EMERGING MATERIALS AND TECHNOLOGIES

Calcium-Based Materials

Processing, Characterization, and Applications

Edited by

S.S. Nanda, Jitendra Pal Singh,
Sanjeev Gautam, and
Dong Kee Yi

CRC Press
Taylor & Francis Group

Calcium-Based Materials

Calcium-based natural minerals are important for a wide range of applications. Though these materials are available in nature, researchers are working toward developing them in the laboratory.

Calcium-Based Materials: Processing, Characterization, and Applications introduces the possibility of designing these materials for particular applications.

- Introduces a variety of calcium-based materials and discusses synthesis, growth, and stability
- Provides in-depth coverage of calcium carbonate
- Discusses applications of calcium-based minerals in different fields
- Includes details on synchrotron X-ray tools for case minerals

This comprehensive text is aimed at researchers in materials science, engineering, and bioengineering.

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

Designed cover image: © Sanjeev Gautam

First edition published 2024
by CRC Press
2385 NW Executive Center Drive, Suite 320, Boca Raton FL 33431

and by CRC Press
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

CRC Press is an imprint of Taylor & Francis Group, LLC

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ISBN: 978-1-032-41955-8 (hbk)
ISBN: 978-1-032-41957-2 (pbk)
ISBN: 978-1-003-36059-9 (ebk)

DOI: 10.1201/9781003360599

Typeset in Nimbus Roman
by KnowledgeWorks Global Ltd.

Dedication

Dedicated to the boundless spirit of exploration,
symbolized by smart materials forging new paths in
self-healing bioengineering.
May our quest for knowledge and innovation lead us not
only to reshape our world,
but also to unravel the mysteries of life beyond Earth.

Contents

Preface

Calcium-based natural minerals play a pivotal role across a wide spectrum of applications. While these materials are naturally occurring, ongoing research is dedicated to their laboratory synthesize, enabling tailored designs for specific applications. This pursuit explores the potential for optimizing these materials' properties to suit particular purposes.

This book serves as a comprehensive guide to various calcium-based natural materials. It places specific emphasize on calcium-based oxides, carbonates, phosphates, and hydroxides. Within its pages, you will find in-depth discussions on the synthesis, growth, and stability of these materials under diverse processing conditions. The exploration extends to a thorough examination of their applications.

In essence, this book encompasses the following key aspects:

- A comprehensive exploration of the fundamental structure, chemistry, synthesis, and properties of both natural and synthetic calcium-based biomaterials.
- An insightful analysis of their current and potential future applications in biomedical engineering, medicine, and environmental contexts.

The compilation of knowledge within these chapters aims to provide researchers, practitioners, and enthusiasts in the field with an authoritative resource to deepen their understanding of calcium-based biomaterials and to inspire innovative advancements in their utilization.

Editors

S.S. Nanda, PhD, was born in Odisha, India, and earned a BPharm (2007) and MPharm (2009) in pharmacy at Biju Patnaik University of Technology, Odisha. In 2009, he became an Assistant Professor at Vikas College of Pharmaceutical Sciences, Suryapet, Telengana. In 2012, he moved to Gachon University and earned a PhD (2015) in bionanotechnology, working with Prof. Dong Kee Yi. He has authored and co-authored more than 50 peer-reviewed international journal articles and worked as an inventor for one patent. In 2015, he became an Assistant Professor at Myongji University. His research interests include tissue engineering and applications of materials in nanomedicine.

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1 Overview of Calcium-Based Materials

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Nanomedicine and tissue engineering overtures have shown great promise in overcoming the main issue confronting orthopedic trauma, including acute infection risk and low burial reconstruction [1]. Nanoparticles have antibacterial properties and can help heal injured tissue [1]. Recently, nanomedicines have shown osseointegration property and stimulating bone process [2]. These characteristics lead toward essential components of orthopedic surgery [2]. Most of the aging population require orthopedic implants, and its estimation is about 600,000 per annum in the USA. Orthopedic implants help bones to grow and prevent infections [3].

Researchers describe nanomedicine for orthopedics as (i) using scaffold with nanomedicine to repair bone and cartilage defects, (ii) improving osteointegration and reducing biofilm preparation by designing implant surfaces, (iii) prolonging drug delivery systems with chemotherapeutic agents and antibiotics, (iv) delivering controlled drugs to combat infections, and (v) providing diagnostic applications for musculoskeletal infections and oncology [4].

