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Research Article

Hydroxyapatite: A Comprehensive Review of Its Properties, Applications, and Future Trends

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Abstract

Hydroxyapatite (HA) is a bioactive ceramic material which has given an important attention in the biomedical field because of its high biocompatibility and structural similarity to human's and mammal's bone. This study provides a comprehensive exploration of HA's properties, applications, and future trends, accentuating its potential in several domains beyond its traditional uses in bone and dental implants. HA's unique characteristics, including its osteoconductivity and ability to promote bone regeneration, make it an ideal candidate for advanced tissue engineering and drug delivery systems. The review discusses the fundamental properties of HA, such as its chemical composition, physical structure, and biological compatibility, which collectively contribute to its effectiveness in medical applications. Furthermore, ongoing research is highlighted, particularly in the development of nanostructured HA and composite materials, aimed at enhancing its mechanical properties and expanding its use in complex medical scenarios. Additionally, the implications of emerging technologies, specifically 3D printing and the potential of 4D printing, are examined. These innovations allow for the creation of personalized scaffolds tailored to individual patient needs, enhancing the prospects for regenerative medicine. The versatility of HA is further illustrated through its applications in non-medical fields, including environmental remediation and as a component in fertilizers and water purification systems. Overall, this review underscores the critical role that hydroxyapatite plays in bridging the gap between biological and synthetic materials. By synthesizing current knowledge and identifying future research directions, this work aims to pave the way for further advancements in the use of HA across various biomedical and industrial contexts, ultimately contributing to improved health outcomes and innovative material solutions.

Keywords

Hydroxyapatite, Biocompatible, Tissue Engineering, Drug Delivery System

1. Introduction

Hydroxyapatite (HA) is a non-toxic and bioactive ceramic material with a structure similar to human bone and teeth. [1] Because of its osteoconductive, bioactive and non-toxic characteristics, hydroxyapatite (HA) can establish chemical

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bonds with living tissues. [2] Although HA is found in nature as calcium apatite, this form cannot be used in the biomedical field and needs to be chemically synthesized to meet certain properties, including, purity and crystal size and morphology.

In this study, we will thoroughly explore HA fundamental properties, application in various fields, and the future trends in development and research. In this study, we will thoroughly explore HA fundamental properties, application in various fields, and the future trends in development and research.

2. Properties of Hydroxyapatite

Before using any biomedical materials in medical applications, there is a need for thorough understanding of their biological, chemical, mechanical, physical, and structural properties. As a crucial component in the calcium orthophosphate group, HA depicts good biological and dielectric compatibility, thermal stability, bioactivity, osteoconductivity, and diamagnetic behavior. [3] Since it has a chemical composition similar to teeth and bones, HA has the potential to be used as implantation in fractured parts of the human skeletal system, however, it has a poor mechanical characteristic and hence it is rarely used in orthopedics. [4] Another interesting property of HA is that it can swap its ions with different foreign ions which can potentially improve its biocompatibility, microstructure, and mechanical properties. Because of HA high biocompatibility, bioactivity, and osteoconductivity, it rarely can be rejected by the human body when used as implantable material. [5] It has also been proved that HA can increase the catalytic surface areas hence enhancing the absorption of pollutants and catalyzing their breakdown. [6] These properties influence how HA is applied in various fields and also act as a limitation from being employed in some other disciplines.

2.1. Chemical Composition and Structure

As a naturally occurring mineral, HA has a typical apatite lattice structure with a chemical formula represented as- $Ca_{10}(PO_4)_6(OH)_2$ which shows that its crystal cell consists of two entities. [7] The mineral crystallizes in a hexagonal crystal system (Figure 1). [8]

HA is composed of calcium phosphate that is crystalline structured to provide stability and strength. The recommended stoichiometric ratio of calcium to phosphate is 1.67, and it is significant in upholding its biological function. [7] It is important to note that in HA, the hydroxyl group can be replaced with chloride, carbonate, or fluoride to form non-stoichiometric minerals, chloropatite, or fluorapatite. [9] When hydroxyapatite is heated, it breaks down forming beta-tricalcium phosphate, water, and tetracalcium phosphate ($Ca_4P_2O_9$). When exposed to higher temperatures, tricalcium phosphate starts to transition from beta- to alpha-phase. At 800 degrees Celsius, hydrated calcium phosphate (hydroxyapatite) starts dihydroxylation to form oxyhydroxyapatite ($Ca_{10}(PO_4)_6(OH)_{2}$-2xOxYx where Y is a vacancy. [10] The magnetic nature of HA depends on the composition of iron present. Therefore, it is these chemical compositions that make HA useful in various disciplines such as dentistry, chromatography, archaeology, and defloration. [11]

