Smart Biomaterial DEVICES

Polymers in Biomedical Sciences

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Preface

Functional polymers are one of the most promising materials finding tremendous application in almost all the areas of science and technology, ranging from industrial to medical domains. With the emergence of new and newer synthetic strategies in chemical and allied sciences, specialty polymers of diversified structures have been designed with tailored properties and applications. The great ability to keep a precise control over the size, shape, molecular weight, functionalities, and physical and chemical properties of resulting polymers has enabled polymer scientists to fabricate materials of own choice, desired properties, and intended end uses. This book attempts to deliver a comprehensive account of various polymer-based materials that are being intensively used as biomaterials for various applications pertaining to human body.

This book consists of nine chapters that encompass almost entire range of applications of polymers in human body. Chapter 1 highlights the basic criteria of materials to be coined as biomaterials for dental, orthopedic, drug delivery, wound dressing, tissue engineering, ocular, and cardiovascular applications. Chapter 2 focuses on the use of polymers for dental applications. This chapter emphasizes the required mechanical properties of a polymer, which are essential for dental applications. It also gives an overview of different types of dental implants and various kinds of polymers being employed in dentistry. Chapter 3 is concerned with the use of polymer materials and nanocomposites that find applications as orthopedic materials. The chapter also covers metal- and ceramic-based hybrid materials, which are in current use in orthopedic surgery.

Chapter 4 describes the use of smart polymers in drug delivery applications. A variety of polymers and other macromolecular entities that have been used for designing smart drug delivery systems have also been discussed in this chapter. Chapter 5 focuses on the use of polymers as wound-dressing materials. This chapter also covers classification of wounds, type of wound dressings, naturally occurring polymers in wound dressing, etc. While Chapter 6 focuses on use of smart polymers in tissue-engineering applications and Chapter 7 pertains to ocular implants. Chapter 8 assesses the role of polymers in cardiovascular implantation and discusses how materials such as polymers, metals, and ceramics are currently being used for cardiovascular applications. Finally, Chapter 9 provides an authentic and conclusive information about the market scenario of biomaterial-based devises.

We are confident that this book will be useful for students and research scholars from different disciplines of science, engineering, and technology.

Authors

Anil Kumar Bajpai earned a PhD in chemistry in 1984. Dr. Bajpai joined Government Science College, Jabalpur, Madhya Pradesh, India in 1986, and since then he has been working as a professor in chemistry. While at service, he earned a DSc. The areas of his research interest include biomedical polymers synthesis, controlled drug delivery systems, nanostructure materials of pharmaceutical relevance, conducting polymer nanocomposites, water remediation using biopolymers nanoparticles, hydroxyapatite nanocomposites, etc. He has published more than 220 papers in reputed and high impact factor journals and contributed more than 15 chapters in encyclopedias of prestigious international publishers. Professor Bajpai has also supervised 40 students for their doctoral degree and successfully completed more than 10 major research projects funded by prime scientific and defense establishments of the government of India. He is associated with editorial boards of a few journals and serves as a regular reviewer of leading journals.

Jaya Bajpai, a postgraduate in chemistry at the University of Jabalpur (1982), earned a PhD at the same university in 1992. Dr. Bajpai has published more than 40 research papers in leading international journals and contributed several chapters as coauthor. Currently, she works as a professor of chemistry and actively engaged in research areas related to biomedical polymers, drug delivery systems, and nanomaterials.

Rajesh Kumar Saini is the coprincipal investigator in several major research projects and postdoctoral fellow in the Department of Chemistry, Government Model Science College, Jabalpur, Madhya Pradesh, India. He has worked as a faculty member in the Department of Chemistry, Shri Rawatpura Sarkar Institute of Technology, Jabalpur. Dr. Saini earned a PhD in 2008 in polymer chemistry and has published numerous research papers in reputed journals and written many book chapters and coauthored a book on the topic responsive drug delivery systems. His fields of interest are macroporous biomaterials, cryogels, and high-performance materials for biomedical applications.

Priyanka Agrawal earned a PhD in 2012 at the R. D. University, Jabalpur, Madhya Pradesh, India. His research areas include water remediation, adsorption studies, and nanoparticles synthesis of biopolymers in drug delivery and water remediation. She has published several papers in reputed journals. Dr. Agrawal has previously worked as an assistant professor of chemistry at the Hitkarini College of Engineering and Technology, Jabalpur, and she is currently working as a TIFAC (Technology Information, Forecasting and Assessment Council), women scientist trainee in Intellectual Property Rights at CSIR-URDIP (Council of Scientific and Industrial Research-Unit for Research and Development of Information Products), Pune, India.