Using gold nanoparticles for drug delivery through nanotechnology has shown promising results. Studies have shown the property of gold in effectively delivering iontophoresis to treat tendinopathy, or the disease and injury to the tendons [5, 6]. Gold nanoparticles and calcium materials together have special properties and uses in various areas. Calcium compounds can influence the structural and mechanical properties of materials. By incorporating them into gold nanoparticle systems, researchers could create materials with improved strength, durability, or other specific characteristics (Figure 1.1).

Selenium nanoparticles have drawn attention as a potential material in orthopedic applications for immobilization and suspension forms [8]. Selenium nanoparticles attributed low toxicity to human cells and served as an attractive antimicrobial agent [9]. Selenium is an essential trace element of human health. Incorporating selenium nanoparticles into calcium-based nutritional supplements could potentially enhance the bioavailability of selenium, leading to improved health benefits. Selenium nanoparticles have been explored for their potential in

DOI: 10.1201/9781003360599-1

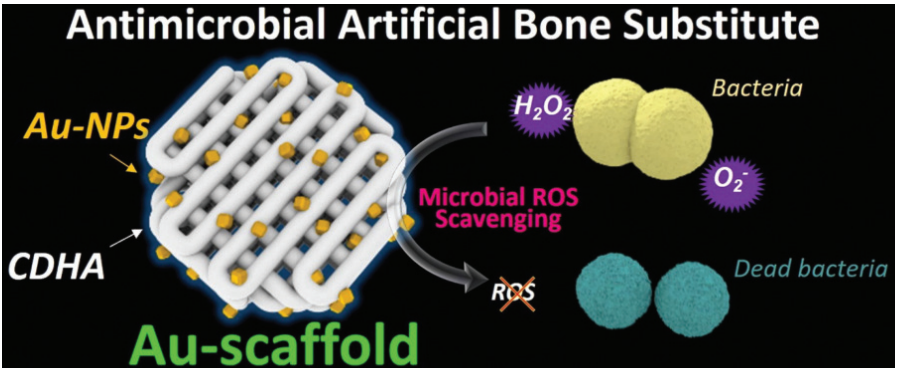

Figure 1.1 Immobilized scaffold with gold nanoparticles (Au-NPs) and ceramic (Calcium-deficient hydroxyapatite, CDHA) worked as a functional bone to antibacterial activity and scavenge microbial ROS at early stages. (Adapted from Reference [7] with permission.)

environmental remediation, such as the removal of heavy metals from water. Combining them with calcium materials might enhance their adsorption capacity and overall effectiveness.

Some examples of these new nanotherapies include a magnetite-hydroxyapatite composite, magnetite-enriched collagen hydroxyapatite biocompatible for bone grafting material, and a three-dimensional (3D) nanomagnetite-chitosan rod for local hypothermia that aids direct bonding to bones [10–12]. Nanotechnology for targeted drug therapy incorporated smaller particles (i.e., silver) into nanostructured materials, through the use of large particles (i.e., growth factors) into nanostructured materials [13–15]. Hydroxyapatite and tricalcium phosphate are extensively utilized as substitutes in bone grafting procedures to promote bone regeneration and support the seamless deposition of new bone tissue in the treatment of bone defects. It can make the entire artificial graft of HA or use HA as a surface coating. But there are high chances of rejection and donor incompatibility. To address these issues, researchers have explored the use of organic/inorganic composite materials that behave similarly to real bones. The combination of the inorganic phase along with the polymer component results in a better biomaterial. The inorganic phase provides strength and structural integrity to the material, allowing it to withstand mechanical stresses and maintain its shape. On the other hand, the polymer component adds toughness and flexibility, enabling the material to resist any deformation under impact or bending forces. Among all the forms of CaP, HA has the slowest degradation rate and excellent osteoconductive properties, and thus it is most preferred for bone grafts. Kim et al. [16] showed that a bone scaffold with up to 70% hydroxyapatite performs better. One approach to fabricating nano-hybrid bone tissue scaffolds involves in situ crystallization of HA within the structure of the polymer scaffold or by incorporating it into the scaffold via 3D printing techniques [17, 18]. Three-dimensional printing technology has also been utilized for the production of complex structures based on medical imaging, enabling the creation of personalized implants or grafts. In addition, these scaffolds can be used for localized drug delivery, which are then released in a controlled manner at the site of implantation or tissue regeneration. It is widely being used for visualization of damaged tissue. Martinez-Vazquez et al. [17]. formed porous silicon containing hydroxyapatite scaffolds using a 3D printing technique, for delivery and controlled release of vancomycin in short time.

