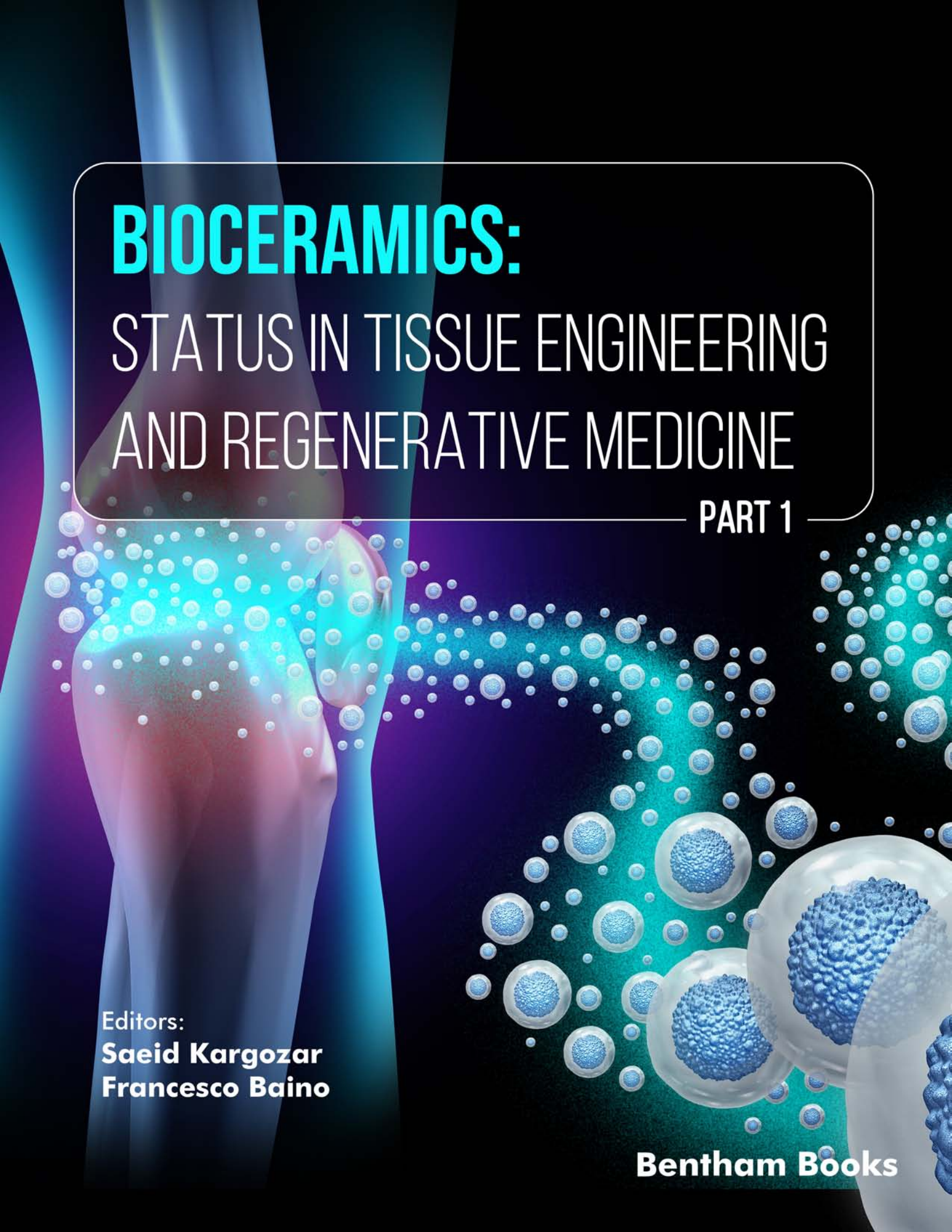
BIOCERAMICS:

STATUS IN TISSUE ENGINEERING AND REGENERATIVE MEDICINE

PART 1



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Bioceramics: Status in Tissue Engineering and Regenerative Medicine

(Part 1)

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Bioceramics: Status in Tissue Engineering and Regenerative Medicine *(Part 1)*

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FOREWORD

The use of bioceramics for tissue engineering and regenerative medicine extends over two centuries. Dorozhkin provided a detailed review of the history of bioceramics [1]. He noted that Johan Gottlieb Gahn and Carl Wilhelm Scheele first described the presence of calcium and phosphorus in bone in the second half of the eighteenth century [1, 2]. The first use of bioceramics in medicine occurred in the late nineteenth century when Junius E. Cravens distributed a calcium orthophosphate powder called "Lacto-Phosphate of Lime" for capping the dental pulp during dental restorations [1, 3, 4]. Larry Hench's discovery in 1969 that a sodium-calcium-phosphorous-–silicate glass possesses bone bonding functionality gave rise to the clinical use of "bioactive glass" materials for bone repair [5, 6]. The term "bioceramics" was first used shortly thereafter in 1971 [7]. The bioceramics field is now truly global in nature and includes research, pre-clinical, and clinical activities involving various types of bioactive and bioinert inorganic materials.

This is Part 1 by Saeid Kargozar, a research fellow in the Department of Radiation Oncology, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, and Francesco Baino, an associate professor in the Department of Applied Science and Technology at the Politecnico di Torino, provides a comprehensive overview of the use of bioceramics for tissue engineering and regenerative medicine. The first part of the book (Part 1) focuses on the fundamentals of biocompatible ceramics, bioactive glasses and composites, and collects 10 chapters. In Chapter 1, Kargozar and Baino provide a description of the status of bioceramics in tissue engineering and regenerative medicine. Chapter 2, by Moghanian *et al.*, provides an introduction to biocompatible glasses, ceramics, and glass ceramics. Batool *et al.* consider recent advances in bioactive glasses and glass ceramics in Chapter 3. Chapter 4, by Bahati *et al.*, describes the structure, properties, and processing of bioactive glasses. Kargozar *et al*. focus on the biocompatibility of bioactive glasses in Chapter 5. In Chapter 6, Moghanian and Nasiripour describe the use of bioinert ceramics for biomedical applications. Moghanian *et al.* review the processing and properties of bioresorbable ceramics in Chapter 7. Dorozhkin reviews the use of calcium orthophosphates in tissue engineering in Chapter 8. In Chapter 9, Hosseini *et al.* consider the use of carbon nanostructures for tissue engineering and cancer therapy. Benedini and Messina describe advances in polymer/ceramic composites for bone tissue engineering in Chapter 10. The second part of the book (Part 2) will be addressed to the applications of the bioceramic materials discussed in the present volume.

In this volume, Professors Kargozar and Baino as well as the chapter contributors have provided the bioceramics community with a comprehensive consideration of the bioceramics field. I anticipate that their volume will be beneficial to students as well as researchers in academia, government, and industry as they continue efforts to improve our understanding of the use of bioceramic materials for tissue engineering and regenerative medicine applications.

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CHAPTER 1

Bioceramics: Status in Tissue Engineering and Regenerative Medicine

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Abstract: Tissue engineering and regenerative medicine seek biomaterials with potent regenerative potential *in vivo*. The bioceramics superfamily represents versatile inorganic materials with exceptional compatibility with living cells and tissues. They can be classified into three distinctive groups including almost bioinert (*e.g.*, alumina and zirconia), bioactive (bioactive glasses (BGs)), and bioresorbable (*e.g.*, calcium phosphates (CaPs)) ceramics. Regarding their physicochemical and mechanical properties, bioceramics have been traditionally used for orthopedic and dental applications; however, they are now being utilized for soft tissue healing and cancer theranostics due to their tunable chemical composition and characteristics. From a biological perspective, bioceramics exhibit great opportunities for tissue repair and regeneration thanks to their capability of improving cell growth and proliferation, inducing neovascularization, and rendering antibacterial activity. Different formulations of bioceramics with diverse shapes (fine powder, particles, pastes, blocks, *etc*.) and sizes (micro/ nanoparticles) are now available on the market and used in the clinic. Moreover, bioceramics are routinely mixed into natural and synthetic biopolymers to extend their applications in tissue engineering and regenerative medicine approaches. Current research is now focusing on the fabrication of personalized bioceramic-based scaffolds using three-dimensional (3D) printing technology in order to support large-volume defect tissue regeneration. It is predicted that more commercialized products of bioceramics will be available for managing both hard and soft tissue injuries in the near future, either in bare or in combination with other biomaterials.

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Keywords: Additive manufacturing, Angiogenesis, Antibacterial activity, Anticancer activity, Bioactive glasses (BGs), Bioinert ceramics, Bioresorbable ceramics, Biofabrication, Bone regeneration, Calcium phosphates, Composite, Clinical trials, Drug delivery, Hydroxyapatite (HAp), Regenerative medicine, Scaffolds, Soft tissue healing, Tissue engineering, Three-dimensional (3D) printing, Wound healing.