Atul Tiwari currently serves as director, Research and Developments at Pantheon Chemicals in Phoenix, Arizona, USA. Previously, Dr. Tiwari was a research faculty member in the Department of Mechanical Engineering at the University of Hawaii, USA. He has achieved double subject majors in organic chemistry as well as in mechanical engineering. He earned a PhD in polymer materials science in 2003 along with earned Chartered Chemist and Chartered Scientist status from the Royal Society of Chemistry, UK. Dr. Tiwari is an active member of several professional bodies in the United Kingdom, the United States, and India. His area of research interest includes the development of smart materials, including silicones, graphene, and bio-inspired biomaterials for various industrial applications. Dr. Tiwari has the zeal to develop new materials and has received eight international patents on his inventions. He has published more than 80 research articles and 16 books. Most of his books are focused on newer developments in the area of materials science and engineering.

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1 Smart Biomaterials in Biomedical Applications

1.1 INTRODUCTION

Time and time again humanity is faced with a unifying global crisis (widespread and insidious disease, harsh treatment of patients, etc.) that has inspired the researcher to create a biological molecular machine, so-called biomaterial, with tailored structures and properties that operate with the same efficiency and complexity as biological machines by uniting supramolecular chemistry, mechanostereochemistry, and nanotechnology, for the common good. Functional polymeric materials are essential components of a variety of biological and biomedical applications including drug delivery, tissue engineering, and medical imaging [1–4] as every day thousands of surgical procedures are performed to replace or repair tissue that has been damaged through disease or trauma. Despite the long history of biomedical engineering, polymers used in these applications have historically been polydisperse, with limited control over functionality and architecture [4,5]. In early stages of development, biomaterial selection focused on inertness and on mimicking the physical properties of the damaged tissue. Later development included design to illicit a specific biological response [6]. Meanwhile, polymer chemistry has experienced increased sophistication in terms of what can be controlled. "Smart" polymers with stimuli sensitivity, new architectures, and greater control over molecular weight (MW) and molecular weight distribution (MWD) have driven polymer research over the last 10–15 years [7–10]. In this context, it is logical that advanced synthetic techniques that can construct precision materials will lead to new applications and uses in biomedical engineering.

Biomaterials can be defined as any nonviable synthetic materials that become a part of the body either temporarily or permanently to replace, augment, or restore the function of a body tissue and are continuously or intermittently in contact with body fluids in a safe, reliably economically, and physiologically acceptable manner; they can be used for any period of time in contact with living tissue, to improve human health and they play a central role in extracorporeal devices, from contact lenses to kidney dialyzers, and are essential components of implants, from vascular grafts to cardiac pacemakers. A variety of devices and materials are used in the treatment of disease or injury. Common examples include suture needles, plates, teeth fillings, etc. However, this definition excludes surgical or dental instruments as they are exposed to body fluids, but do not replace or augment the function of a human tissue [11].

In the last decade, driven by the needs from engineering applications, various new materials such as metal and semiconductor nanocrystals, encoded nanoparticles (nanoparticles bearing biochemical information on their surfaces), functional nanoparticles (nanoparticles engineered to perform specific physical and/or chemical functions), functional magnetic nanostructures (nanoparticles where the release of drugs and/or biomolecules is triggered by the application of an external magnetic field), stimuli-responsive nanocarriers (designed to react on certain stimuli such as pH, temperature, redox potential, enzymes, light, and ultrasound), and so on have been developed for enhanced performance and/or new functions due to their optical, electrical, and magnetic properties, as they can be used to produce biologically relevant transformations [12,13].

Among them, stimuli-responsive polymer materials have gained much interest in recent years due to their ability to sense and react to environmental conditions or respond to a particular stimulus such as heat (thermo-responsive materials), stress/pressure (mechano-responsive materials), electrical current/voltage (electro-responsive materials), magnetic field (magneto-responsive materials), pH change/solvent/moisture (chemo-responsive materials), and light (photo-responsive materials) by means of altering their physical and/or chemical properties. Various smart materials have already existed, and are being researched extensively in biomaterials, bioinspired materials, functional nanomaterials, sensors, actuators, etc. [14].