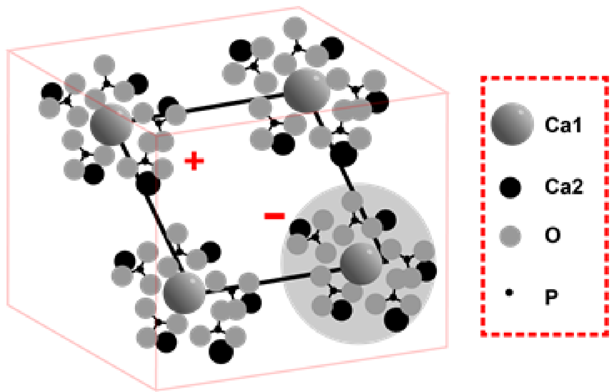

Figure 1. *Schematic representation of hexagonal structure of hydroxyapatite. [Treboux et al. 2000].*

2.2. Physical Properties

HA exhibits a high affinity for living organisms and organic compounds. This physical property is crucial as it facilitates wastewater treatment and remediation of the environment. [12] This property also is key component in cancer treatment through targeting therapies. [13] Although mechanical properties of HA are different from those in bone material, it is used to cover titanium implants because it offers better adhesion and supports bone cell reproduction on its surface. [14] In addition, HA has low solubility and long degradation ratein physiological conditions, making it good candidate for implantable applications. [15] Due to its porous nature, HA supports nutrient exchange and cellular infiltration and this makes its a preferred component in bone tissue engineering. [16] Naturally occurring HA is comprised of impurities hence it is dependent on supplying phosphate and other phosphorus-containing compounds. While HA binds directly with the body catalyzing bone formation, it is weak and hence needs to be combined with biopolymers like polyethylene glycol for strengthening. [17]

2.3. Biological Properties

The calcium phosphate found in HA has made it a significant material due to its effective ability to initiate osteoblast differentiation into bone cells. Researchers have established that its composition is similar to that of human bones or teeth and hence its application in medical treatments involving orthopedics. [18] HA shows great osteoconductive and vasculogenesis properties making it an effective material for forming strong bonds with the host bone and initiating vascular formation. In addition, it is highly biodegradable meaning that when implanted in the human body, it dissolves with time and this prevents the stress shielding effect. [19] Moreover, the osteoconductibility nature of HA allows bone conduction which is the process by which bone tissues grow in the internal pore or along the surface of the surface of the implant. Another biological property is that HA has osteoinductive properties that take part in stimulating and recruiting immature cells to develop into preosteoblasts. [20] This is a critical property that supports the healing of fractured bones through osteoinduction.

3. Application of HA

3.1. Biomedical Application

HA has become a crucial component in the biomedical field, especially in the treatment of bone fractures and bone-related diseases. In the case of bone fractures, the use of metal for repairs comes with complications of allergy due to rejection. However, HA is the preferred component due to its biocompatibility with the body hence reducing human body rejection. [21] Since human bones and teeth are made of HA, it is used as a filler in dental clinics. Moreover, it is used in cancer treatment through nanohydroxyapatite which acts as a highway for anti-tumor drugs. [22]

3.1.1. Bone Regeneration

The increasing bone disease and abnormalities lead to bone loss as they become weak hence easily breaking when less energy is exerted on them. HA plays a role in bone regeneration which is the process by which a bone regains its functionality without the formation of a scar. [23] HA supports osteoinduction and osteoconduction. In other words, HA boosts bone regeneration hence playing a part in bone repair. It is also used widely by healthcare professionals in various treatments by combining HA with synthetic polymers in a bid to imitate natural structure of bones. [21]