INTRODUCTION

Tissue engineering is a multidisciplinary field that aims to regenerate damaged tissues by applying the principles of engineering, materials science, biology, and medicine. Pioneers in the field have introduced biomaterials, cells, and bioactive molecules as the three main building blocks of tissue engineering and regenerative medicine field [1]. Naturally, human tissues are formed from differentiated or undifferentiated cells located in an extracellular matrix (ECM) (mostly collagen) containing bioactive molecules (*e.g.*, growth factors). As a rule of thumb, the ECM of tissues is greatly destroyed following severe injuries and damages; therefore, various biocompatible materials can be utilized as three-dimensional (3D) scaffolds to restore the destroyed ECM. Up to now, many types of natural and synthetic materials have been successfully processed, developed, and used for managing different tissue damage and injuries [2, 3]. Naturally occurring substances suffer from critical restrictions including the risk of disease transmission, batch-to-batch variations, and limited availability [4, 5]. Accordingly, there is a great interest in the use of synthetic materials in tissue reconstruction approaches. Regarding the nature of hard tissues (*e.g.*, bone), bioceramics are recognized as the ideal implant materials for the replacement of degenerated or traumatized osseous tissues.

Bioceramics represent biocompatible ceramic materials that are being continuously developed for use as medical implants. In fact, they are inorganic biomaterials that comprise crystalline ceramics, amorphous glasses, and glass-ceramics. In other words, the bioceramics superfamily members can be classified into three distinct generations, *i.e.*, almost bioinert (*e.g.*, alumina and zirconia), bioactive (*e.g.*, bioactive glasses (BGs)), and bioresorbable (*e.g.*, most calcium phosphates (CaPs)). These substances are commonly synthesized in the laboratory using high temperatures and used in different formats, including fine powder, granules, and dense blocks. Furthermore, bioceramics can be fabricated into tissue-mimicking scaffolds through well-established techniques and protocols (*e.g.*, sponge replication method). In recent years, great efforts have been made to produce bioceramics-based constructs using 3D printing machines in order to fit the size and shape of the lost tissues. It should be mentioned that some types of

bioceramics (BGs) are being utilized as coatings for other ceramics or metal implants.

The most fascinating feature of bioceramics for orthopedic and dental applications is related to their mechanical properties which are in the range of naïve hard tissues. In addition, bioceramics (*e.g.*, BGs and glass ceramics) exhibit excellent biological properties, including the ability to induce osteogenesis, osteoconduction, osteoinduction, and osteointegration. Moreover, bioceramics can be employed for the loading and delivery of various drugs, chemicals, and bioactive molecules to desired locations in the body. Although the first and foremost application of bioceramics is to restore hard tissue lesions, recent trends have also confirmed their suitability in soft tissue repair and regeneration (*e.g.*, skin wound healing). In this sense, they can be utilized as additives in polymeric substrates for improving particular biological events (*e.g.*, angiogenesis), and the reported data have been quite interesting. Still, some challenges remain to be solved regarding the widespread use of bioceramics in soft tissue healing strategies, including defining the most suitable composition and formulation. Since implantable materials must be compatible with living systems (*e.g.*, cells and tissues), bioceramics have been extensively examined for their potential adverse effects (toxicity) *in vitro* and *in vivo*. In general, bioceramics are known as safe substances for human beings; their main components (elements like silicon, calcium, phosphorus, *etc*.) are commonly found in low concentrations in the body and needed for the proper function of human cells [6]. However, some potentially toxic elements (*e.g.*, cobalt) can be incorporated into the basic composition of bioceramics for rendering particular activities, such as improving angiogenesis. In this case, caution should be taken to avoid any unwanted adverse effects on the human body at molecular and cellular levels. In addition, the positive potential effects of any new formulation of bioceramics may be of interest to researchers and scientists in the field.

In this chapter, we first introduce the structure, properties, and classifications of bioceramics and then highlight their possibilities in tissue engineering and regenerative medicine. The main challenges ahead will be discussed to shed light on their future applications for managing injured tissues.

BIOCERAMICS: STORY AND SIGNIFICANCE

The human body is a “marvelous machine” that efficiently incorporates different materials for different functions, such as structural support, filtration capacity, energy generation and storage, gas exchange, flexibility, and self-healing/regenerative ability, into one fascinating, integrated, and well-orchestrated bio-system. In other words, the human body is an exceptional “collection” of

CHAPTER 2

Introduction to Biocompatible Glasses, Ceramics, and Glass-Ceramics

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Abstract: Glass ceramics and ceramics have a vast range of applications in tissue engineering and regenerative medicine. Biocompatible glasses and ceramics, including bioinert ceramics, bioactive glasses (BGs), and calcium phosphate have been reviewed in this chapter detailing the history, properties, structure, and application. Ceramics and glasses with bioactivity and biocompatibility properties are pioneer solutions for a variety of clinical needs. The capacity of ceramics in hydroxyapatite formation (HA) has also been explained in this section. This chapter includes the invention of the first generation of ceramics and an explanation of how significant are their clinical applications.

Keywords: Hydroxyapatite, Tissue engineering, Bioceramics, Glass-ceramics, Ceramics, Bioactivity, Biocompatibility, Hydroxyapatite (HA), Calcium phosphate (CP), Bioactive glasses, Sol-gel, Bone tissue engineering, Bioinert, Dentistry, Melt-quench, Arthrodesis application, Bone-fillers applications, Scaffolds, Implantation, Dentin hypersensitivity.

INTRODUCTION

Biomaterials appeared 2000 years ago when applied for prosthetics and similar cases [1]. Biomaterials are selected to mimic both the physical and chemical properties of human organs and tissues [2]. Forming a bond with the host tissue, and defining the fidelity of an appropriate environment for cell and bone growth

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[1, 3]. Among current biomaterials, ceramics such as cement, porcelain, and glass are used in energy, environment, health, and transportation sectors because of their corrosion resistance, osteoconductivity, brittleness, and stiffness [5]. In clinics, ceramics have been used for bone reconstruction and implantations (known as bioceramics) [4].

Dental regeneration is a recent application because of its 3D scaffold structure [6 - 8]. To illustrate, teeth composition contains dentine and enamel, and teeth cannot self-repair like bones when injured. Bioceramics have been recognized as materials that meet the significant demands for different dental repairs and treatments. Bioceramics are categorized based on their composition, solid structure, non-metallic or inorganic substrate content, and response to the host tissue [4]. Bioinert ceramics are known for corrosion resistance without inflicting on the tissue. Bioactive ceramics, including glass and BGs, have excellent bioactivity properties and interact with the targeted tissue for other processes. Bioresorbable ceramics involve calcium carbonates, calcium phosphates, and calcium silicates. Several glass ceramics can have magnetic properties for different clinical applications. Glass ceramics have shown thermal, chemical, biological, and dielectric properties leading to significant recognition of glass ceramics for clinical treatments [9].

CERAMICS

Structure

Ceramic materials have different atoms arrangements, which depend on the size of atoms and the bonding in the structure [10]. The bonding between atoms in ceramics is covalent or ionic and can be a combination of both, affecting their chemical and physical system [11].

Classifications

Bioinert Ceramics

Bioinert ceramics are characterized by their hardness, excellent mechanical behavior, corrosion resistance, and durability. Zirconia (ZrO_2) and alumina (Al_2O_3) are two famous bioinert ceramics in this field [12, 13] being promising materials for orthopedic applications because of their compressive strength [13, 14]. The first generation of Al_2O_3 was introduced in the 1970s, not only being applied in dentistry [15], but also used to replace corneal and bone, dental implants, and maxillofacial regeneration [16]. On the other hand, ZrO_2 has a different crystalline structure depending on the temperature: below 1170 °C, it has a monoclinic system, at 1170 °C, it is tetragonal, and lastly, at 2370 °C, it is cubic.

The structural transformation is visible on the ceramics' surface when placed in body fluid, improving the implant's durability [19]. ZrO_2 enhances differentiation and cell proliferation for osteogenic and osseointegration applications [20]. Alumina-toughened zirconia (ATZ) or zirconia-toughened alumina (ZTA) is a mixed composition of Al_2O_3 with ZrO_2 to increase the toughness degree and versatility [17, 18]. Bioactive materials differ from inactive materials because of the chemical reaction when placed in the biological fluid [21]. Both Al_2O_3 and ZrO_2 are biocompatible while they are passive without a direct bond with the bone and tissue.

Glass-Ceramics and Bioactive Glasses (BGs)

Glass-ceramics and BGs are superior materials in tissue engineering. When glass is heated, it crystallizes and improves its toughness and strength. Glasses contain main ions, including silica (Si), sodium (Na), calcium (Ca), and phosphate (P), which are released when BGs dissolve. By releasing ions, BGs can promote various biological events such as angiogenesis and vascularization [22 - 24]. The first generation of biomaterials, invented by Larry Hench, was called 45S5 bioactive glass. It contained 45%SiO_2, 24.5%Na_2O, 24.5%CaO and 6%P_2O5 (mol.%). Studies showed that 45S5 has good osteoconduction and biocompatibility, playing an important role in bone regeneration [25]. The *in vivo* and *in vitro* evaluations on 45S5 highlight properties such as bioactivity and its capacity to interact with the host tissue by forming hydroxyapatite (HA) particles. 45S5 is a silica-based BG, with Si particles playing an important role in bone regeneration by improving osteogenesis [26]. Phosphates (PO_4) are found in a tetrahedral shape and are asymmetric in nature; consequently, it has a high level of solubility when placed in biological fluid [29]. Similar BGs involve a network containing SiO_4 tetrahedrons and oxygen surrounded by two numbers of silicon; this open structure breaks into a solution [27]. The first applicable glass based on borosilicate was discovered by Brink in 1997. This glass had reactive properties with a lower level of chemical durability.