1.2 SCAFFOLD REQUIREMENTS

Recently, numerous biomaterials have been used in biomedical devices in attempts to regenerate different tissues and organs in the body. The tissue response to an implant depends on a myriad of factors ranging from the chemical, physical, and biological properties of the materials to the shape and structure of the implant. Regardless of the tissue type, the ideal material or material combination should exhibit the following properties:

1. *Biocompatibility*: Biocompatibility can be defined as a dynamic two-way process that involves the time-dependent effects of the host on the material and the material on the host. The performance of a biomaterial should not be affected by the host and the host should not be

negatively affected by the implanted biomaterials. No clear, absolute definition of biocompatibility exists yet, mainly due to the fact that the biomaterial area is still evolving. It is the very first criterion of any polymeric device that is used in the regeneration of any type of tissue, that is, the chemical composition of device must be biocompatible to avoid adverse tissue reactions or must elicit a negligible immune reaction in order to prevent it, causing such a severe inflammatory response that it might reduce healing or cause rejection by the body after implantation.

2. *Biodegradability*: Biodegradation is an important property for biomaterials which refers to the process of break down into small molecular fragments by nature, that is, the rate of breakdown mediated by biological processes (e.g., the cleavage of hydrolytically or enzymatically sensitive bonds in the polymer leading to polymer erosion) inside the body that cause a gradual breakdown of the material [15]. The scaffolds that are used as implants must be biodegradable so as to allow cells to produce their own extracellular matrix [16]. Therefore, the implanted material should have appropriate permeability and processibility for the intended application acceptable. It should have acceptable shelf life to match the healing or regeneration process, should not evoke a sustained inflammatory or toxic response upon implantation in the body, as well as the degradation products should be nontoxic, and be able to get metabolized and cleared from the body. The chemical, physical, mechanical, and biological properties of a biodegradable material will vary with time, and degradation products can be produced that have different levels of tissue compatibility compared to the starting parent material.

3. *Mechanical properties*: The material should have appropriate mechanical properties consistent with the anatomical site into which it is to be implanted and, from a practical perspective, it must be strong enough to allow surgical handling during implantation for the indicated application and the variation in mechanical properties with degradation should be compatible with the healing or regeneration process. In attempting to engineer bone or cartilage tissues, the implanted scaffold must have sufficient acceptable strength to sustain cyclic loading endured by the joint, a low modulus to minimize bone resorption, high wear resistance to minimize wear-debris generation, as well as mechanical integrity to function from the time of implantation to the completion of the remodeling process [17]. In orthopedic applications, a patient's age must be considered for designing scaffold as the healing process rate differs in both young and elderly cases. In young individuals, fractures normally heal within six month and acquire weight-bearing capacity in 6 months but complete mechanical integrity develop after 1 year. In elderly patients, the rate is very slow than young individual.

4. *Scaffold architecture*: The interaction between implanted materials and blood depends on the composition of device and blood, device geometry (surface topography and high surface area provide additional available sites for protein adsorption, thereby enhancing the cell/material interaction), surface charge (anionic or cationic can influence plasma protein adsorption on the device surface), ratio of hydrophilicity and hydrophobicity (hydrophilic surfaces tend to adsorb fewer amounts of proteins than hydrophobic ones due to strong attraction between water molecules and the polymeric material), and local condition of flow of blood. The hemocompatibility of materials can be improved by surface modification, that is, by creating a surface that shows minimum nonspecific interactions with biological materials such as proteins and blood cells [18–20]. Therefore, the scaffold architecture is also one important factor that must be accounted for before manufacturing implantable materials. Materials must have an interconnected pore structure and high porosity. Its pores must be large enough to allow cells to migrate into the structure, where they eventually bound to the ligands within the scaffold, but are small enough to establish a sufficiently high specific surface, leading to a minimal ligand density to allow efficient binding of a the critical number of cells to the scaffold. They ensure cellular penetration and adequate diffusion of nutrients to cells within the construct and to the extracellular matrix formed by these cells as well as to allow the diffusion of waste products out of the scaffold, and the products of scaffold degradation should be able to exit the body without interference with other organs and surrounding tissues [21–26].

5. *Manufacturing technology*: The main objective of manufacturing technology must be to develop cost effective and clinically viable implant materials [27]. It must be scalable, efficiently developed and delivered, and made available to the clinician.

6. *Choice of materials*: The final criterion for scaffolds in tissue engineering, and the one on which all of the criteria listed above are dependent, is the choice of biomaterial from which the scaffold should be fabricated.