1.1 CONCLUSION

Research has focused on developing osteoconductive materials for bone remodeling, as existing materials do not show the osteogenic properties required for bone regeneration. The mesenchymal stem cells derived from bone marrow play a crucial role in tissue repair due to their differentiation and regeneration abilities. Efforts are also being made to load bone scaffolds with drugs and use them for their controlled and effective release in damaged tissue without affecting the live tissue. Furthermore, the incorporation of magnetic materials with calcium phosphate nanoparticles into bone scaffolds has shown promise in promoting bone healing, particularly when combined with external stimulation (Figure 1.2). Overall, advancements in calcium-based biomaterials, including composite scaffolds and 3D printing technology, hold significant potential for orthopedic, dental, and oral surgery applications. These innovations in calcium-based biomaterials aim to improve the compatibility, functionality, and therapeutic effectiveness of bone grafts and implants.

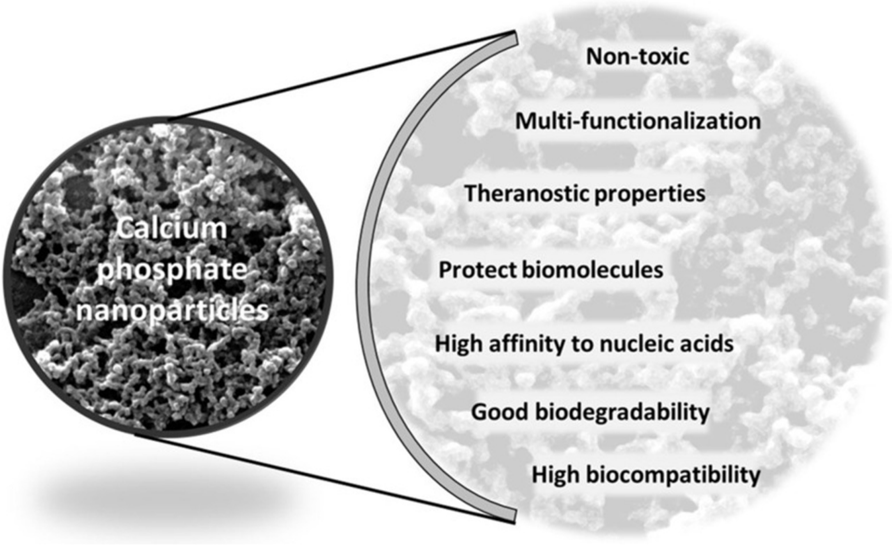

Figure 1.2 Benefits of calcium phosphate nanoparticles as a carrier system. (Adapted from Reference [19] with permission.)

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2 Calcium Phosphate

Synthesis and Applications

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2.1 INTRODUCTION

Biomaterials are man-made substances designed to function in intimate contact with biological systems and are utilized in therapy and diagnosis applications in treatment of diseased living tissues and organs. In an ideal scenario, a biomaterial intended to replace natural tissue should closely match its properties while ensuring the absence of any unwanted harmful effects within the living system.

Various calcium phosphate (CaP)-based synthetic biomaterials, like hydroxyapatite (HA), biphasic calcium phosphate (BCP), and tri-calcium phosphate (BCP) are extensively studied in the biomedical field. Trauma, osteoporosis, osteoarthritis, and surgical procedures are responsible for a significant number of musculoskeletal diseases, making it the second most prevalent cause of disabilities globally, as recognized by World Health Organization (WHO). Statistically, approximate 2.2 million individuals undergo bone grafting procedures annually for the treatment of bone regeneration and defects due to accidents, trauma or tumor resection but the absence of adequate bone replacement facilities has resulted in the loss of 1.2 million lives. Additionally, data suggests a global demand for dental implants in the range 10,000–30,000 annually [1, 2].