In 1987, BGs were first defined as materials with specific biological responses [30]. BGs became essential for bone applications because of their ability to form an HA layer on a bone surface and provide a substrate for the generation of injured tissue [31 - 33]. It is also recognized because of their high bioactivity property by placing these materials in simulated body fluid (SBF) solutions with a similar composition to the human body plasma. The formation of HA on the surface is essential and determining in some processes such as regeneration, treatment of injured tissue, and osteoblast stimulation [33].

CHAPTER 3

Recent Advances in Bioactive Glasses and Glass Ceramics

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Abstract: Bone is a self-healing part of the body, which if damaged, repairs itself in the natural course of events. However, this healing process is deficient if the defect is too large or malignant to mend naturally. Bone regeneration is an age-dependent phenomenon where the older generation is at a disadvantage as compared to the younger generation due to the compromised biological performance as a result of aging. Therefore, it is crucial to create novel and effective ways to treat bone-related troubles. Bioactive glasses (BGs) and glass ceramics (GCs) belong to the third-generation bioactive materials. They not only have the potential to survive in the harsh physiological environment but can also renovate the defects present around them. They also come with the advantage of tunable chemical, physical, and biological properties. Designing an implant or scaffold while playing with distinct characteristics of metals, polymers, and ceramics, bestows a large selection pane in front of humankind for customized and patient-specific products. In this chapter, an overview of the recent advances in the BGs and GCs application in coatings and hydrogels for bone tissue engineering (BTE) is presented. BGs and GCs incorporated coatings and hydrogels loaded with metallic ions, growth factors, and biomolecules provide a complete bundle of features essential for bone repair and growth. Although many BGs and CGs-based products have made it into the market, some inherent challenges like high brittleness and low fracture toughness persist to overcome to date.

Keywords: 3D printed, Antibacterial, Bioactivity, Bioceramics, Biomaterials, Biopolymers, Bone, Coatings, Degradation, Electrospinning, Glasses, Hydrogels, Hydroxyapatite, Metallic ions, Osteoconductive, Osteointegration, Regeneration, Resorbable, Scaffolds, Tissue engineering.

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INTRODUCTION

Bioactive glasses (BGs), since the invention of the original 45S5 Bioactive glass (Bioglass®) in 1969 have revolutionized the spectrum of biomaterials [1]. Professor Larry Hench developed Bioglass® in search of materials capable of bonding with natural tissues [2]. Hench's research idea centered around the hypothesis that good bonding ability can be obtained in implant materials using elements/ ions already available abundantly in physiological environment (such as Ca & P) [3]. This invention introduced a new dimension of bioactive materials that are potentially able to develop bonds with tissues in the physiological environments [4]. The developed Bioglass® could bind to the natural bone so strongly that the detachment was not possible without breaking the bone [5]. Originally, BGs were prepared for bone substitute [6], but later they have found applications in dentistry [7] and soft tissue engineering (TE) [8]. BGs belong to class A bioactive materials which apart from employing already differentiated bone cells (osteoconduction), can also stimulate primitive undifferentiated cells to yield bone-related cells (osteoinduction) for enhanced osteoblasts' proliferation [9]. Moreover, BGs also upregulate genes for revascularization, enhance enzyme activity, exhibit antibacterial character, and deliver drugs [10, 11]. This set of unique properties have made them a biomaterial of significantly high research interest for almost half a century [11, 12].

Despite an extremely attractive set of biological properties, the major limiting factor for BGs is their inadequate mechanical performance [13]. Numerous efforts have been made to address this shortcoming, centered around doping, architectural designing, structure control and synthesis techniques [14, 15]. The glass ceramics (GCs) could exhibit similar biological performance along with good mechanical stability [16]. GCs are potentially similar to BGs but crystalline phases are yielded in the glassy matrix using a special heat treatment [17]. Kokubo *et al*. [18] developed Apatite and β-Wollastonite (A-W) BGC in $3Cao.P_2O_5$-$CaO.SiO_2$-CaO. $MgO.2SiO_2$ system. When the melt-quenched glass of above mentioned system was exposed to 1050 °C (slow heating rate 5 °C/ min), the formation of fibrous wollastonite and fine crystals of oxyapatite took place [19]. The crystallization of wollastonite and oxyapatite yield bending strength (215 MPa) higher than that of cortical bone (*i.e.* 160 MPa) and enhanced fracture toughness (*i.e.* 2 MPa · $m^{1/2}$) [20, 21]. However, in comparison to the fracture toughness of the cortical bone (*i.e.* 2–12 MPa · $m^{1/2}$), this enhancement is negligible and a marked improvement is needed to compete with the natural bone [22]. Currently, the size of crystallites in GCs is in the micrometer range and it is believed that if the crystallite size can be decreased to nanometer range, a marked increase in mechanical performance can be achieved [23, 24]. Several

BGC products have been developed commercially for bone and dental applications including: Bioverit®, Biosilicate®, Cerabone®, and Ceravital® [25].

During this journey of more than half a century, BGs and glass ceramics have witnessed several important milestones. They have been employed for a wide range of applications from hard and soft TE to theranostics [26]. After the discovery of Bioglass® in 1969, its first clinical trial was reported in 1977 for the replacement of middle ear (small) bones and later in 1978, as an ocular implant. For the liver cancer treatment, BG was employed in 1987 and later in 2004, lungs treatment was also carried out using it. More recently in 2018, TheraSphere® (a radioactive BG) has been employed to treat colorectal liver cancer. On the other hand, A-W GC found its application as a prosthesis for the reconstruction of iliac crest in 1987. Bioverit®, which is a common name for two types of mica-apatite GCs, had been implanted in more than 850 patients as middle ear implant or bone spacers till 1992 [27]. A relatively new GC (Biosilicate®), which exhibited bioactivity as high as that of Bioglass® 45S5 and mechanical performance similar to that of A-W was patented in 2007 for the dental ailments [28]. Fig. (**1**) shows the list of publications on BGs per year for the last ten years.

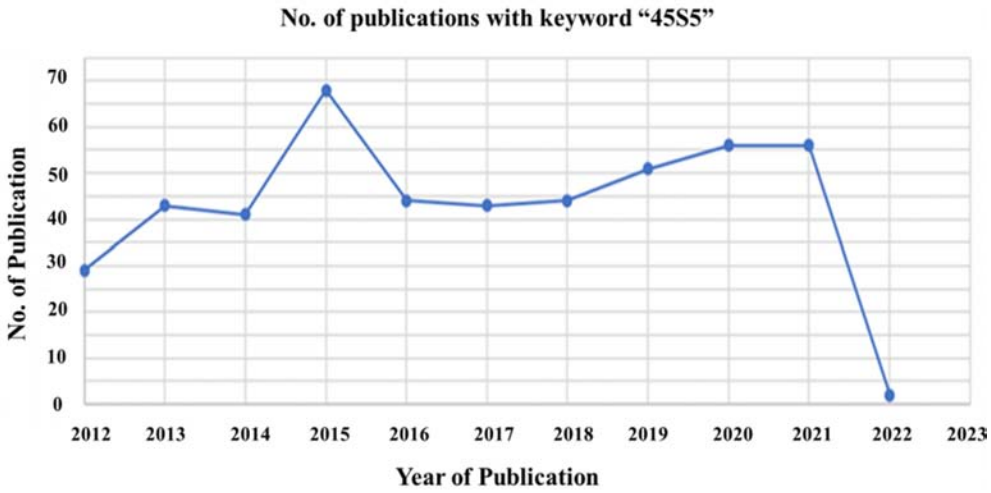

Fig. (1). List of publications on BGs.

Recent Developments in GCs and BGs Incorporated Coatings

GCs and BGs are used in medical applications due to their unique interaction with human body. Following the discovery of BGs in 1971, clinical uses of BGs were not achieved until the 1980s. The successful implantation of middle ear replacement prosthesis (MEP) [29] and endosseous ridge maintenance implants

CHAPTER 4

Bioactive Glasses: Structure, Properties, and Processing

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Abstract: Bioactive glasses, as pioneering artificial biomaterials, uniquely establish strong bonds with hard and soft native tissues by forming a bone-like hydroxyapatite layer in contact with physiological body fluid. This hydroxyapatite layer, mimicking the inorganic phase of natural bone, adds a fascinating dimension to their biomedical significance. Comprising three primary components; network formers, network modifiers, and intermediate oxide components; bioactive glasses allow tailored properties through component variation. While extensively explored for broadening biomedical applications, especially in regenerative medicine, their use is constrained by inherent mechanical shortcomings such as brittleness, fragility, and poor elasticity. Ongoing studies focus on incorporating bioactive glasses into composite/hybrid biomaterials with biopolymers, aiming to optimize mechanical properties for diverse biomedical applications, especially in load-bearing sites of hard tissues. Despite successful applications, the mechanical limitations persist, prompting investigations into the influence of composition and processing methods on bioactive glass properties. Notably, doping bioactive glasses with metallic ions at lower concentrations emerges as a promising avenue, enhancing mechanical and biological attributes, including bioactivity, osteogenicity, osteoinductivity, and antibacterial effects. This chapter provides a comprehensive examination of three bioactive glass types, accentuating their structures, properties, and processing methods. Additionally, it delves into property modifications facilitated by metallic ion dopants, contributing valuable insights to the evolving landscape of biomaterials.

