Biodegradable Polymeric Nanocomposites

Advances in Biomedical Applications

Edited by Dilip Depan

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Preface

Biomaterials based on polymers are of prime importance and are a cornerstone for biomedical applications. Biomaterials are primarily supposed to perform a time-limited architectural or a related function but, being foreign, should disappear from the body once that function has been fulfilled. A wide range of materials have been considered for biomedical applications such as drug delivery, biosensors, and tissue engineering.

Biodegradable polymers are a unique category of materials that opened up an entirely novel concept in the biomedical industry, with research more focused on the development of more sophisticated biomedical applications to solve patients' problems. The involvement of nanotechnology has further helped in making some significant advancements in this field. An overview of degradation properties and mechanism of biodegradable polymers, focusing on relevant aspects of biomedical applications, is provided in this book.

Efforts have been made to not only focus on biomaterials but also give priority to the general topics on successful designing and applications of biomaterials. So, the book presents the unique advantages and limitations of various biomaterials, such as biopolymers, ceramics, biodegradable nanocomposites, and natural products–based biomaterials. The book also deals with the state-of-the-art recent advancements in drug delivery devices.

I thank all contributors for their efforts on writing comprehensive chapters. I extend my sincere thanks to all the readers of the book and look forward to receiving comments and feedback.

Dilip Depan, PhD
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Preface

Biomaterials based on polymers are of great interest and have a wide range of biomedical applications. Biomaterials are primarily engineered to perform a dedicated architectural or structural function but are not immunogenic and should disappear from the body once the function has been fulfilled. A wide range of materials have been considered for biomedical applications such as drug delivery, diagnostics, and tissue engineering.

Biodegradable polymers, [illegible] currently most of concern in the biomedical industry, with research increasingly focused on the development of more selective and biocompatible [illegible] to solve [illegible] problems. The involvement of nanotechnology has further enhanced [illegible] significant advances in this field. An overview of degradable polymers and mechanism of biodegradable polymers, focusing on relevant aspects of biomedical applications is provided in this book.

Efforts have been made to not only focus on fundamentals but also provide [illegible] the general aspects in successful designing and applications of biomaterials. So, the book presents the unique advantages and limitations of various biomaterials, such as polyphosphazenes, polyesters, [illegible] and natural polymers-based biomaterials. The work also deals with the state-of-the-art recent advancements in drug delivery devices.

I thank all contributors for their efforts in making [illegible] Thanks to all the readers of this book and look forward to receiving feedback.

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Editor

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1 Calcium Phosphate–Reinforced Polyester Nanocomposites for Bone Regeneration Applications

Mehdi Sadat-Shojai

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1.1 INTRODUCTION

Defects that result in the need for bone tissue replacement pose a major clinical problem in orthopedic surgery. To restore the function of damaged or diseased bone tissue, bone replacement grafts have conventionally been used. These bone grafts are usually derived from tissues harvested from a second anatomic location of the same patient (autografts) or from other patients (allografts) [1–4]. The use of donor tissue, however, suffers from several limitations, including donor site morbidity, occurrence of immune-related problems in the recipient's body, difficulties in shaping explanted bone, limited supplies of suitable bone grafts, risk of disease transmission, and lessening or even complete loss of bone inductive factors. Additionally, both autografting and allografting require a second surgery site, which is expensive and sometimes associated with hematoma formation [2,3,5].

In the past two decades, various man-made biomaterials have offered a promising alternative approach to bone treatment. These biomaterials must be biocompatible and meet certain minimum mechanical requirements to be functional. On the other hand, techniques for bone regeneration based on tissue engineering have also been proven to be very effective [4–7]. By taking advantage of the body's natural regenerative capacity to form new bone, tissue engineering has progressed in the last two decades to become a powerful alternative for treatment of damaged bone tissues. The basic concept of tissue engineering techniques is schematically illustrated in Figure 1.1.