3.1.2. Dental Applications

While many people suffer from untreated dental decay-globally, the use of HA toothpaste has been effective in preventing dental carries. [24] Even though fluoride has been used as a primary prevention mechanism for dental caries, there has been an increased need to have an alternative product due to a general dislike and the risk of fluorosis among children. [25] As a result, HA-containing toothpastes have become the preferred alternative because they are fluoride-free and are friendly to children. In addition, HA is used as a dental filler due to its biocompatibility properties. Therefore, HA is widely used in dental repairs and in toothpaste since it eliminates fluoride and also prevents dental caries and decay (Figure 2). [26]

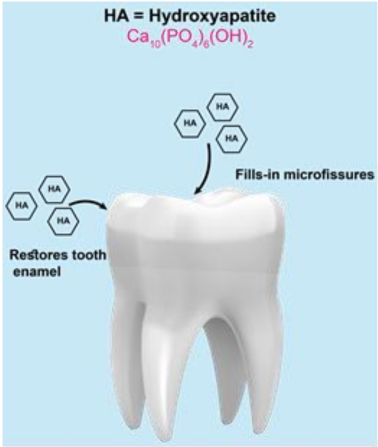

Figure 2. *Hydroxyapatite importance in oral health. [Meyer at el. 2022].*

3.2. Non-Medical Applications

HA is not only used in the medical field but also in industries. Other applications include environmental remediation, production of drug carriers and fertilizers, water purification, and in gas sensing. This shows that HA has a wide range of applications and is a component depended upon in various processes.

3.2.1. Environmental Remediation

HA is widely used for contaminant removal because it is made up of calcium phosphate minerals that is inorganically biocompatible. [27] Its composition is particular in that specific methods such as wet methods, dry methods, and high-temperature processes can be produced from biogenic sources in conjunction with the highlighted methods. The applied HA synthesis route leads to variance in its porosity and this influences its absorption properties. In addition, HA is preferred for environmental remediation since it is available in bulk, its mineral composition, and its durability in that it can be used without losing its functionality, acid-based ion exchange capability, and thermal stability. [28] These properties are crucial since they are responsible for absorbing many contaminants like heavy metals, dye, and fluoride in the water. In addition, HA is used in contaminant immobilization through calcium ion substitution, dissolution-precipitation, sorption-ion exchange, and adsorption. [29] When HA is combined with other materials, its adsorption potential is enhanced.

3.2.2. Drug Delivery System

HA is a biomaterial in the sense that it can replace a material or a part of a living system targeted to be in direct contact with living tissues. Bioceramics have high mechanical strength, biocompatibility, and chemical stability. HA is a bioactive ceramic that is osteoconductive and biocompatiblehence can easily lead to the development of direct bonds with living cells. [30] While there is controversy over the safety of nanoparticles, biocompatibility and biodegradability of HA are preferred over other nanoparticles. HA also has a higher biocompatibility and pH-dependent dissolution than polymers. In addition, it is more stable than micelles and liposomes which tend to lose their properties under certain concentrations. [31] Further, it is less toxic than SiO_2, TiO_2, carbon nanotubes, quantum dots, and magnetic particles and is soluble. All these factors coupled with being the most stable CaP, then it is considered to be a suitable drug carrier.

4. Future Trends

In the recent past, bone tissue engineering has gained popularity and attracted interest amid the increasing cases of tissue damage and degenerative diseases. As a result, with the improved technology, HA will be used to provide personalized medicine through the advancement of 3D printing. Researchers are also finding ways of improving the mechanical properties of HA through nanostructured hydroxyapatite.

4.1. Nanostructured Hydroxyapatite

Nanostructured HA has drawn much interest due to its potential to be applied in catalysis, nanofluids, imaging, data storage, colloidal photonics, and environmental remediation. In addition, research is ongoing on the possibility of using nanostructured HA in biomedical applications in fields like nano-medicine and regenerative medicine while utilizing its magnetic properties. [32] Moreover, nanostructures HA development can increase HA surface area hence enhancing its biological performance and mechanical properties. Since HA is applied in drug delivery, nanoparticles could enhance the process and its application in regenerative medicine. According to Calabrese et al given the effectiveness of nano-functionalization and the significant antibacterial properties depicted by HA scaffolds, future developments will concentrate on coming up with nano-functionalized scaffolds that meet both osteo-regenerative and antimicrobial properties. [33]

