Nanostructures in Therapeutic Medicine Series

Nanostructures for Oral Medicine

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Foreword of the Series

Material science and engineering at the nanoscale have brought revolutionary advances to the biomedical sciences, overturning many of the known traditional approaches. Nanotechnology has driven many of the most successful innovative technologies, and their impressive record of accomplishment has made nanostructures promising candidates for future therapy. 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 highly 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 together in one place all the most recent and innovative aspects regarding the impact of nanomaterials in both current and future therapy. The book is organized in 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 in this volume was paid 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. The design of nanoscale agents in order to specifically and safely carry therapeutic agents to their final destination is an intriguing approach to future targeted therapeutics. 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 book 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.

The third volume, *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 very real and worrying issue growing throughout the world, the development of more efficient antimicrobial agents has a high priority to allow control of infections in the future. Antimicrobial nanosystems have proved to be highly efficient against drug-resistant microorganisms, are able to fight biofilm-associated infections and control the social behavior of microbial communities. Nanostructures can also reduce microbial virulence factors and reduce pathogenesis mechanisms thus offering a promising alternative for future therapy.

The fourth volume, 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 advances have been recently made in this area, and the aim of this book 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 novel findings, while also discussing possible improvements in more established types of nanosystems to increase the efficiency of cancer therapy.

Last but not least, the fifth 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 and in dentistry. Readers will have the chance to 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 will provide a state-of-the-art compendium of knowledge, and a crystal ball to see into the future of biomedical nanotechology and nanomedicine. It will appeal to researchers, clinicians, engineers, pharmacologists, pharmacists, oncologists, infectious disease experts, and dentists. More many interested general readers may 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

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 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, since nanostructured therapeutics proved their efficiency and amazing impact in improving therapy, prophylaxis, and diagnosis. The emerging field of nanosized materials have 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 in order 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 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 are dissected. The field of oral diseases represents a wide-interest and priority field since 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 contain very recent but accessible information regarding the progress of nanostructures in therapeutics and give a novel perspective about future therapy of severe diseases.

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ABOUT VOLUME V

The fifth volume of the series *Therapeutic Nanostructures* is entitled *Nanostructures for Oral Medicine.* This volume reveals numerous applications of nanostructures in oral medicine. Various key approaches, such as drug design and delivery, oral vaccines, and therapeutic systems for oral applications, are

discussed and exemplified in this volume. Oral medicine represents a widely investigated field, where nanotechnology has found numerous applications. From improved implantable materials to specialized drug-delivery systems, nanomaterials have offered solutions to serious clinical conditions from diagnosis to therapy. The book describes not only the preparation of oral nanomedicines but also their main properties, applications and principal advantages and drawbacks. Applications and impact on human life quality of recently developed nanomaterials aimed at oral therapy are also presented here. Similar to general medicine, the trend in oral medicine seems to follow technological progress, the specificity and sensibility of nanostructured drugs playing an important role in the design of tailored approaches for oral therapy. Aspects related to oral cancers, oral drug delivery, personalized therapy, regenerative local medicine, and disease-preventing oral nanoagents are widely dissected in this book.

Volume V contains 29 chapters, prepared by outstanding international researchers from Turkey, India, Pakistan, South Korea, Brazil, Portugal, Iran, China, Poland, France, Argentina, Japan, Taiwan, Mexico, Singapore, Iran, Saudi Arabia, and the United Kingdom.

In Chapter 1, entitled *Bacterial Polyester Nanoparticles for Drug Delivery*, Mohsin Shah and Sung Chul Yoon describe the methods of preparation and characterization of drug-encapsulated polymeric nanoparticles formulated with various copolymers, drug release kinetics, and evaluation of their localization in cancer cells in vitro and in vivo.

Rosa Martha Perez Gutierrez et al., in Chapter 2, entitled *A Novel Approach to the Oral Delivery: Nanostructures and Biomaterials for Systemic Disease*, shed light on oral delivery nanostructures researched in medicine, including synthesis techniques and materials that can be effectively used for controlled oral drug delivery application used in disease treatments.

