability. Different ways for the control of the load capacity and release profile are also analyzed in many of the chapters.

Volume II contains 30 chapters, prepared by outstanding researchers affiliated in the USA, Canada, Argentina, Ireland, Italy, New Zealand, Poland, Serbia, Romania, Russia, Turkey, Egypt, Iran, Pakistan, India, and China.

In Chapter 1, entitled *Therapeutic Nanomaterials: From a Drug Delivery Perspective*, C. Ganesh Kumar et al. focus on the synthetic routes and applications of nanomaterials as potential drug delivery agents. Different nanomaterial types including polymeric nanomaterials, dendrimers, nanoparticles, carbon nanotubes, quantum dots, and their applications have been discussed and a number of case studies have been presented in this chapter.

Nily Dan, in Chapter 2, entitled *Core–Shell Drug Carriers: Liposomes, Polymerosomes, and Niosomes*, reveals the three types of main formulations used as drug nanocarriers and summarizes studies of their performance in biomedical applications such as cancer therapy (tumor targeting) or transport through the blood–brain barrier.

Chapter 3, entitled *The New Nanocarriers Based on Graphene and Graphene Oxide for Drug Delivery Applications*, prepared by Somayeh Mohamadi and Mehrdad Hamidi, gives an overview about a new carbon-based carrier for drug delivery applications. The unique properties of graphene nanosheets such as two-dimensional planar structure with  $sp^2$  hybridation, large surface area, chemical and mechanical stability, super conductivity, and good biocompatibility provide the opportunity to design drug carriers with dual-targeting function.

In Chapter 4, entitled *Nanostructured Nanoparticles for Improved Drug Delivery*, Jean Michel Rabanel et al. provide a comprehensive view of the different types of structures found in nanoparticles intended for medical use reported so far in the literature, together with some insight regarding their fabrication processes and their physicochemical properties and how this nanoparticles deliver active compounds in a controlled fashion to the human body or developed imaging strategies.

Chapter 5, entitled *Design of Functionalized Materials for Use in Micro and Nanoscale Drug Delivery Devices and Smart Patches*, prepared by Ashleigh Anderson and James Davis, provides a critical overview of the latest developments in functional materials and nanoscale device architectures that can facilitate controlled drug delivery.

Chapter 6, entitled *Niosomes: A Novel Approach in Modern Drug Delivery Systems*, prepared by Sepideh Khoee and Morteza Yaghoobian, discusses about new drug delivery vehicles and gives a brief description on the preparation, applications, advantages and disadvantages of particular delivery system—niosomes.

Fatemeh Zamani et al., in Chapter 7, entitled *Nanofibrous and Nanoparticle Materials as Drug-Delivery Systems*, emphasize on the emerging area of nanoparticles synthesis through electrospinning technique to generate biomimetic nanofibers and nanoparticles as drug delivery devices that are responsive to different stimuli, such as temperature, pH, light, and the electric/magnetic field for controlled release of therapeutic substances.

Yun Yu et al., in Chapter 8, entitled *Brush Polymer-Based Nanostructures for Drug Delivery*, give an overview on the advantages of brush polymer (BP)-based drug delivery systems. Also, future research directions of BP-based drug delivery systems are highlighted.

Magdalena Jarosz et al., in Chapter 9, entitled *Drug Delivery Systems Based on Titania Nanostructures*, focus on different titanium ( $\text{TiO}_2$ ) nanostructures used as drug delivery systems, such as nanotubular and nanoporous  $\text{TiO}_2$ ,  $\text{TiO}_2$  nanoparticles, and nanowhiskers.

Houman Alimoradi et al., in Chapter 10, entitled *Redox Activated Polymeric Nanoparticles in Tumor Therapy*, focus on the biochemical basis for oxidative stress in tumors, its role in cell-signaling, the pathophysiology of tumor vasculature, and the differences in the redox-metabolism between cancer cells and nonmalignant tissues. The recent developments toward designing redox responsive drug delivery systems which have been classified as polysulfide, polyselenide, quinones, metal complexes, arylboronic esters, aryl oxalate, and other miscellaneous examples are also discussed.

Chapter 11, entitled *Polymeric Micro- and Nanoparticles for Controlled and Targeted Drug Delivery*, prepared by Magdalena Stevanović, reports the production and applications of polymeric micro- and nanoparticles with a special emphasis on obtaining polyester particles, the incorporation of different active substances within polymer matrix, the degradation and release process of active substances from the polymeric particles, the physiochemical and biological properties of such obtained systems, as well as their application as drug delivery systems.

Chapter 12, entitled *Novel Gels: Implications for Drug Delivery*, prepared by Swarnali D. Paul et al., describes all the emerging prospects of novel gels along with their formulation aspects, manufacturing technologies, and current applications, focusing on therapeutic potential.

Chapter 13, entitled *Nanosuspension Drug Delivery System: Preparation, Characterization, Post-production Processing, Dosage Form, and Application*, prepared by Jiahong Zhang et al., gives an overview about nanosuspension drug-delivery system (DDS) discussing preparation methods, characterization methods, postproduction process including the solidification techniques and surface modification process, common dosage forms, and clinical applications of nanosuspension DDS.