Keywords: Amorphous solids, Bioactive glass, Bioactivity, Borate, Bridging oxygen atom, Doping, Melt-quench, Network connectivity, Network formers, Network modifiers, Non-bridging oxygen atom, Phosphate, Silicate, Sol-gel.

INTRODUCTION

Bioceramics can be grouped into naturally occurring, like coral-derived apatite or synthetic ones [1]. Synthetic bioceramics can either be nearly bioinert such as

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Alumina and zirconia or bioresorbable such as tricalcium phosphate, or bioactive like calcium phosphate (hydroxyapatite), bioactive glasses, and glass-ceramics [1, 2]. Bioceramics have been used in orthopedics to replace, repair, or enhance the regeneration of diseased and damaged hard tissues, including hips, knees, teeth, tendons, spinal fusion, jawbones, and other maxillofacial surgical applications such as the treatment of periodontitis disease [1]. Calcium phosphate-based compositions are preferred due to their chemical and structural similarity in composition with the main mineral phase of the bone [3, 4]. Alumina and zirconia are bioinert ceramics that have been used in orthopedic applications, mainly in total hip prostheses and teeth implants, due to their high wear resistance and chemical stability [2]. However, bioceramics are generally brittle, fragile, have low mechanical stability, poor elasticity, and low fracture toughness. In addition, their degradation rates are not very predictable [4], thus limiting their use in medical applications. Composite materials composed of polymers as bulk matrix and bioceramics as fillers have been studied recently [5 - 8]. Bioactive glasses are widely studied artificial biomaterials, especially for medical applications. This chapter highlights bioactive ceramics, focusing mainly on bioactive glasses, particularly their properties, synthesis techniques, and property enhancement through adding dopant ions.

Calcium Phosphate Ceramics

Calcium phosphate-based bioceramics (CaPs) have been primarily used in orthopedics due to their chemical and structural similarity with the inorganic phase of natural bone. The most studied CaPs are hydroxyapatite (HA) [$Ca_{10}(PO_4)_6(OH)_2$] with a calcium to phosphate ratio of 1.67 and tricalcium phosphate (TCP). The latter can either be α-TCP or β-TCP with a similar chemical composition [$Ca_3(PO_4)_2$] but different in crystal phases leading to different absorption characteristics [9, 10]. The solubility of α-TCP is higher than that of β-TCP resulting in faster release of Ca^{2+} and PO_4^{3-} when in contact with body fluid, facilitating fast precipitation to form HA and new bone formation compared to the similar situation employing β-TCP [9]. In this comparison, β-TCP was more soluble than synthetic HA [10]. However, rapid solubility may result in too high ionic concentration leading to ineffective cellular responses. On the other hand, too slow solubility results in low ionic concentration to trigger cellular activities for extracellular matrix deposition.

An *in vivo* comparison based on the time required for complete bone restoration between 45S5 Bioglass and HA showed that complete bone restoration could be archived in 2 weeks with 45S5 bioglass while HA required about 12 weeks to produce comparable results [11]. Yuan *et al*. [12] conducted an *in vivo* comparison between α and β-TCP on their ability to induce bone formation in the

soft tissue of dogs. Bone tissue was observed after 45 and 150 days of β-TCP implantation, while no bone tissue was observed during the same period with α-TCP. It was concluded that a higher local ionic concentration of Ca^{2+} and PO_4^{3-} resulting from the rapid dissolution of α-TCP could resist bone formation. In contrast, too slow dissolution of β-TCP could be inadequate to trigger the cellular activities for new bone deposition. The rapid dissolution of α-TCP leads to supersaturating local ionic concentration of Ca^{2+} and PO_4^{3-} which may negatively impact the migration, proliferation, and differentiation of bone-forming cells (osteoblasts) and subsequently ossification process [13].

Bioactive Glasses

As an alternative to nearly bioinert substitutes, Larry Hench discovered the first bioactive glass in the 1960s. The discovery originated from a friendly discussion between Hench and a US Army colonel who had just returned from the Vietnam War in 1967. When Hench explained his previous research work with his colleagues about their research results on a glass material (vanadium phosphate, V_2O_5-P_2O_5) resistant to high radiation exposure, the colonel asked him if he could make a material resistant to human body exposure. Then Hench changed his research paradigm towards new ceramic material that could resemble or stimulate the formation of hydroxyapatite *in vivo* similar to the inorganic phase of the natural bone with the assumption that it could not be rejected by the human body [14].

About ten years later, it was found that the bioactive glass could stimulate osteogenesis when used in particulate form, which led to the concept of tissue regeneration [15, 16]. This bioactive glass had quaternary composition with the main components being silicon dioxide, calcium oxide, sodium oxide, and phosphorous pentoxide (45 wt% SiO_2, 6 wt% P_2O_5, 24.5 wt% CaO and 24.5 wt% Na_2O). It was made through the melt-quenching method and finally was termed as 45S5 Bioglass® [14, 16]. It is worth noting that the term Bioglass only stands for the original bioactive glass (45S5), and therefore it cannot be used referring to any other composition of bioactive glass. The *in vitro* test of 45S5 bioglass showed that it could develop a hydroxyapatite layer (HA) when socked in solutions that did not contain calcium or phosphate ions. The formed HA was equivalent to observed interfacial HA bonded to collagen fibrils produced by osteoblasts at the interface of the 45S5 implant and the native bones of a rat femoral in an *in vivo* study by Dr. Ted Greenlee. The first *in vivo* tests were for six weeks in which at the end, Greenlee reported, *"These ceramic implants will not come out of bone. They are bonded in place. I can push on them, I can shove them, I can hit them, and they do not move. The controls easily slide out"* [14, 16]. The *in vitro* and *in vivo* results of the 45S5 bioactive glass were published for the first time in 1971 in

CHAPTER 5

On the Biocompatibility of Bioactive Glasses (BGs)

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Abstract: Bioactive glasses (BGs) form a versatile class of biocompatible materials that can be utilized for various therapeutic strategies, including bone tissue engineering, soft tissue healing, and cancer therapy. Commonly, BGs are classified into three distinct categories, namely silicate, phosphate, and borate glasses. Several commercial BG-based products are now available on the market, and new generations with unique therapeutic features are also expected to introduce them in the near future. Due to their clinical significance, the biological behaviors of BGs have been one of the most interesting topics in tissue engineering and regenerative medicine. Although BGs are generally recognized as biocompatible materials in medicine, any new composition and formulation should be carefully tested through a series of standard *in vitro* and *in vivo* tests provided by international agencies (*e.g.*, Food and Drug Administration (FDA)) and regulatory bodies (*e.g.*, the International Organization for Standardization (ISO)). As a rule of thumb, the release of ionic dissolution products from BGs into the surrounding biological environment is regarded as the main parameter that modulates cellular and molecular phenomena. This process is even more crucial when specific elements (strontium, copper, *etc*.) are added to the basic composition of BGs to improve their physico-chemical properties, mechanical strength, and biological performance. Moreover, it is now well-established that some physical (*e.g.*, the topography) aspects of BGs can directly affect their compatibility with the living systems (cells and tissues). Therefore, a multifaceted design and testing approach should be applied while synthesizing BGs in the laboratory, and the collaboration of materials and chemical engineers with biologists and medical experts can be really helpful for producing optimized formulations.

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Keywords: Angiogenesis, Antibacterial activity, Bioactive glasses (BGs), Bioactivity, Biocompatibility, Borate bioactive glasses, Bone tissue engineering, Cytotoxicity, Tissue compatibility, Genotoxicity, Hemocompatibility, Glass-ceramics, Inflammatory response, International Organization for Standardization (ISO), *In vitro* study, *In vivo* animal study, Phosphate bioactive glasses, Polymers, Silicate bioactive glasses, Soft tissue engineering, Three-dimensional (3D) printing, Wound healing.

BIOLOGICAL EVALUATION OF MEDICAL DEVICES

One of the most critical aspects of medical devices is related to their compatibility with living systems (cells, tissues, and organs). Accordingly, several attempts have been made to determine a comprehensive definition of "biocompatibility" over the years. The first definition of biocompatibility was issued as "the ability of a material to perform with an appropriate host response in a specific application" [1]. However, the emergence of new technologies (*e.g.*, tissue engineering) in the concept of modern medicine led to a redefinition of this term. For instance, two important features of materials, *i.e.* bioactivity and biodegradation, were later specified and explained; then, they indeed needed to be considered in the new definition of biocompatibility. Nowadays, biocompatibility is identified as "the ability of a material to perform its desired function concerning a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy" [2]. Over the years, the list of criteria for biocompatibility of materials is constantly being updated. Governmental agencies and regulatory bodies are indeed the developers of these rigid criteria. In this regard, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are known as the leading international agencies. In addition, the International Organization for Standardization (ISO), American Society for Testing and Materials (ASTM), and the United States Pharmacopeia (USP) are recognized as regulatory bodies that provide valid procedures, protocols, guidelines, and standards to appraise all medical devices before implantation into the human body.