Hard tissues, like bone and teeth, exhibit a high degree of mineralization. The mineral content in bone and dentin ranges from 45% to 70% by weight, while enamel reaches an impressive 96% by weight. The mineral phase of hard tissues is referred to as bioapatite which is a naturally occurring form of calcium phosphate found in biological systems. Its chemical formula ($Ca_5(PO_4)_3(OH)$) is similar to the hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). The nature of the apatite phase found in bone mineral is nonstoichiometric. Bioapatite consists of various cations and anions like Sr^{2+}, Mg^{2+}, Na^+, K^+, Cl^-, F^-, CO_3^{2-}, etc. but it is OH^- deficient. These bioapatite crystals are made up of smaller units called crystallites. The size of these crystallites can vary among individuals depending on factors such as age and genetics. For ages

DOI: 10.1201/9781003360599-2

0–25, the individual crystal domain within the bioapatite mineral structure has a diameter of approximately 28 nm. The chemical structure of natural bone mineral, at the nanolevel, consists of inorganic calcium phosphate based hexagonal apatite-like structures and organic collagen bone matrix. These components combined provide the bone its strength and flexibility.

Its similarity with natural bone mineral has made it perfect for bone-tissue engineering applications [3]. It has many uses in toothpaste and pharmaceutical industry.

The second most studied bioceramic after HA is tricalcium phosphate(TCP). In nature, there are two stable polymorphs of tri-calcium phosphate called β and α-TCP. Out of these, β-TCP is more stable at ordinary temperature and exhibits a rhombohedral symmetry group. Due to high reactivity of α-TCP at high temperatures, β-TCP converts to α-TCP at around 1125 °C. However, the third polymorph, α'-TCP, is highly unstable and is of limited practical significance as it is only observed at temperatures exceeding 1430 °C and rapidly converts back to α-TCP upon being cooled below the temperature threshold [4].

Biphasic calcium phosphate(BCP), which is the combination of HA and β-TCP, is considered a better option for biomaterials. However, one major limitation of BCP, is its poor functional and mechanical properties. To address this drawback, extensive research has been conducted on the isomorphic substitution of various ions within the lattice structure of HA and TCP. This approach aims to overcome the limitations and enhance the properties of BCP.

Another form of calcium phosphate studied is tetracalcium phosphate (TTCP) which is found as the mineral "hilgenstockite" formed in the industrial slag. It has a monoclinic crystal structure and contains calcium, phosphate and oxide ions. It is represented by the chemical formula $Ca_4(PO_4)_2O$. This compound is not very rich in phosphorus. It is formed through a high temperature solid-state reaction at 1300 °C. It involves the combination of calcium oxide (CaO) and phosphorus pentoxide (P_2O_5) ions in an oxygen rich and high temperature environment. The unique feature of TTCP is its higher Ca/P ratio compared to hydroxyapatite(HA). It is commonly used to obtain composite coatings by plasma spray technique. TTCP reacts with acidic calcium phosphates like dicalcium phosphate anhydrous (DCPA, monetite) or dicalcium phosphate dihydrate (DCPD, brushite) and gets completely soluble simultaneously to form HA as the end product. Due to these properties, TTCP is used for bone repair and regeneration as it forms a crucial component in self-setting cements. Upon contact with the physiological environment, the cement undergoes a setting reaction that transforms it into a calcium phosphate based matrix, that gradually hardens and has similar properties with natural bone. TTCP is a metastable compound as its synthesis is done in a controlled environment with low humidity or in a dry atmosphere to maintain its stability. One way to achieve this is through fast quenching, which involves rapidly cooling the synthesized TTCP to room temperature after the calcination process. This prevents it from transforming into HA and lime. Another approach to prevent decomposition is by ensuring the absence of moisture during the synthesis process. Moisture can trigger the hydrolysis of TTCP, leading to the formation of HA and lime [5].

$$3Ca_4(PO_4)_2O + H_2O \rightarrow 2Ca_5(PO_4)_3OH + 2CaO \tag{2.1}$$

The pursuit of artificial bone substitute materials has been a driving force behind substantial advancements in the field of biomaterials. Both biological and synthetic bone grafts can be used for bone grafting and hard bone tissue restoration and regeneration therapies. Biological bone graft materials are biocompatible materials derived from natural sources used to promote bone healing. They are broadly classified into three types:

- *Autografts*: The grafts used are extracted from the patient's own body, mostly from the iliac crest.
- *Allografts*: The bone scaffold is made using hard tissues of a donor, generally obtained from cadavers.
- *Xenografts*: The grafts are derived from different species, mainly animals.

While biological materials closely mimic the properties of natural bone, there is always a high risk of immunorejection and microbial contamination. Also, there is a very limited supply of biological materials.

Synthetic bone graft materials are artificially created materials that are designed to mimic the properties of natural bone and promote bone regeneration. These synthetic implant materials are of three types (Figure 2.1).