Chapter 14, entitled *Polymer-Based Nanocarriers for Therapeutic Nucleic Acids Delivery*, prepared by Weien W. Yuan and Hui H. Li, describes the challenges, advantages, and recent progress of polymer-based nanocarriers for therapeutic nucleic acids delivery. Considerations for manufacturing, safety issues, and regulatory requirements for these novel nanocarriers are also discussed.

Chapter 15, entitled *Multifunctional Therapeutic Hybrid Nanocarriers for Targeted and Triggered Drug Delivery: Recent Trends and Future Prospects*, prepared by Gulbin Kurtay et al., presents new generation and promising hybrid nanocarriers based on noble metal, porous silica, polymer, and core/shell therapeutics which exhibit active targeting, triggered release of cargo, and imaging capability for in vivo studies.

Ragwa M. Farid et al., in Chapter 16, entitled *Lipid-Based Nanocarriers for Ocular Drug Delivery*, give an up-to-date overview about lipid-based nanocarriers that can enhance the corneal absorption of both hydrophilic and lipophilic drugs and improve their ocular bioavailability. Nanostructured lipid carriers (NLCs) and lipid drug conjugates (LDCs) have emerged as a new generation of solid lipid



nanoparticles (SLNs) to overcome problems of low entrapment efficiency and drug expulsion during storage.

Rajeev Sharma et al., in Chapter 17, entitled *Nanoparticulate Carrier(s): An Emerging Paradigm in New Generation Vaccine Development*, summarize the cutting edge technologies of nanoparticulate-carrier-based new generation and vaccine development, including design, trials, and clinical outcomes.

Chapter 18, entitled *Pathogen-Specific Nucleic Acid Aptamers as Targeting Components of Antibiotic and Gene Delivery Systems*, prepared by Canan Ozyurt et al., presents an overview of current cell-specific aptamer-conjugated nanoparticles. Also, the authors address two issues: nanoparticle-based antimicrobial gene delivery and modification of nanocarriers with aptamers.

Tamilvanan Shunmugaperumal et al., in Chapter 19, entitled *Multifunctional Nanosized Emulsions for Theragnosis of Life Threatening Diseases*, envision the use of the multifunctional oil-in-water (o/w) nanosized emulsions (NE) that carries imaging agents, anticancer or lipid lowering or antiatherosclerotic drug molecules and homing devices together for simultaneous imaging/diagnosing and treatment of cancer and atherosclerosis. A complete outline is given on the formulation of drug-loaded NE together with active and passive targeting moieties for accessing the unreachable organs present inside the human body.

Chapter 20, entitled *Therapeutic Nanostructures for Pulmonary Drug Delivery*, prepared by Yousef Javadzadeh and Shadi Yaqoubi, discusses about pulmonary drug delivery, inhalers, nanoparticles, and the advantages and fate of inhaled nanoparticles.

Najma Bibi et al., in Chapter 21, entitled *Nanostructures in Transdermal Drug Delivery Systems*, dissect the benefits of transdermal drug delivery over other delivery systems, arguing about the barriers in the skin to be faced by nanomaterials and their permeation pathways. Physicochemical characteristics required for the good penetration of nanostructures are also discussed.

Chapter 22, entitled *Advancement in Pulmonary Drug Delivery Systems for Treatment of Tuberculosis*, prepared by Tarun Garg et al., presents an overview about the importance of pulmonary drug delivery systems such as liposomes, niosomes, nanoparticles, microparticles, dendrimers, solid lipid nanoparticles, micelles, nanosuspensions, nanoemulsions, and microemulsions for an effective treatment of tuberculosis. The advances in delivery devices from conventional metered dose inhalers to dry powder inhalers are also discussed along with their applications.

Chapter 23, entitled *Nanosized Devices as Antibiotics and Antifungals Delivery: Past, News and Outlook*, prepared by Pio M. Furneri et al., discusses about developments in the field of (nanosized) delivery systems encapsulating antibacterial and antifungal drugs. A specific attention has been given to the pharmaceutical, microbiological, and clinical outcomes of systems for which authors have provided in vitro microbiological data and, more hopefully, in vivo results.

Chapter 24, entitled *Drug Delivery Mediated by Confined Nanosystems: Structure-Activity Relations and Factors Responsible for the Efficacy of Formulations*, prepared by Lucia Zakharova et al., presents different ways for the control of the load capacity and release profile. The chapter also discusses about the ability of formulated drug to integrate with cell membrane and penetrate through the blood-brain barrier.

Daniela Alejandra Quinteros et al., in Chapter 25, entitled *Therapeutic Use of Monoclonal Antibodies: General Aspects and Challenges for Drug Delivery*, identified and described the major issues associated with therapeutics approaches, formulating drawbacks, and delivering antibody drugs, particularly focused on the challenges and opportunities that these present for the future.