The ISO-10993 is among the most well-known standards that set a series of procedures for assessing the biological risk of any medical device to the human body. In fact, the ISO-10993 comprises different parts in which assays and tests are classified according to the nature of body contact (surface device, external communicating device, and implant device) (Table **1**).

Table 1. The ISO-10993 standard provides a framework for the biocompatibility evaluation of biomaterials and medical devices.

Medical Device Categorization by			Biological Effects							
Nature of Body Contact		Contact duration A= Limited (≤24h) B= Prolonged (>24 to 30 d) C= Permanent (>30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute)	Genotoxicity	Implantation	Hemocompatibility
Category	Contact									
Surface Device	Skin	A	X	X	X	-	-	-	-	-
		B	X	X	X	-	-	-	-	-
		C	X	X	X	-	-	-	-	-
	Mucosal membrane	A	X	X	X	-	-	-	-	-
		B	X	X	X	-	-	-	-	-
		C	X	X	X	-	X	X	-	-
	Breached or compromised surface	A	X	X	X	-	-	-	-	-
		B	X	X	X	-	-	-	-	-
		C	X	X	X	-	X	X	-	-
External Communicating Device	Blood path, indirect	A	X	X	X	X	-	-	-	X
		B	X	X	X	X	-	-	-	X
		C	X	X	-	X	X	X	-	X
	Tissue/ Bone/ Dentine	A	X	X	X	-	-	-	-	-
		B	X	X	X	X	X	X	X	-
		C	X	X	X	X	X	X	X	-
	Circulating blood	A	X	X	X	X	-	-	-	X
		B	X	X	X	X	X	X	X	-
		C	X	X	X	X	X	X	X	-
Implant Device	Tissue/ Bone	A	X	X	X	-	-	-	-	-
		B	X	X	X	X	X	X	X	-
		C	X	X	X	X	X	X	X	-
	Blood	A	X	X	X	X	X	-	X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

Cell culture systems represent the most common types of biocompatibility assays utilized for identifying cytotoxicity, cell adhesion, cell activation, or cell death. In fact, the compatibility of new biomaterials with cells is among the most extensively used tests before further biological evaluations [3]. The investigator is strongly suggested to use a cell type for which the device and biomaterial under examination are planned for clinical use. For instance, the cytocompatibility of materials designed for bone tissue repair and regeneration should be assessed by using osteoblast cells rather than “osteoblast-like” cell lines that are derived from the tissue of bone tumors, mostly osteosarcoma [4]. Most of these cells show a significant reduction in cell viability upon exposure to the well-known 45S5-bioactive glass composition when compared to the effects on primary bone marrow derived stromal cells (bone precursor cells) or primary human osteoblasts

CHAPTER 6

Bioinert Ceramics for Biomedical Applications

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Abstract: Bioinert ceramics are a form of bioceramics that is characterized based on how they react biologically in the human body. Bioinert ceramics are often classified as biologically inert nature or bioinert ceramics that do not elicit a suitable reaction or interact with nearby living tissues when implanted into a biological system. In other words, exposing bioinert ceramics to the human environment will not cause any chemical interactions between the implant and the bone tissue. Bioinert ceramic materials have been used in the form of medical devices and implants to replace or re-establish the function of degenerated or traumatized organs or tissue of the human body due to their excellent chemical stability, biocompatibility, mechanical strength, corrosion restriction behavior, and wear resistance. Materials based on titanium, alumina, and zirconia are used in bioinert nanoceramics., In a biological environment, they are bioinert, fracture-tough, and have high mechanical strength. Because of their corrosion resistance, titanium and titanium-based alloys are widely used in bone tissue repair.

Keywords: Alumina, Biocompatibility, Biomaterials, Bioceramics, Bio-inert, Carbon, Coating, First-generation, Non-oxide bio-inert ceramics, Oxide bioinert ceramics, Repair, Titanium, Tissue, Implant, Zirconia.

INTRODUCTION

Biomaterials are materials that are used to examine, treat, improve, restore, or replace biological tissues or organs. Biomaterials were initially developed in the 1960s. Its goal was to have the biomaterial work as well as the replacement tissue while causing the lowest amount of toxicity to the host [1].

Any inorganic, nonmetallic solids are classified as ceramics. Ceramics are a group of materials composed of inorganic, non-metallic materials. This material cate-

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gory can be subdivided in a variety of ways [2]. Ceramic materials can be divided into two categories, traditional and advanced. These ceramics can have a crystalline or non-crystalline structure [3]. Ceramics are synthesized in different ways, the most widely used method is the synthesis method at high temperatures [3].

One of the types of ceramics is bioceramic, which is used as a biomaterial because of its good properties. It is used as one of the most biocompatible material in the body of living organisms. Its applications can be mentioned as implants in the tooth, bone tissue, and so on [4]. Fig. (**1**) shows the bioinert ceramic material category [3].

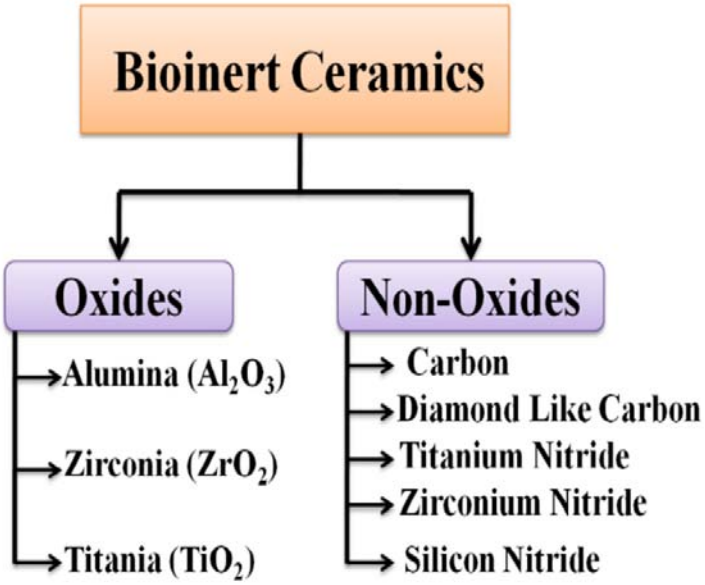

Fig. (1). Bioinert ceramic material category [3].

Brittleness in ceramics is caused by the absence of deformation tolerance in their lattice structures' covalent or ionic connections. Because of the stress concentration effect, structural defects are the preferred locations of deformation. As a result, flaws in ceramics have a significant impact on their mechanical performance. As a matter of fact, the fracture of ceramics is always initiated by the unavoidable microscopic flaws (microcracks and micropores) that result during cooling after the melt, with particular sensitivity to surface defects. Chemical bonds are broken as a result of the concentrated stresses (*i.e.* deformation) surrounding these faults, which propagate as linear fractures, which commonly run along crystal planes. However, minuscule imperfections cannot be

eradicated during manufacture, and their position, whether within the material or on its surface, is random, resulting in a wide range of fracture strength in ceramic materials (scatter). The compressive strength of a material is usually ten times that of its tensile strength. Because of this, ceramics are good structural materials under compressive stresses (*e.g.*, bricks in homes, stone blocks in pyramids), but not under tensile stress (*e.g.*, flexure). To summarize, the stress concentration effect, and hence the existence of material defects, has a significant impact on the mechanical performance of ceramics. Ceramics should not be employed in situations where tensile, bending or concentrating stresses exist. They are primarily employed at compressive load-bearing places where stresses are dispersed uniformly throughout the bulk material [2].

Bioceramics have different sub-categories that can be referred to as oxide and nitride-based bioinert ceramics, bioresorbable calcium phosphate-based materials, and bioactive glasses/glass-ceramics. Ceramics (crystalline inorganic, nonmetal materials), glasses (amorphous inorganic, nonmetal materials), and glass-ceramics are the three subgroups based on crystallinity (partially crystalline inorganic, nonmetal materials) [2]. Each of which has different applications based on its interaction with the biological environment [5].

Bioinert Ceramics

Biomaterials are substances that interact with the biological environment around them. These materials exist naturally and synthetically and also have various applications in medicine, especially tissue engineering. The reactivity of bioceramics in the living body and the initial responses to them are considered a criteria for classifying bioceramics [1]. Biomaterials are divided into 4 categories bioactive, biodegradable, bioinert, and/or biotolerant based on the degree of biocompatibility they have in a living organism [4]. Bioinert ceramics are known as first-generation bioceramics and bioactive and absorbable ceramics are known as second-generation bioceramics [1].