Chapter 3, prepared by Andreza Maria Ribeiro et al., entitled *Biodegradable Polymeric Nanostructures: Design and Advances in Oral Drug Delivery for Neurodegenerative Disorders*, highlights the main advances in polymeric nanocarriers as vehicles for oral delivery systems used in the therapy of neurodegenerative disorders. First, a brief introduction into the field of biodegradable polymeric materials used in nanostructures formulation is presented. Considering their structure and characteristics, the next section offers a detailed description of the technologies and recent modifications to improve their specificity. Finally, new approaches are presented with clinical applications in neurodegenerative disorders.

Chapter 4, entitled *Nanostructured Systems for Transbuccal Drug Delivery*, prepared by Michelle Franz-Montan et al., outlines the use of nanostructures as tools for the development of new formulations for topical use at the oral mucosa in dental clinical practice. Topics covered in this chapter include the structure, organization, and permeability of oral mucosa; permeation pathways at oral mucosa; chemical permeation enhancers for oral mucosa topical formulations; mechanisms of permeation enhancers; and the use of the following nanostructures to improve transbuccal drug delivery for the treatment of oral mucosa infections, inflammation, and pain conditions: liposomes, polymeric nanoparticles/micelles, nanostructured lipid carriers, and cyclodextrins.

Chapter 5, entitled *Trends in Orally Viral Vector Gene Delivery and Therapy*, prepared by Jingqi Xie and Ruian Xu, highlights the merits and disadvantages of novel applications and their relationship between sizes and structures of nanoparticles and the efficacy of oral gene delivery and therapy. In addition, this chapter reveals orally viral vector gene delivery timing, and systematically discusses the effect of age, delivery route, cell preference, organ distribution, and so on on orally viral vector delivery and trends in oral viral vector gene delivery and therapy.

Virginie Busignies et al., in Chapter 6, entitled *Nanostructures for Oral Delivery of Therapeutic Nucleic Acids*, discuss the barriers to oral delivery of nucleic acids and review the various technologies already tested in preclinical study and the experimental models available to assay oral delivery systems.

Pragasam Viswanathan et al., in Chapter 7, entitled *Challenges in Oral Drug Delivery: A Nano-Based Strategy to Overcome*, offer an overview about the strategy to override such drawbacks by ushering in various nanotechnology platforms, such as polymer-based nanocarriers, lipid-based nanocarriers, and metal- and inorganic-based nanoparticles.

Thi Trinh Lan Nguyen et al., in Chapter 8, *Oral Pellets Loaded With Nanoemulsions*, present an up-to-date review about nanoemulsion and its subsequent transformation into pellet systems that offer several advantages for improving solubility and dissolution rates of poorly water-soluble drugs for oral delivery in order to overcome the poor absorption of some active pharmaceutical ingredients.

Anurag Kumar Singh et al., in Chapter 9, entitled *Oral Drug Delivery Potential of Dendrimers*, focus on the oral potential applicability of dendrimers for delivering various categories of drugs, such as antimicrobial agents, antifungal drugs, and certain catheter-related substances.

Chapter 10, prepared by Sayali Karandikar et al., entitled *Nanovaccines for Oral Delivery-Formulation Strategies and Challenges*, summarizes nanoformulation strategies for oral delivery of vaccines, which can potentially help to overcome existing problems. Also, this chapter briefly presents their challenges and regulatory aspects.

Chapter 11, prepared by Prachi B. Kharkar et al., entitled *Nanosystems for Oral Delivery of Immunomodulators*, gives an insight into nanostructurated immunomodulators, their routes of administration, and newer sophisticated methods of their formulation for better therapeutic effect.

Chapter 12, entitled *Tannic Acid Modification of Metal Nanoparticles: Possibility for New Antiviral Applications*, prepared by Malgorzata Krzyzowska et al., presents an up-to-date overview about tannic-acid-modified silver nanoparticles consisting of a novel potential microbicide for herpes virus infection in the mucosal tissues.

Chapter 13, *Polyelectrolyte-Drug Ionic Complexes as Nanostructured Drug Carriers to Design Solid and Liquid Oral Delivery Systems*, prepared by Maria E. Olivera et al., deals with the description of main pharmaceutical applications of drug-delivery systems based on the unique properties of complexes of polyelectrolytes with ionizable drugs.

Chapter 14, prepared by Md Nurunnabi et al., entitled *Polysaccharide Based Nano/Micro Formulation: An Effective and Versatile Oral Drug Delivery System*, focuses on potential applications of polysaccharides for oral drug delivery, their biocompatibility, as well as their advantages and disadvantages over conventional strategies. The authors also highlight recent advances in oral drug delivery based on specific polysaccharides, including chitosan, heparin, hyaluronic acid, beta glucan, and chondroitin sulfate.