According to Figure 1.1, tissue engineering applies principles and methods from engineering, biology, and medicine to create constructs for regeneration of new tissues. Tissue engineering is now frequently used in conjunction with the more encompassing descriptor of regenerative medicine [3,8–10]. The aim of regenerative medicine is to recreate tissues and organs typically using a combination of cells, scaffolds, and bioactive molecules. One common approach in regenerative medicine is to isolate specific cells through a small biopsy from a patient to grow them on a 3D scaffold under controlled culture conditions. The construct is subsequently delivered to the desired site in the patient's body with the aim to direct new tissue formation into the scaffold. The scaffold must have the ability to undergo a progressive degradation as the new tissue regenerates. An alternative approach is to implant scaffolds for tissue ingrowth directly in vivo with the purpose to stimulate and direct tissue formation in situ [8].

In many cases of bone tissue engineering, development of biodegradable materials with appropriate mechanical properties, suitable degradation rate, and high osteoconductivity is desirable. Indeed, biodegradable materials, which can be resorbed in the human body fluids, are always excellent candidates to serve as scaffolding materials [11,12]. Today, these materials are usually biodegradable polymers, both natural and synthetic, such as polysaccharides, polyesters, and hydrogels [7,8].

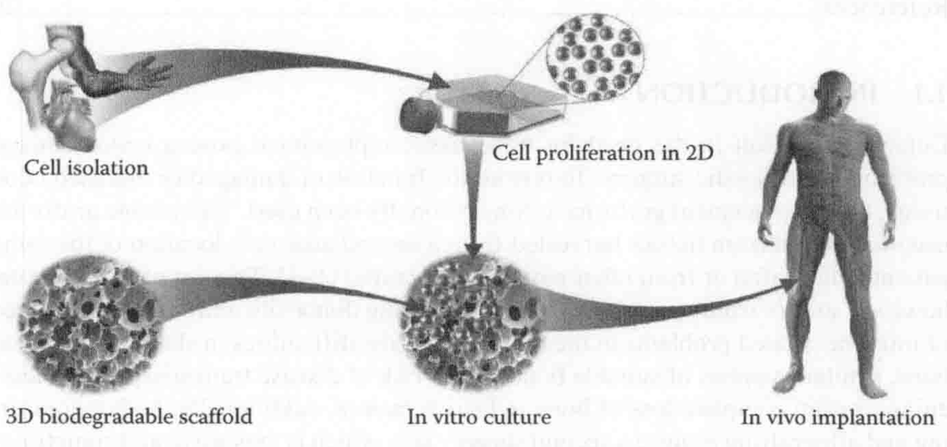

FIGURE 1.1 Basic principles of tissue engineering approach. Cells are first isolated and then expanded in a tissue-culture flask. Once 2D cell proliferation sufficiently occurs, they can be placed in a 3D scaffold and cultured in vitro in a bioreactor or incubator. When the engineered scaffold is matured enough, then it can be implanted in the area of defect.

Other important categories of systems are bioactive materials, mainly calcium phosphate (CaP) ceramics and bioactive glasses or glass–ceramic combinations [12–15]. However, as demonstrated by the increasing research efforts, polymer/ceramic composite systems combining the advantages of polymers and ceramics seem to be a more promising choice to fulfill many requirements of an ideal scaffold, in particular, for bone tissue engineering. Currently, various polymers and bioactive ceramics are being combined in a variety of composite systems with the aim to increase the mechanical stability of scaffold and to improve tissue–scaffold interaction [6–9].

It is obvious that the requirements of composite materials for bone tissue engineering are manifold and challenging: biocompatibility of the composite is definitely necessary; that is, the material must not elicit an unresolved inflammatory response nor demonstrate immunogenicity or cytotoxicity. The composite material should also have a suitable biodegradability at a rate commensurate with the rate of bone tissue formation. In addition, its mechanical properties must be sufficient so that the scaffold does not collapse or break during the patient's normal activities. The composite materials should also have the ability to support cell adhesion, migration, proliferation, and differentiated function [6–8,11]. As soon as a suitable composite material is selected, the next step is to fabricate a 3D scaffold. A certain minimum requirement for a 3D scaffold construct, particularly in bone tissue engineering, is a controllable interconnected porosity with a multiple pore size distribution to direct the cells to grow into the desired physical form, to facilitate diffusion of nutrients and gases, and finally to support vascularization of the ingrown tissue [8,11]. Moreover, it is desirable if the fabricated scaffold truly mimics the natural extracellular matrix (ECM) in terms of physiological functions [10,12]. Another highly desirable feature concerning the processing of bone scaffold is scalability for cost-effective industrial production [8].