4.2. Composite Material

The bone tissue is made of a hierarchical hybrid nanocomposite inorganic HA phase and the organic extracellular matrix is organized in a structure that is porous and complex in nature. They help HA in enhancing its mechanical properties to expand its scope of application in fields like tissue engineering. This can contribute immensely to bone fracture fixation, joint replacement, and deformity correction since these are problems that are primarily unmet in medicine. [2] Autografts and allografts are the current treatment plans for bone repair. Understanding the combination of HA with composite material and the various chemical and biological factors influencing bone tissue can help develop synthetic bone scaffolds that are designed with special structures and compositions to facilitate the formation of new tissue. [34]

4.3. 3D Printing

The 3D printing technology facilitates the development of tailor-made scaffolds that meet individual needs of patients, however, technology produces microstructures that are stationary posing some limitation of HA full potential. The alternative is improving to 4D printing technology which has the potential to create sophisticated and spontaneous structures that can change and react in various ways when outside the stimuli. [35] Therefore, the adoption of 4D will improve its capability beyond 3D technology.

5. Conclusion

In conclusion, hydroxyapatite (HA) is a remarkable compound with notable biocompatibility, making it well-suited for medical applications such as bone fracture repair and dental treatments. The primary components of HA, calcium and phosphate, provide it with excellent mechanical properties, including low solubility and high compressive strength. The porous structure of HA supports nutrient exchange, making it ideal for bone tissue engineering and bone regeneration. Other applications such as its use influoride-free toothpastes, water purification, and environmental remediation highlights its versatility. Looking ahead, advancements such as 4D printing technology and nanostructured HA promise to further enhance its applications, particularly in drug delivery. Continued research and exploration of potential of HA across various fields are crucial, given its proven significance and evolving capabilities.

Abbreviations

HA	Hydroxyapatite
3D	Three-Dimensional
4D	Four-Dimensional
Ca	Calcium
PO_4	Phosphate
Osteo	Related to Bone

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography

Ibraheem Redhwi is a senior researcher at King Abdullaziz City for Science and Technology (KACST), Advanced Material Institution. He completed his PhD in Nanomanufacturing from Iowa State University in 2021, and his Master of Engineering in Robotics from the Vanderbilt University in 2015. Over the last 14 years, Dr. Ibraheem has been working in many research projects that contribute to several mechanical engineering fields with KACST, Vanderbilt, and Iowa State University. In addition, he participated in many collaborations in the United States and Saudi Arabia. His experimental work contributes also and some mechanical engineering fields in addition to other fields like electrical engineering, education, and management.

Fahad Alshabouna earned his undergraduate degree in chemical engineering from King Saud University (KSU), where he also completed a master's in polymer engineering. Acknowledging his capabilities, he pursued further studies at Imperial College London, obtaining his PhD in the bioengineering department. His doctoral research centered on creating thread-based wearable and implantable sensors for healthcare applications. Currently, at King Abdulaziz City for Science and Technology (KACST), Fahad is involved in various research projects, including water treatment and desalination, the development of innovative polymeric materials, and 3D printing technology, with a primary emphasis on creating healthcare devices.

Ahmad Fallatah is a senior researcher at the Future Mobility Institute of King Abdullaziz City for Science and Technology (KACST). He earned his Master's Degree in Mechanical Engineering from University of Dayton in 2015, then he completed his Ph.D. in Mechanical Engineering from Iowa State University with a focus in Material Science, Biosensor, and Photoelectrochemical measurement in 2022. He has made significant contributions to research in Biosensing using metal oxide nanomaterials to detect several analytes: glucose, cholesterol, lactic acid, and pesticides. As well as his contribution to photoelectrochemical water splitting to produce hydrogen gas from water with the help of solar energy using the metal oxide nanomaterials.

Research Field

Ibraheem Redhwi: Robotics Systems, Mechatronics devices, Nanomanufacturing, Material Science, Additive Manufacturing, Composite Materials, Mechanical Components Desing, Finite Element Analysis

Fahad Alshabouna: Water Desalination, Water Treatment, Membrane Fabrication, 3D printing, Implantable, Wearables, Nanocomposite materials, Conducting Polymers

Ahmad Fallatah: Material Synthesis, Nanomaterials, Electrodeposition, Biosensor, water splitting, Renewable Energy, Hydrogen Production, Food Safety, Photocatalysis