Raje Chouhan et al., in Chapter 15, entitled *Recent Advancements in Oral Delivery of Insulin: From Challenges to Solutions*, present an overview of diabetes highlighting various aspects of insulin therapy, including insulin analogs, oral delivery of insulin, mechanistic action of insulin, challenges of oral administration of insulin, and breakthroughs in insulin delivery at the global level. The chapter also discusses economical aspects related to the commercialization level of insulin.

Madhu Gupta et al., in Chapter 16, *Nanotechnology for Oral Delivery of Anticancer Drugs: An Insight Potential*, review the challenges encountered in oral delivery with various nanoconstructs employed for oral anticancer drug delivery comprehensively as well as their applications.

Chapter 17, entitled *Nanomaterials: Promising Structures for the Management of Oral Cancer*, prepared by Görkem Eskiizmir et al., presents the role and potential effectiveness of using nanomaterials in different aspects of oral cancer. Recently, nanotechnology has offered new strategies in cancer management: (1) early detection of cancers via specialized probes and biosensors, (2) better diagnosis and staging via improving the imaging systems, (3) nanoscale drug-delivery systems that may provide a significant decrease in adverse effects and toxicities of chemotherapeutics, and (4) nanotheranostics that integrate both diagnosis and therapy simultaneously.

Hiroshi Sakagami et al., in Chapter 18, entitled *Therapeutic Potential of Solubilized Nanolignin Against Oral Diseases*, offer relevant information about the lignin-carbohydrate complex and its excellent anti-HIV activity and anti-UV activity, in contrast to its weak tumor-selective cytotoxicity.

Chapter 19, prepared by Hafsa Ahmad et al., *Novel Lipid Nanostructures for Delivery of Natural Agents With Antioxidant, Antiinflammatory, and Antistroke Potential: Perspectives and Outcomes*, presents many bioactive nanocombinations with antioxidant, anti-inflammatory, and neuroprotective effects that might promote alleviation of neuronal and tissue damage following stroke and reverse pathophysiological changes in ischemia-reperfusion injury that fail clinically due to degradation, poor aqueous solubility, and subsequent bioavailability.

Sougata Jana and Sabyashachi Maiti, in Chapter 20, entitled *Chitosan-Based Nanoparticulate Systems for Oral Drug Delivery*, discuss various methods of preparation of chitosan-based nanoparticles, structural modifications of chitosan, and the latest developments in the field of oral drug delivery.

Chapter 21, prepared by Lohanathan Bharathi Priya and Viswanadha Vijaya Padma, entitled *Phytonanoconjugates in Oral Medicine*, focuses on the role of nanostructures conjugated to phytochemicals (phytonanoconjugates) in oral medicine by extensively reviewing of the latest research findings.

Chapter 22, entitled *Design and Development of Pharmaceutical Microprocesses in the Production of Nanomedicine*, prepared by Norma Angélica Noguez Méndez et al., presents an up-to-date overview about the microfluidics and examples of nano- and microparticles involved in this field: liquid crystals (LCs) and solid lipid nanoparticles (SLNs). Also, the authors present details about synthetic polymersomes that imitate biological membrane functions.

Chapter 23, prepared by Shou-Cang Shen et al., entitled *Mesoporous Materials and Technologies for Development of Oral Medicine*, presents recent progress in the development of mesoporous materials as drug carriers for applications in oral medicine formulation according to the types of mesoporous excipients, drug loading techniques, characterization and stability studies, and applications in oral medicine.

Nehi Sinha et al., in Chapter 24, entitled *Nanodentistry: Novel Approaches*, focus on the role of nanostructures to keep teeth and oral tissues healthy and functioning. The challenges faced by this technology for the betterment of human health are also discussed.

Chapter 25, entitled *The Role of Nanomedicine, Nanotechnology, and Nanostructures on Oral Bone Healing, Modeling, and Remodeling*, prepared by Mohamadreza Baghaban-Eslaminejad et al., covers the most important information regarding manufacturing methods, available and future options, and the role of nanostructures on bone health, healing, and repair based on their basic to clinical evidence.