1.3 TYPES OF SMART POLYMERIC MATERIALS

Polymers such as proteins, polysaccharides, and nucleic acids are present as basic components in living organic systems that respond to its environment from the molecular to the macroscopic level due to their ability to adopt conformations according to the conditions in their surrounding environment, because response to stimulus is a basic process of living systems for maintaining normal function as well as fighting disease [28]. Similar adaptive behavior can be imparted to synthetic (co)polymers by incorporating multiple copies of functional groups such that their utility goes beyond providing structural support to allow active participation in a dynamic sense [29]. These examples have inspired scientists to fabricate "smart" materials that respond to light, pH, temperature, mechanical stress, or molecular stimuli. In the rapidly changing scientific world, scientists and engineers are designing biomolecule mimic materials as opportunities for treating and curing disease, and are leading to a variety of approaches for relieving suffering and prolonging life [30]. In recent years, the importance of smart polymers has increased significantly in the area of biotechnology, medicine, and engineering because of their response to internal and external stimuli as well as their shape, surface characteristics, solubility, viscoelasticity, transparency, conductivity, etc. can be controlled by modifying the structure and organization of the polymer chains [31]. Due to their own special physical or chemical properties and applications in various areas, these polymers are coined as "stimuli-responsive polymers" [32] or "smart polymers (SP)" [33,34] or "intelligent polymers" [35] or "environmentally sensitive" polymers [36] (Figure 1.1).

Smart materials can be classified into different ways on the basis of types of polymers, external stimuli, and their given response (Figure 1.2). Some important types of smart polymeric materials have been discussed in the following sections.

1.3.1 Classification on the Basis of Physical Form

Smart polymers can be classified into three categories such as linear free chains in solution, covalently cross-linked gels and reversible or physical gels, and chain-adsorbed or surface-grafted according to their physical forms (Figure 1.3).

1. *Linear free chains in solution*: In an aqueous solution, if the macromolecular chains are linear and solubilized, the solution will change from monophasic to biphasic due to polymer precipitation and the polymer undergoes a reversible collapse after an external stimulus is applied. This polymer phase transition is controlled by a delicate balance under hydrophobic and hydrophilic conditions and can be achieved either due to the reduction in the number of hydrogen bonds that the polymer forms with water or because of the neutralization of the electric charges that are present on the polymeric network. For example, aqueous solutions of thermo-responsive polymers show phase transition at temperature above their lower critical solution temperature (LCST) that is the temperature at which the phase transition occurs, also called demixtion denoted as T_d or the critical point (CP). Soluble pH (such as Eudragit S-100 [copolymer of methylmethacrylate and methacrylic acid] and the natural polymer, chitosan [deacetylated chitin]) and temperature-responsive polymers (poly-*N*-isopropylacrylamide) that overcome transition at physiological conditions (37°C and/or physiological pH) have been proposed as minimally invasive injectable systems for implant or scaffold useful for the drug delivery system (DDS) or tissue engineering applications [37,38].

2. *Covalently cross-linked gels and reversible or physical gels*: They can be either microscopic or macroscopic networks that are highly swollen material whose swelling behavior is controlled by environmental conditions. They do not dissolve in an aqueous environment due to the presence of extensive infinite crosslinking between polymeric networks. The gel-phase transition of such polymeric networks between a collapsed and an expanded state occurs due to chain reorganization under external stimuli. These phenomena are reversed when the stimulus is reversed, although the rate of reversion often is slower when the polymer has to redissolve or the gel has to reswell in an aqueous medium. Such systems are very useful in pulse DDSs [36].

3. *Chain-adsorbed or surface-grafted form*: These types of polymers either reversibly swell or collapse on the surface under external stimuli due to the conversion of the interface from hydrophilic to hydrophobic and vice versa. They may show other types of transitions in comparison to soluble