Bioinerts are a group of biomaterials. A good feature of bioinert materials is that they are chemically stable, compatible with hard tissues, and have good mechanical strength [4]. These materials have stable physicochemical properties. When implanted into the body, the materials will not trigger a physiological reaction or produce an immune response. Hosts are capable of retaining their physiochemical and biomechanical properties. Furthermore, there is no interaction between the implant and the tissue. This leads to no adhesion between the tissues and the implant [6]. Corrosion and wear are repelled by them. There are no fractures due to their strong strength. Bone screws and bone plates, for instance, are structurally-supporting implants made out of bio-inert materials [18, 19].

CHAPTER 7

Bioresorbable Ceramics: Processing and Properties

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Abstract: In synthetic ceramic materials, the types of interactions that occur in the physiological environment during body implants and tissues are defined as bioinert, bioactive, and bioresorbable. Bioresorbable materials, whether polymers, ceramics, or composite-based systems, are widely used in a variety of biomedical applications. Designing a bioresorbable device requires careful consideration of an accurate way of forecasting the biosorption of this class of materials. Bioresorbable ceramics possess the ability to undergo *in vivo* absorption and consequent replacement by the newly formed bone. They have a bonding pattern that is similar to bioactive ceramics. However, the fact that bioresorbable ceramics frequently fail to make solid contact with bone limits their potential medical uses. Bioactive and bioresorbable ceramics have a narrower application range than bioinert ceramics.

Keywords: Absorb, Bioresorbable, Bone, Bioresorbable implant, Ceramics, CaP, Degradation, DCPD, Host response, Hydroxyapatite, Inflammatory response, OCP, Resorption process, TCP, Tissue engineering.

INTRODUCTION

The ability of a bioceramic to form a bond with living tissue following transplantation is used to categorize the material, According to the statement, bioinert ceramics such as alumina and zirconia exhibit no interaction with the adjacent tissue post-implantation; (a) The material in question exhibits favorable fracture toughness, as well as resistance to corrosion and wear. (b) Bioactive ceramics (*e.g.*, bioglassesand glass-ceramics) form direct bonds with living tissues, following the pattern of bonding osteogenesis. (c) Bioresorbable ceramics

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(*e.g.*, calcium phosphates (CaPs), calcium phosphate cements (CPCs), calcium carbonates, and calcium silicates) undergo gradual absorption within the living organism and are ultimately substituted by osseous tissue [1].

Many materials, including ceramics, polymers, and metals, have recently been studied for bone repair and substitution. The high proportion of inorganic apatite (70%) and organic collagen (30%) in bone makes ceramics a popular choice for bone repair. In terms of how they react in the body, ceramics used to repair or replace bones are classified into three categories. Biologically inert ceramics generate a thin, non-adherent fibrous layer where they come into contact with the bone. Implanted artificial materials often develop immunoreactions, leading to fibrous tissue enclosing them and isolating them from the surrounding bone. The second category pertains to bioactive ceramics that possess the ability to adhere immediately to the bone. Bioresorbable ceramic is the third kind. The bioresorbable ceramic progressively dissolves over time, eventually being replaced by natural bone [2]. Fig. (**1**) illustrates the category of bioceramics.

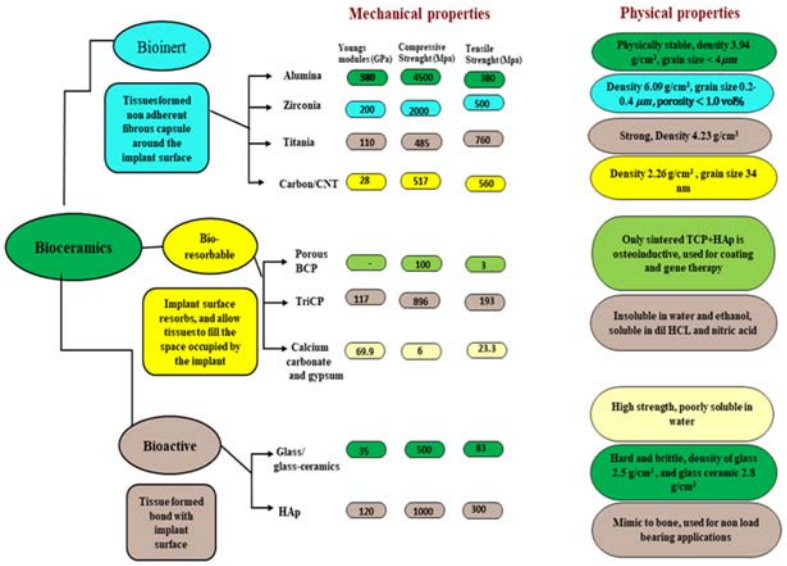

Fig. (1). Bioceramics category [2].

Biodegradable Implants

Biodegradable implants, as compared to their nondegradable counterparts, lead to a more patient-friendly treatment. The process of implant degradation facilitates the regeneration of tissue within the implanted site and does not impede radiological imaging in the absence of subsequent removal surgery.

Biodegradable materials are accessible in a variety of new forms, including biodegradable polymers, injectable *in situ* forming implants (ISFIs), bioresorbable ceramics, and biodegradable metal alloys. Different mechanical properties may be achieved, making it possible to tailor the implant to a specific use. The structural chains of biodegradable materials (often polymers or metal alloys) break down into smaller bits, then macrophages phagocytose the particles, and finally, the substance is dissolved chemically. Other types of biodegradable materials include bioceramics and metal alloys, which are made up of resorbable ingredients [3]. Their use is intended to enhance the performance of compromised biological frameworks like those seen in orthopedics and dentistry [4 - 6]. The following requirements should be met by the ideal biodegradable implant: (i). When viewed physiologically, it is biodegradable without harming the body. The pace of implant disintegration and the generation of debris particles should not be faster than the tissue's tolerance. (ii). The biocompatible implant surface is expected to facilitate favorable cellular proliferation in the adjacent tissue. (iii). Similar rates of implant degradation and healing of tissues are desirable. On the pace at which implants deteriorate, several variables have an impact, including implant shape, interaction with bodily fluids, implant position within the body, temperature, motion, component molecular weight, crystallinity, and formulation. To maintain a consistent drug release profile, the breakdown rate of biodegradable drug-loaded implants must stay constant [7].

Bioresorbable ceramics are special because they may degrade over time and be replaced by healthy tissue [8]. Ceramics that are both bioactive and resorbable find widespread usage in the field of bone repair, especially in the production of implants that form strong bonds with the bone (*e.g.*, in skull restorations after operations or trauma), tooth-root implants, biological tooth fillings, and the cure of periodontal disease (tissue around teeth).

They are also used in maxillofacial reconstruction, grafting and stabilizing skull bones, joint reconstruction, endoprosthesis of hearing aids, cosmetic eye prostheses, and so on. Resorbable ceramics can also be utilized to restore tendons, ligaments, tiny blood vessels, and nerve fibers [9, 10].

TCP ($Ca_3(PO_4)_2$), a kind of tricalcium phosphate [11] and calcite ($CaCO_3$) [12] are examples of bioresorbable ceramics. Because bone is a kind of calcium phosphate, different calcium phosphates are commonly employed in the production of bone replacements [11]. Typical monohydrate (MCPM) is the most acidic of the calcium phosphates, exhibiting exceptional solubility in an aqueous solution. Consequently, although MCPM cannot be employed in isolation, it can serve as a fundamental constituent in calcium phosphate cement when combined with -TCP. Calcium phosphate cement also employs dicalcium phosphate

CHAPTER 8

Calcium Orthophosphates in Tissue Engineering

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Abstract: $CaPO_4$ (calcium orthophosphate) is an ideal class of materials for bone tissue engineering applications due to the similarity of its set of chemical compositions and structures with mammalian bones and teeth. The use of $CaPO_4$-based biomaterials in dental and orthopedic applications has become widespread in recent years. The biocompatibility, biodegradability, and varying stoichiometry of $CaPO_4$ scaffolds make them suitable candidates for drug loading and tissue engineering strategies. Therefore, calcium phosphate compounds, particularly hydroxyapatite (HA) and tricalcium phosphates (TCP) are highly attractive as bone grafts or drug delivery agents. Specifically, three-dimensional (3D) scaffolds and carriers made from calcium phosphate are created to promote osteogenesis and angiogenesis. These scaffolds are typically porous and can accommodate a range of drugs, bioactive molecules, and cells. In recent years, stem cells and calcium phosphate compounds have been used increasingly as bone grafts. This chapter explores the advantages, sources, and fabrication methods of $CaPO_4$ scaffolds for possible usage in tissue engineering.

Keywords: Calcium orthophosphates ($CaPO_4$), Hydroxyapatite (HA), Tricalcium phosphate (TCP), Scaffolds, Tissue engineering.

INTRODUCTION

Bones represent a supportive organ for living structures and give shape and form to the entire body. In the musculoskeletal system, bones are pivots and levers that enable movement direction and a range of motion to be controlled. Furthermore, bones protect vital organs and store vitamins and nutrients (*e.g.*, calcium). The bone cannot fully heal on its own when its repairing process is ignored when the defect is large or when the usual repair process is interrupted [1].

Commonly, the standard treatment for complex bone fractures is to use various types of fixation devices or implants combined with autografts or artificial bone replacement materials. The advantages of using autogenous bone grafts are clear.