Although diverse bone scaffold constructs have been developed, most of them differ substantially from natural bone either compositionally or structurally. At the lowest structural level, human bones are a natural nanocomposite consisting nanosized CaP crystals embedded in a collagen-rich organic matrix [12,16]. Therefore, considering the bone as the biological template, nanocomposite systems comprising CaP bioceramics, especially hydroxyapatite (HAp) and tricalcium phosphate (TCP), and synthetic biodegradable polymers, especially polyesters, have attracted great attention worldwide from both academic and industrial points of view [7–9]. These nanocomposite systems can effectively combine the ductility and processability of polyester matrices and bioactivity and the osteoconductivity of CaP nanoparticles. The most widely used polyester matrices include poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), polyhydroxyalkanoates (PHAs), and their blends. Up to now, various combinations of synthetic polyesters and CaP nanoparticles have been developed and proved to be bioresorbable with excellent processability, bioactivity, and mechanical properties [8,9]. Accordingly, this chapter focuses on the state of the art of CaP-reinforced polyester nanocomposites for regenerative medicine and tissue engineering applications. In this chapter, we will try to provide an outline of current research on the CaP nanoparticles in the direction of nanocomposite preparation and to discuss the variety of biodegradable polyesters that have been used as orthopedic materials. Moreover, biological and mechanical characteristics of different CaP/polyester combinations, along with their degradation features with focus on bone regeneration, will be discussed and compared. This chapter is expected to be a useful reference for specialists and advanced students to gain an insight on CaP-reinforced nanocomposites with application to bone tissue engineering.

1.2 BONE AS A NANOCOMPOSITE

The design strategy of an ideal composite bone scaffold may not be straightforward without understanding the fundamentals of bone composition and architecture. As shown in Figure 1.2, humane bone can be considered a true anisotropic nanocomposite at the nanoscale level, consisting of biominerals embedded in a protein matrix, other organic materials, and water.

The biomineral phase, which is one or more types of CaPs, comprises 65%–70% of bone, water accounts for 5%–8%, and the organic phase, which is mainly in the form of collagen fibers along with a low amount of non-collagenous proteins and lipids, accounts for the remaining portion [16,17]. The collagen matrix as a structural framework gives the bone its elastic resistance and acts as a template for deposition and growth of tiny plate-like CaP minerals. Among several possibilities of CaPs, HAp has been demonstrated to possess the most similarity to these tiny biominerals [17,18]. In fact, naturally occurring CaP is usually carbonated and calcium-deficient HAp with a Ca/P ratio of less than 1.67. The bone HAp is also enriched with some trace elements (e.g., sodium, potassium, magnesium, chloride, and fluoride) for various metabolic functions [19]. Therefore, bone not only supports and protects the organs of the body but also serves as a reservoir of diverse minerals. Bone is also a good example of a renewable tissue since it has the capability of self-repairing to a certain extent [19]. Considering the natural bone as an archetype, various 3D biomaterials have been developed up to now. While less complex, the structure of these systems is usually similar to that of natural bone. Such composite materials in combination with cells and bioactive agents have also been shown to be a promising candidate as scaffolding material in bone tissue engineering.

1.3 WHY BIOACTIVE CALCIUM PHOSPHATES?

For decades, CaP ceramics have been of interest owing to their excellent biocompatibility, affinity to biopolymers, ability to replace toxic ions, and high osteogenic potential [16]. It has been well documented that CaP ceramics can promote new bone ingrowth through osteoconduction mechanism without causing any local or systemic toxicity, inflammation, or foreign body response [16,20,21]. When a CaP-based ceramic is implanted, a fibrous tissue-free layer containing biological carbonated apatite forms on its surfaces and contributes to the chemical bonding of the implant to the host bone, resulting in earlier implant stabilization and superior fixation of the implant to the surrounding tissues. This carbonated apatite that forms on the implant is chemically and structurally similar to the minerals found in human bone [8,16]. The in vivo bone-bonding behavior of CaP ceramics, which is referred to as bioactivity, can also be reproduced in contact with biological fluids, especially