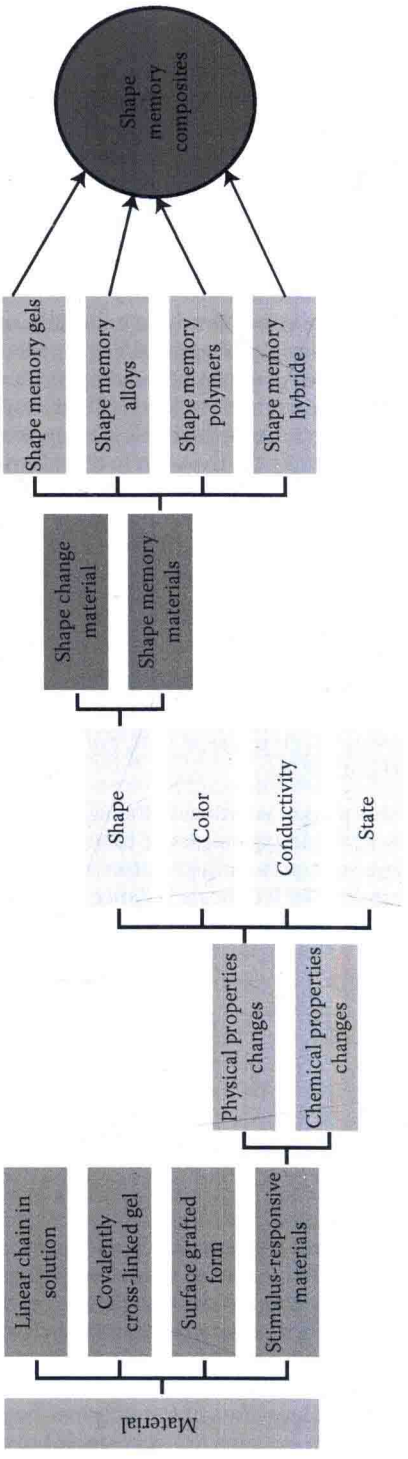

Figure 1.1 Location of various types of SMMs within the world of materials.

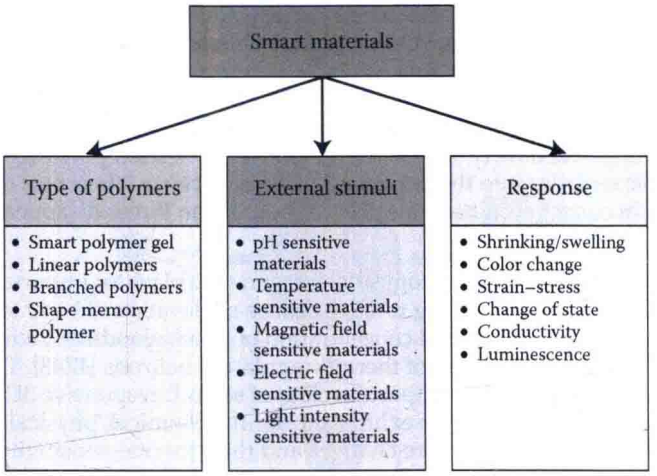

Figure 1.2 Schematic representation of classification of smart materials.

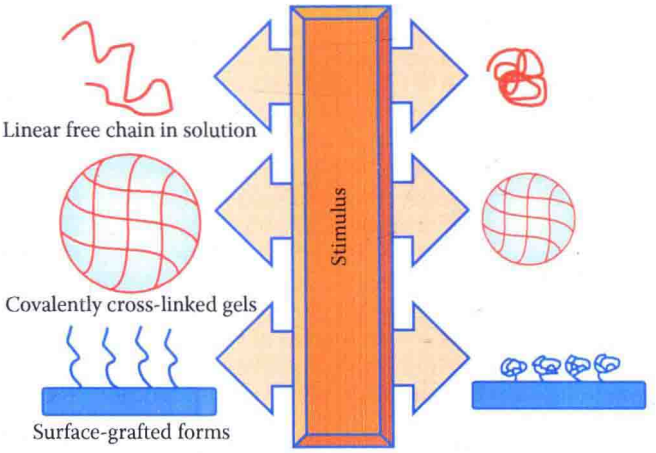

Figure 1.3 Different physical forms of stimuli-responsive polymers.

polymers due to change in surface hydrophobicity attributable to changing temperature, and can easily be exploited to allow the separation of substances that interact differently with the hydrophobic matrix.

The three forms of smart polymers as mentioned above can be easily conjugated with biomolecules such as proteins and oligopeptides, sugars and polysaccharides, single- and double-stranded oligonucleotides and DNA plasmids, simple lipids and phospholipids, and other recognition ligands and synthetic drug molecules, which are capable of responding to biological, physical, and chemical stimuli for widening their potential applications in many biomedical fields [39–42].

1.3.2 Classification on the Basis of External Stimulus

1. *pH-sensitive polymers*: pH-sensitive polymers show transition in phase in response to changes in environmental pH because they contain a large number of ionizable groups such as pendant acidic or basic groups that either accept or release protons in environmental pH. Those with weak acidic pendant groups in their polymer chain show high swelling in the basic medium due to the ionization of acidic groups that is not possible in the acidic medium due to the common ion effect. However, the polymers that contain a large number of weakly basic groups show a reverse response in the basic medium [43–45]. It is noticed that pH-sensitive polymers