Muhammad Sohail Zafar et al., in Chapter 26, entitled *Therapeutic Applications of Nanotechnology in Dentistry*, highlight recent developments regarding therapeutic applications of nanomaterials in dentistry. In addition, chemistry, synthesis, properties, and benefits of therapeutic nanomaterials over conventional materials in relation to dentistry are discussed.

Chapter 27, prepared by Gabriel Henrique Hawthorne et al., *Oral Nanomedicine and the Emergent Process of Clinical Translation*, discusses the translational research from laboratory approaches to clinical applications inside oral nanomedicine. Analyzing the clinical trials conducted in a field is the only way of predicting the potential for clinical impact of the new approaches, and oral nanomedicine stands in a promising position.

Chapter 28, prepared by Sevinc Kurbanoglu et al., entitled *Carbon-Based Nanostructures for Electrochemical Analysis of Oral Medicines*, gives an up-to-date overview about electrochemical assay of oral drugs using carbon-based nanostructures such as fullerene polymers, carbon nanotubes, carbon nanohorns, carbon nanodiamonds, and grapheme. Also, advantages and disadvantages of producing techniques are detailed.

Chapter 29, entitled *Scientometric Overview Regarding Oral Cancer Nanomedicine*, by Ozcan Konur, highlights important papers influencing the development of the research field as well as in determining the key research fronts in the field of cancer nanomedicine. This book chapter presents the first bibliometric study focusing on the 25 citation classics in oral cancer nanomedicine following a brief bibliometric overview of the research in these underlying research areas.

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CHAPTER

BACTERIAL POLYESTER NANOPARTICLES FOR DRUG DELIVERY

1

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CHAPTER OUTLINE

1 INTRODUCTION

Over the past few decades, there has been considerable progress in developing biodegradable nanoparticles as effective drug delivery devices (Jendrossek and Handrick, 2002). Different types of biodegradable polymers both synthetic and natural have been utilized in the preparation of nanoparticles

(Anderson and Dawes, 1990; Doi, 1990). Nanoparticles are submicron-sized polymeric colloidal particles with a size range 1–1000 nm and drugs may be encapsulated, adsorbed, or dispersed in them (Jendrossek et al., 1996; Jendrossek and Handrick, 2002; Verlinden et al., 2007). In the preparation of particles for drug-delivery systems, biodegradable materials are preferably used in order to prevent the side effects associated with nonbiodegradable polymers. The products result after the degradation of the biopolyesters that must be biocompatible and nontoxic. In general, nanoparticles prepared from polymers can be divided into three different categories, depending on their structure. Capsules are the first category. Nanocapsules are submicroscopic colloidal drug carrier systems composed of an oily or an aqueous core surrounded by a thin polymer membrane (Madison and Huisman, 1999). Another example of a vesicular system is the liposomes. In an aqueous environment, phospholipid molecules form a lipid bilayer, resulting in the formation of liposomes. Several types of liposomes can be prepared, including unilaminar, multilaminar, and multivesicular (Sun et al., 2007). The disadvantages of liposomes are the unreliable reproducibility of liposomes and exchange of phospholipids with certain blood components (Sudesh and Doi, 2000). The second category is polymeric micelles. Polymeric nanoparticles are nanosized, supramolecular core/shell structures formed by self-aggregation of individual amphiphilic macromolecules comprised of inner concealed hydrophobic and outer exposed hydrophilic domains (Jendrossek and Handrick, 2002; Jendrossek et al., 1996; Verlinden et al., 2007). This core–shell structure enables the solubilization of hydrophobic drugs in the core hydrophobic domain (Kumagai and Doi, 1993). The micelles are formed spontaneously above a certain copolymer concentration: the critical micelle concentration (CMC) (Kim et al., 1999; Kumagai and Doi, 1993). The third category of nanoparticles is particles that consist of a more or less homogeneous polymeric matrix. Analogous to microspheres, these particles are generally referred to as nanospheres. These particles are larger than micelles and may be more polydispersed in terms of size (Pötter and Steinbüchel, 2005).