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In brief, calcium phosphate compounds serve as a matrix that facilitates cell attachment and migration, resulting in bone formation (osteoconductive properties). They also may serve as a source of therapeutic proteins like growth factors to boost osteogenic differentiation (osteoinductive properties). A similar scenario applies to living cells with osteogenic properties. However, autografts have limitations such as limited tissue availability, the need for another operation (*e.g.*, iliac crest harvest), and the possibility of donor site morbidity. Therefore, allografts and xenografts have been studied and applied as alternatives to autografts. Accessibility to allografts in different shapes and sizes is easier; they provide substances that act as osteoconductive and osteoinductive substances as part of the healing process (if growth factors are kept intact). However, allografts do not show osteogenic properties due to the absence of living cells. As a result of the poor remodeling capacity of allografts and the risk of disease transmission and immune reactions, bone grafts have a significantly higher complication rate and need for reoperation than autografts [2].

Thus, medical professionals are exploring innovative approaches to address the restrictions of existing intervention approaches for complex bone defects. The goal of tissue engineering and regenerative medicine is to repair tissues by using scaffolds, biologically active compounds, and cells. Bone tissue engineering represents an advanced and widely studied field in this area of science [3].

This chapter aims to assess the role and impact of calcium orthophosphate ($CaPO_4$) materials in the repair and regeneration of injured hard tissues. The focus of this chapter is on the development of new formulations that can be translated into scaffolds with the required shape and structure. A variety of techniques can be used to influence the structure of materials, and factors affecting their effectiveness are discussed. In Table **1**, you will find a list of $CaPO_4$ products available, along with their standard abbreviations and key properties [4, 5].

Table 1. Existing calcium orthophosphates and their main properties [4, 5].

Ca/P Molar Ratio	Compounds and Abbreviations	Chemical Formula	Solubility (25 °C, -log(K_s))	Solubility (25 °C, g/L)	Stability Range pH (Aqueous Solutions) (25°C)
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2·H_2O$	1.14	~ 18	0.0 – 2.0
0.5	Monocalcium phosphate anhydrous (MCPA or MCP)	$Ca(H_2PO_4)_2$	1.14	~ 17	[c]
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$CaHPO_4·2H_2O$	6.59	~ 0.088	2.0 – 6.0

(Table 1) cont.....

Ca/P Molar Ratio	Compounds and Abbreviations	Chemical Formula	Solubility (25 ºC, -log(K_s))	Solubility (25 ºC, g/L)	Stability Range pH (Aqueous Solutions) (25°C)
1.0	Dicalcium phosphate anhydrous (DCPA or DCP), mineral monetite	$CaHPO_4$	6.90	~ 0.048	[c]
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	96.6	~ 0.0081	5.5 – 7.0
1.5	α-Tricalcium phosphate (α-TCP)	α-$Ca_3(PO_4)_2$	25.5	~ 0.0025	[a]
1.5	β-Tricalcium phosphate (β-TCP)	β-$Ca_3(PO_4)_2$	28.9	~ 0.0005	[a]
1.2 – 2.2	Amorphous calcium phosphates (ACP)	$Ca_xH_y(PO_4)_z \cdot nH_2O$, n = 3 – 4.5; 15 – 20% H_2O	[b]	[b]	~ 5 – 12 [d]
1.5 – 1.67	Calcium-deficient hydroxyapatite (CDHA or Ca-def HA)[e]	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ ($0<x<1$)	~ 85	~ 0.0094	6.5 – 9.5
1.67	Hydroxyapatite (HA, HAp or OHAp)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	~ 0.0003	9.5 – 12
1.67	Fluorapatite (FA or FAp)	$Ca_{10}(PO_4)_6F_2$	120.0	~ 0.0002	7 – 12
1.67	Oxyapatite (OA, OAp or OXA)[f], mineral voelckerite	$Ca_{10}(PO_4)_6O$	~ 69	~ 0.087	[a]
2.0	Tetracalcium phosphate (TTCP or TetcP), mineral hilgenstockite	$Ca_4(PO_4)_2O$	38 – 44	~ 0.0007	[a]

[a] There is no precipitation of this type of compound from aqueous solutions.
[b] It is not possible to measure precisely. Still, the following values were reported: 25.7±0.1 (pH = 7.40), 29.9±0.1 (pH = 6.00), 32.7±0.1 (pH = 5.28). In the acidic buffer, ACP dissolves more readily than α-TCP >> β-TCP > CDHA >> HA > FA.
[c] Stable at temperatures over 100°C.
[d] Metastable at all times.
[e] The precipitated HA may also be called PHA (precipitated HA).
[f] There is some doubt regarding the existence of OA.

TISSUE ENGINEERING

Repairing tissues and organs has been the goal of surgery from antiquity to the present [6, 7]. This repair has traditionally taken place in two main ways: organ transplantation followed by tissue transplantation and replacement with allogeneic or synthetic materials. It is clear that both approaches have some limitations. Transplantation requires a second surgical site that can lead to morbidity, and organ transplants are in particular constrained by the limited amount of available material. The poor integration of synthetic materials with host tissues may lead to failure after implantation because of wear, fatigue, or adverse reactions inside the

CHAPTER 9

Carbon-Nanostructures for Tissue Engineering and Cancer Therapy

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Abstract: Carbon nanostructures have enticed significant attention in biomedical areas over the past few decades owing to their unique electrical, physical, and optical features, biocompatibility, and versatile functionalization chemistry. These nanostructures can be categorized into diverse groups based on their morphology, including fullerenes, nanotubes (*e.g.*, single-walled carbon nanotube (SWCNT) and multi-walled carbon nanotube (MWCNT)), nanodiamonds, nanodots, graphite, and graphene derivatives. Emerging biomedical trends indicate the usefulness of carbon nanostructures in gene/drug delivery, cancer theranostics, and tissue engineering and regenerative medicine, either alone or in combination with other biocompatible materials. This chapter presents a comprehensive overview of various types of carbon family nanostructures and their characteristics. We further highlight how these properties are being utilized for various medical applications.

Keywords: Biocompatibility, Biomedical imaging, Cancer therapy, Carbon nanostructure, Drug delivery, Gene delivery, Graphene, Graphite, Fullerenes, Multi-walled carbon nanotube (MWCNT), Nanodiamonds, Nanodots, Scaffold, Single-walled carbon nanotubes (SWCNT), Tissue engineering.

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INTRODUCTION

In recent years, the rapid advances in the nanobiomedical research, mainly the utilization of engineered nanomaterials have fetched many fascinating ideas and opportunities to diagnose and treat diseases and utilization in tissue engineering applications [1]. Nanostructures are materials with different structures that have at least one dimension in the range of nanometers (1-100 nm). Self-assembly of nanomaterials is a common phenomenon in nanotechnology and refers to a spontaneous assembly of components to form an intricate nanostructure without significant external intervention [2]. Since it provides the direction for the aggregation of very small structures, this phenomenon is extremely useful to reform individually into organized patterns that often give different roles to the materials. Several factors can affect self-assembly such as particle size, particle shape, and their interactions [3]. On this point, self-assembled nanomaterials demonstrate a typical mechanism of induced noncovalent interactions [4]. These nano-assembled structures were applied to create nanostructures of hierarchical protein, one-dimensional (1D) structures (nanowires/strings/tubules), two-dimensional (2D) structures (networks/nanorings), and three-dimensional (3D) structures (crystalline frames and hydrogels) [5]. The most fundamental self-assembled 3D nanostructures are primary forms of carbon materials that play a crucial role in the development of the latest nanotechnologies with suitable mechanical and multifunctional surface properties, outstanding optical activity, and high aspect ratio [6, 7].

Elemental carbon continues to astonish with the bonding diversity that leads to its different forms with distinct physico-chemical, mechanical, and biological characteristics. Nano-carbons are regarded as artificially composed structures with a modifiable construction since the 1990s following their discovery [8 - 10]. Carbon is a very adaptable material with a wide range of arrangements and allotropes (clusters, crystallites, or molecules) (Table. **1**). The hybridization of carbon (sp3, sp2, and sp1) and its bonding around the atoms determine the kind of allotrope. All allotropic modifications of carbon are formed on a nanometer-scale and independent of their synthesis methods. Carbon nanostructures (CN) or nano-carbons consist of sp^2 carbon atoms with different spatial arrangements and mainly include fullerenes (F, 0D), carbon nanotubes (CNT, 1D), graphene (G, 2D), and graphite/diamond/Mackay crystals (3D) (Fig. **1**) [11]. In addition, carbon nanocones, carbon nanohorns, carbon nanofibers, carbon nano-onion, carbon nanodot, nanocraters, and nanoscale carbon toroidal structures are other known structures of nano-carbons [12].