First-generation materials, such as titanium or stainless steel, are bioinert, that is, they generate limited response to the presence of foreign implants while second generation materials like calcium phosphate based materials, form covalent or other types of chemical bonds with surrounding living tissues and are bioactive. In contrast, third generation materials interact with cells at a highly intricate level, influencing their behavior and functions at a molecular scale. They can actively promote desired cellular responses such as proliferation, differentiation, migration, and tissue regeneration.

2.2 OVERVIEW: CALCIUM

2.2.1 STRUCTURE

Calcium phosphate refers to a group of compounds composed of calcium ions (Ca^{2+}) and phosphate ions (PO_4^{3-}). The crystal structure differs as the stochiometric ratio of calcium phosphate changes.

HA exists in two phases- hexagonal and monoclinic. Hexagonal phase is preferred more as it has more resemblance with natural bone mineral. It has hexagonal shaped nano-crystallite structure. Researchers are aiming to achieve a material that closely mimics the characteristics of natural bone tissue by synthesizing heavily ion-doped HA as Hydroxyapatite is capable of preserving its crystal symmetry when the calcium-to-phosphorus (Ca/P) molar ratio remains at 1.3, compared to the ideal Ca/P ratio of 1.67. HA crystal can be doped with multiple ions and elements by replacing

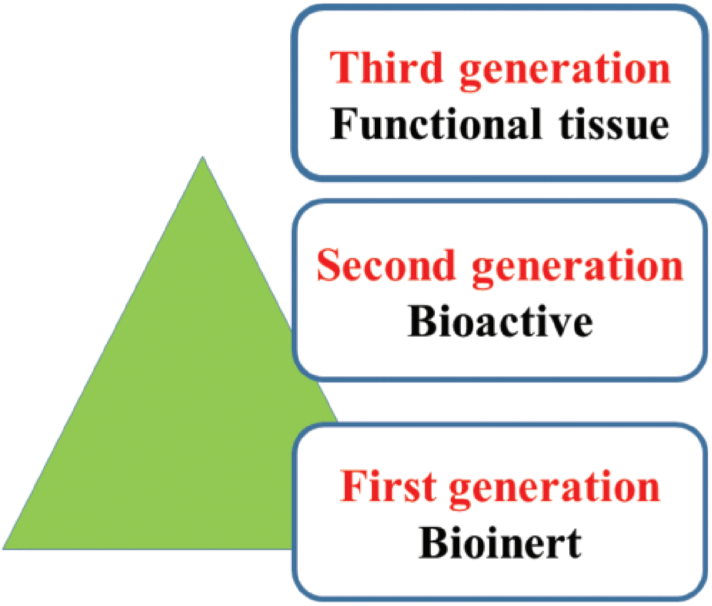
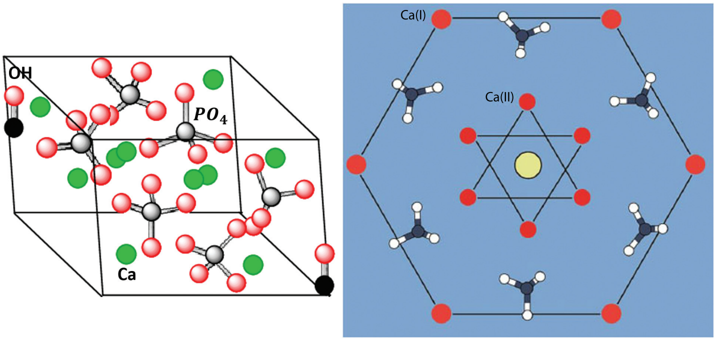


Figure 2.1 Different generations of synthetic implant materials [3]. (Adapted with permission from Wu *et al. J. Hazardous Mater.* 387, 2020. Copyright 2020 Elsevier.)



(a) (b)

Figure 2.2 (a) Crystal structure of hydroxyapatite. (b) Typical diagram of unit cell of hydroxyapatite with hexagonal phase [6, 7].

calcium ions with cations, and phosphate or hydroxyl ions by anions. The hexagonal HA exhibits *P63/m* symmetry (Figure 2.2) with specific locations for two different Ca atoms while monoclinic HA possesses *P21/b* crystallographic symmetry [6]. Ca(I) atoms have simple cubic structure and are positioned only at the edges, while Ca(II) atoms form an equilateral triangle with the ion channel at the center of the unit