2 AMPHIPHLIC BLOCK COPOLYMERS

Amphiphilic copolymers can be synthesized by introducing hydrophilic groups, such as hydroxyl, carboxyl, amine, glycol, and hydrophilic polymers, such as polyethylene glycol (PEG), poly(vinyl alcohol), poly(acryl amide), poly(acrylic acid), poly(hydroxyethyl methacrylate), poly(vinyl pyridine), and poly(vinyl pyrrolidone) to a hydrophobic central moiety (Mergaert et al., 1994). In the amphiphilic block copolymers, the hydrophilic part is covalently linked with strongly hydrophobic polymers. On exposing to the aqueous environments, the hydrophobic core of the polymer is buried inside with exposed hydrophilic domains (Klingbeil et al., 1996). In such amphiphilic structure of polymeric micelles, hydrophobic drug molecules are solubilized within the hydrophobic core, which acts as a cargo for loading high amounts of drugs, whereas the shell maintains a hydration barrier that protects the integrity of each micelle (Kumagai and Doi, 1993). Moreover, the hydrophilic moiety used as surface coating also protect the nanoparticles from the induction of immune response. The use of biodegradable amphiphilic nanoparticles as drug carriers is advantageous because it releases the drug via two steps; first, diffusion release of the mPEG segment, and second, degradation release of the biodegradable polymer segment (Jendrossek et al., 1995). Several studies have been performed over the past few years with micelle-forming block copolymers. Most of these have been conducted on loading of hydrophobic

drugs in the amphiphilic copolymers with core–shell morphology (Bhatt et al., 2008; Cui et al., 2002; Kim et al., 1999). Various hydrophobic drugs, including griseofulvin (Cui et al., 2002), doxorubicin (DOX) (Preusting et al., 1993; Wong et al., 2002), and amphotericin B (Martin and Williams, 2003) have been successfully loaded into the micelle compartments of these copolymers. Some of these have been used in clinical trials and the in vitro and in vivo efficacies of these micelles have been evaluated.

3 POLYMERIC NANOPARTICLES IN DRUG-DELIVERY APPLICATIONS

With the development of new materials and a combination of nanotechnology and biotechnology it could be possible to make artificial organs and implants through cell growth, which could repair damaged nerve cells, replace damaged skin, tissue, or bone (Williams et al., 1999). Another application of bionanotechnology in medicine is drug delivery where research is especially intensive on the possibility of manipulating nanoparticles to deliver drugs because nanoparticles can have a better solubility and absorption potential than bigger particles (Verlinden et al., 2007). The nanoparticles can carry the drug and perhaps release it in fine-tuned doses over an extended time period to a targeted area, reducing the side effects of the traditional drugs.

Polymeric nanoparticles in pharmaceutical applications have gained plenty of research attention during recent decades (Zhang et al., 1997). Although, the research concerning formulation of polymer based nanoparticles into drug delivery devices has been extensive, only a few polymeric nanoparticulate products have reached the market. One known product, Abraxane, consist of intravenously administered 130-nm nanoparticles prepared from the protein albumin bound with paclitaxel, a drug used in cancer therapy (Zhang et al., 1995). Another cancer drug, DOX transdrug, consisting of DOX-loaded poly(isohexylcyanoacrylate) nanoparticles is currently at the Phase II/III clinical trials (Xiong et al., 2010). In particular among the drugs used in nanoparticle formulations, cancer therapeutics are widely studied because their formulation might reduce toxicity of the drug while improving efficacy of the treatment (Mei et al., 2006). In addition to drug molecules, other candidates to be encapsulated in or coupled with nanoparticles include macromolecules like proteins, peptides, and genes (nucleic acids) (Zhao et al., 2003). These kinds of molecules tend to be inactivated in the body by enzymatic degradation. In terms of controlled release, nanoparticles provide protection against the body conditions resulting in sustained release and maintenance of bioactivity before the drug reaches the target. The most effective strategy adopted by these nanoparticulated drug carriers to selectively target the solid tumors is the exploitation of anatomical and pathophysiological abnormalities of the tumor vasculature, utilizing the principle of enhanced permeability and retention (EPR) effect (Williams et al., 1999). The difference between normal inflammatory tissues and tumor tissues is reflected in their clearance velocities. Usually the macromolecules like nanoparticles, nanocapsules; lipid nanoparticles delivered into the interstitial space of normal inflammatory tissue is cleared more rapidly. On the other hand tumor tissues have leaky vessels and poor aligned lymphatic vessels as results the macromolecules leak out more easily into the tumor tissues and retain longer due to their defective lymphatic system. This phenomenon is called as EPR effect as explained by Maeda et al. (2001). The size and surface of the nanoparticulate carrier plays a very crucial role with respect to uptake by the tumor. Particles $<$200 nm in size with hydrophilic surfaces tend to exhibit improved EPR effect, which has been attributed to the increased residence time of the carrier in blood (Williams et al., 1999). Moreover, this increased plasma half-life of particulate

drug carrier, as well as accumulation in tumor is strictly correlated to the molecular weight of the macromolecule or polymer used for making the nanoparticles long circulating.