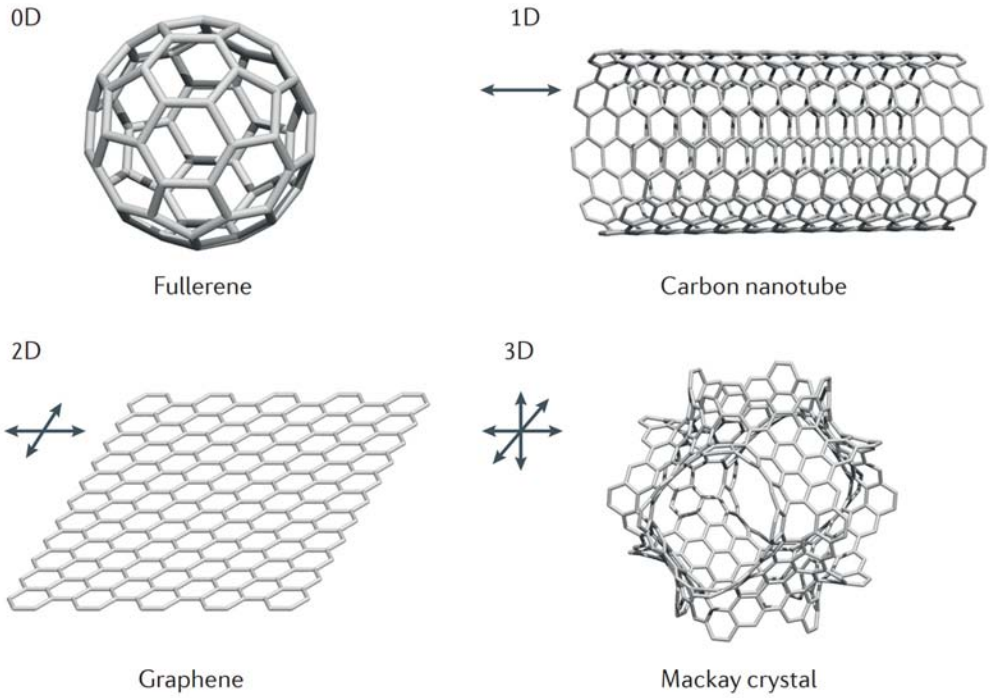

Fig. (1). Classification of typical nano-carbon structures based on their dimensions. Fullerenes **(0D)**, carbon nanotubes **(1D)**, graphene **(2D)** and Mackay crystals **(3D)** represent. Reproduced from [16].

There are several approaches for the synthesis of nano-carbons which are divided into two main classes the bottom-up and top-down approaches [13 - 15]; however, currently applied methods result in mixtures of particles with a range of structures and characteristics. Thus, a big challenge in the field of nano-carbon science is to obtain pure nano-carbons and the ability to synthesize structurally uniformed nano-carbons, ideally as single molecules, which is critical for the progression of functional materials. In this regard, organic synthesis (bottom-up construction) is a promising approach to attaining precise nano-carbons with atomic design [16]. These carbon-based nanostructures, which display unique forms and features, are practical in numerous biosystems like nanocarriers, diagnostic probes, and biomarkers for adjusting and controlling biological processes at the cellular and subcellular level [17 - 19]. Moreover, manufactured carbon nanomaterials, including fullerenes, carbon nanotubes (CNTs), and graphene, are very useful for several medical applications such as nanomedicine and drug/gene delivery [20]. Interestingly, several studies have also shown the feasibility of particles prepared using this method in tissue regeneration (*e.g.*, the skin, cartilage, bone, heart,

CHAPTER 10

Advances in Polymer/Ceramic Composites for Bone Tissue Engineering Applications

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Abstract: Tissue engineering and regenerative medicine have accomplished enormous progress in the last few years. The application of recently designed nano-textured surface characteristics has shown increased enhancement in bone tissue regeneration. The development of materials that fulfill the exact requirements of bone tissue is still under investigation. However, we are approaching this aim. Composite materials are some of those materials under consideration, and they have emerged as a consequence of the logical unraveling of bone composition. Principal components of bone tissue are inorganic and organic matrices and water, in other words, ceramics and polymers. Accordingly, the design of these materials by combining different types of ceramics and polymers has opened a wide range of possibilities for bone regeneration treatments. Not all polymers nor all ceramics can be used for this purpose. Materials must gather particular properties to be applied in bone tissue engineering. Both types have to be safe, which means biocompatible and non-toxic. They, additionally, should have efficient surface behavior, bioactivity, and suitable mechanical properties. Sometimes, composites could behave as *in situ* drug delivery systems. Composites are engineering materials formed by two or more components, each bringing a unique physical property, and generating synergism. For these reasons, in this work, we will discuss features of host tissue, concepts such as bioactivity, osteoconductivity, and osteoinductivity, and the most significant polymers and ceramics used for developing composed materials. Finally, we focus on examples of composite materials based on these components applied for bone tissue regeneration.

Keywords: Alginate, Bioactive glass, Bioactivity, Bioadhesive, Biocompatible, Biodegradability, Bone pathologies, Bone tissue engineering, Calcium phosphate, Collagen, Compact and spongy bone, Gelatin, Hyaluronic acid, Hydroxyapatite, Non-immunogenic, Non-toxic, Polycaprolactone, Polymer/ceramic composites, Tunable properties.

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Saeid Kargozar and Francesco Baino (Eds.)

INTRODUCTION

Scientists have worked, for years, using different materials to improve the life quality of people with bone pathologies. These pathologies can be produced by illnesses, accidents, or attributes of aging of human beings. It would be desirable that the properties of materials can be tunable for the different requirements considering the type of pathology, the type of bone, that means long, short, or flat, and the features of the tissue sponge or compact [1].

Autografts have been frequently used strategies for addressing bone defect treatments. It is referred to transplant from one part of the body to another zone of the same patient. Autograft is an optimal material because it provides an osteoconductive surface and contains cells that contribute to the osteointegration process. However, autografts are not osteoinductive in a not orthotopic site because they are reabsorbed. In the orthotopic zone, they also exhibit reabsorption, but their osteogenic properties are enough for bone regeneration. A limited quantity of bone is obtained, with pain or loss of sensitivity in the donor site, and the risk of infection are some disadvantages of autografts. Consequently, allografts (same species), xenografts (different species), and later synthetic bone substitutes have become alternative strategies to overcome these situations [2, 3]. In this work, we will focus on this last strategy.

When we talk about bone pathologies, we immediately think of the bones of the legs or arms, which is correct. However, some particular treatment features are shown in bones containing teeth as short dimension defects and a low quantity of materials applied. Therefore, these materials can be applied for the potential treatment of moderate and severe periodontal disease and require a special section [4]. It is crucial to define the strategic approach for addressing these problems. Many different materials, such as implants based on metals or smart gels, have been proposed for treating bone pathologies [5]. Among those materials, composite materials have been widely spread during the last years [6]. The treatment of several bone-related disorders, diseases, or ailments has been addressed using biodegradable polymer-ceramic composites materials. Therefore, materials used for bone reparation or as filler materials have evolved from inert materials to those that strongly interact with the tissue, and thus, they achieve tissue requirements [7, 8].

Bone is a natural composite material formed by 55-70% (w/w) of inorganic components, 20–30% (w/w) matrix, and 10–20% (w/w) water. The main inorganic mineral constituent of bone is a substituted calcium phosphate with similar composition and structure to hydroxyapatite [9]. The organic component is formed by highly aligned triple helix type I collagen fibrils. The inorganic

component provides mechanical properties to the bone, and the organic one offers flexibility [10]. By observing this natural structure, it is possible to propose the development of materials based on organic (or blends) and inorganic components (or combinations) for application in bone tissue pathologies. Consequently, for obtaining the materials and tailoring their properties, tissue engineering has emerged as a new discipline combining biological and engineering principles for creating a new organ or repairing and promoting the regeneration of damaged tissue. Today, regenerative medicine is applied in cardiovascular, nervous, musculoskeletal, and orthopedic therapies [11].

The first section of this work describes the structure of bones, functions, and formation. The second section addresses bone tissue as a nanostructured material. This view depicts principal architectures, compositions, and sizes that must be considered for designing bone tissue implants or devices. The third section shows an overview of the main types of biomaterials, their features, and concepts such as bioactivity, osteoconductivity, and osteoinductivity. The following section deals with groups of materials such as polymers and ceramics used for developing devices for bone tissue applications. Finally, the remarkable composite materials used for bone tissue engineering are described.

Bone Structure and Mechanical Properties, Functions and Formation

Structure and Mechanical Properties

Two types of bone are recognized: spongy, trabecular, or cancellous, and compact, cortical, or dense. This last type is mainly limited to the external shell of the bone or cortex. Cortical bone is composed of osteons. These are a group of cylindrical structures constituted by 4 to 20 concentric lamellas oriented following the axis of the bone named Haversian systems. The unit of this system shows a transversal section of 250 μm and encloses the center of the Haversian canal that connects with the narrow cavity. Along this canal passes the neurovascular system [12]. Osteocytes, the living bone cells, are disposed circumferentially around the lamellas in specific places named lacunae. Each bone type (wet human bones) confers different mechanical properties. Three relevant mechanical parameters must be considered, compressive strength, tensile strength, and Young's modulus. The compressive strength in the compact bone of the femur, tibia, and radius varies from 167 to 115 MPa, and for the spongy bone in vertebrae 8.4. The tensile strength for those large bones is from 120 to 150 MPa and 3.7 for vertebrae. Finally, the Young's modulus of compact bone in large bones is from 17 to 19 GPa [10].

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