The benefits of drugs loaded in the polymeric nanoparticles include protection of the encapsulated pharmaceutical substance, improved efficacy, fewer adverse effects, controlled release and drug targeting to tumor tissues by the EPR effect resulting from defective tumor vascular architecture and impaired lymphatic drainage. Polymeric micelles provide a "shielding effect" in intracellular drug delivery, wherein drugs remain inside micelles upon endocytosis.

4 BIODEGRADABLE BACTERIAL POLYESTERS POLY(R)-HYDROXYALKANOIC ACIDS

Poly(R)-hydroxyalkanoic acids (PHA) are a group of storage compounds of carbon and energy that are accumulated during unbalanced growth by many bacteria, that is, in the presence of an excess of a carbon source and if growth is limited by another nutrient, such as nitrogen (Jendrossek and Handrick, 2002; Jendrossek et al., 1996; Verlinden et al., 2007). When the supply of limiting nutrient is restored, the PHA can be depolymerized and subsequently metabolized as carbon and energy sources (Anderson and Dawes, 1990; Doi, 1990). PHA in bacterial cells is deposited intracellularly in the form of inclusion bodies (granules) and it forms up to 90% of the cellular dry weight (Anderson and Dawes, 1990; Doi, 1990; Jendrossek et al., 1996) as shown in Fig. 1.1A. The many different types of PHA isolated to date are primarily linear; head-to-tail polyesters composed of 3-hydroxy fatty acids monomers (Madison and Huisman, 1999). In such types of

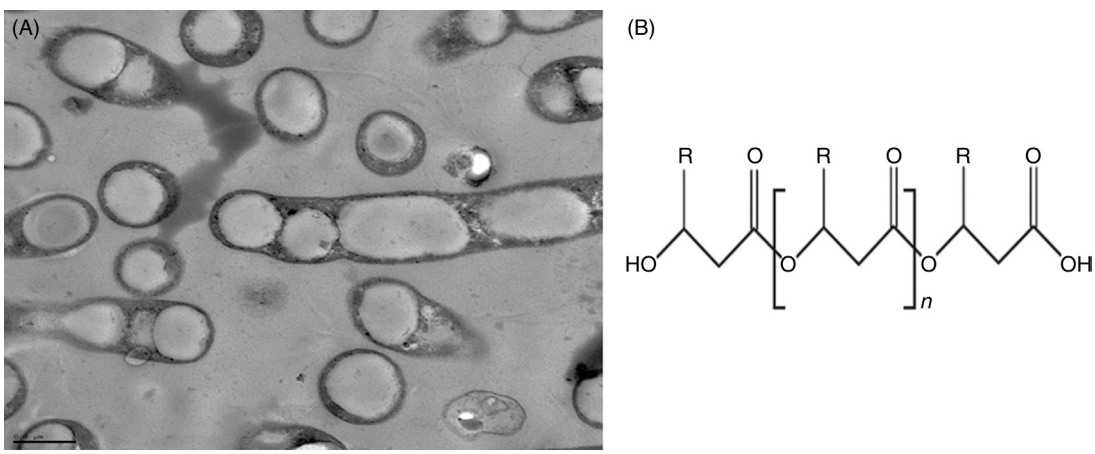

FIGURE 1.1

(A) Transmission electron microscopic image of accumulated of PHA granules in *Hydrogenophaga pseudoflava*. About 70%–90% of bacterial weight consists of accumulated PHA granules in bacterial cytoplasm. Scale bar = 0.5 μm. (B) Chemical structure of polyhydroxyalkanoates (PHAs)

Part B: Reprinted with permission from Sun, Z., Ramsay, J.A., Guay, M., Ramsay, B.A., 2007. Fermentation process development for the production of medium-chain-legth poly-3-hydroxyalkanoates. Appl. Microbiol. Biotechnol. 75, 475–485.