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In-vitro and in-vivo examination for bioceramics degradation

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ABSTRACT

Bone is a composite of collagen fibers that are organized by calcium phosphates nanocrystals. Bone tissue engineering has been continuously developing since the concept of "tissue engineering" has been proposed. Biomaterials that are used as the basic material for the fabrication of scaffolds play a vital role in bone tissue engineering. Calcium phosphates and bioactive glasses were the first bioceramics that were specifically developed for bone repair. Biological responses such as bone bonding and the biodegradation properties of these materials are very important in clinical applications. This paper aims to introduce a strategy to review the difference between the in-vivo and in-vitro investigation of such bioceramics since there are several differences between mechanisms of in-vitro and in-vitro investigations. In this regard, various biological degradation mechanisms are discussed and the effects of additives such as ions and metals on the performance of the degradation behavior of bioceramics scaffolds are reviewed. It was found that additives can enhance the performance of the bioceramics scaffolds by affecting their biodegradation performance. We can change the bioceramics composition indefinitely and in a controlled fashion to tailor their dissolution rate. The presence of some additives of mineral origins within the calcium phosphate structure can affect the crystal lattice, and therefore can accelerate their dissolution as well as their biodegradability. ©2022 UGPH.
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1. Introduction

Bioceramics are a group of materials that show special biological and physiological functions that can be used directly in the body or used in related applications. This group of materials is used to detect and effectively treat diseases and improve bone tissue function.

Bioceramics have been widely utilized for orthopedic applications in which the biocompatibility and mechanical properties of the materials are vital characteristics to be considered for their clinical use. Extensive studies have been devoted to developing a range of scientific ways for tailoring the microstructure of bioceramics in order to attain the trade-off of mechanical properties and biocompatibility of the final product. Owing to low reactivity, earlier stabilization and longer functional life of bioceramics, the developed implants are capable of replicating the mechanical behavior of the original bone [1] .

Bioceramics due to their promising properties have been broadly used for orthopedic applications. Meanwhile, it is important to consider their mechanical properties and biocompatibility for clinical applications. The microstructure of bioceramics has been investigated in several studies with the aim of obtaining a product with optimal biocompatibility and mechanical properties. Due to characteristics such as longer functional life, earlier stabilization and less reactivity, the mechanical behavior of bone can be replicated in bioceramic implants [1].

Bioceramics can be classified into several groups including, Zirconia, Alumina, Titania-based materials, bioactive glass (BG), calcium sulfate, hydroxyapatite, tricalcium phosphate (TCP)-based ceramics, TCP/hydroxyapatite biphasics, CaP cement, Si-substituted hydroxyapatite, CaP coatings, ceramic-polymer composite, dental ceramics, etc. [2].

The bioceramics used in bone tissue engineering (BTE) are bioactive, which means that they are surface active, and a layer of hydroxyapatite is created on its surface over time. This layer is structurally similar to the bone mineral phase and is an interface for creating strong bonds between active biological material and bone tissue [3].

According to bioactivity, bioceramics are divided into bioinert and bioactive. The classification is based on creating a chemical bond between the bioinert implant and the living tissue after implantation. Bioactive ceramics (BACs) are basically biodegradable and degrade over time and are osteoconductive, while bioinert ceramics have good mechanical strength and high chemical stability and also biocompatible [4].

The decomposition of a substance into simpler components could be called degradation. If the degradation is in the vicinity of an environment such as cell culture medium, serum, or simulated body fluid in laboratory conditions, it is *in-vitro* biodegradation. If it is after implantation inside the body, it is *in-vivo* degradation [4].

The decrease in mechanical strength and changes in density that occur in the form of changes in porosity in micro and macro dimensions, as well as changes in the weight or size of materials, are among the physicochemical changes that occur during biodegradation. Changes in pH can also be due to changes in the concentration of ions near the scaffolds [4, 5].

There are two basic approaches in biological research to predict pre-clinical tests: the first approach is *in-vitro* laboratory cultures, including tests of biological degradation of scaffolds over time, the toxicity of scaffolds, animal or human cells (such as hMSCs,24 BMSCs,23, etc.), and the second approach is animal experiments which is called *in-vivo*, such as the repair of rat skull bone defects. Biomaterials play an essential role in the performance of scaffolds, and the biocompatibility and non-toxicity of scaffolds are the basis of repairing bone defects. Therefore, biological materials have drawn the attention of scholars due to their application in BTE [6].

This article, reviews the types and mechanisms of degradation of the two most essential classes of degradable ceramics, including bioresorbable and bioactive ceramics *in-vivo* and *in-vitro*. This classification can be helpful in better understanding the performance of researchers in the area of degradation properties in BTE as well as the future perspective of this field of study.

2. Type of bioceramics

2.1. Inert bioceramics

In the early 1950s, bio-inert ceramics, due to their partucular physical properties and being chemically inert, were included in the first generation of bone substitutes with the aim of substituting without reacting with living tissues. First, they were not developed for such an application, but they were available from industrial materials with various applications outside the medical field. These ineffective materials cause a response from the living tissue even after cultivation inside the living organism [7, 8]. A classification of ceramics is shown in Fig.1.

Bioinert ceramics can be further classified into three types Alumina, Zirconia, and Titania, most widely used in musculoskeletal and other fields [9-11]. Table 1 shows some crucial properties of bio-inert ceramics.

The microstructural properties of Alumina are the basis of the applications of this metal oxide as a biological material, which can occur in many metastable phases. If it is heated to more than 1200 °C, it irreversibly turns into alpha Alumina, and the material used for Biomedicine. If it contains some impurities, also called corundum or emery [12].

The chemical stability of Alumina is due to its phase stability [12]. Alumina has a lower mechanical strength than Zirconia despite its good chemical stability. Compared to Alumina and other ceramics, Zirconia ceramics have unique properties, including higher fracture toughness and much higher strength [13].

Alumina and Zirconia implants release very few substances in the surrounding tissues after implantation, and systemic and local effects have not been reported. For this reason, they are used as dental implants and alternatives for surgical metal alloys in complete hip prostheses [14].

Zirconia ceramics offer advantages compared to aluminum ceramics, e.g., better flexural strength, lower Young's modulus and fracture toughness. Considering these characteristics, ZrO ceramics have been developed in complete hip prostheses for bearing surfaces. Failures during service, especially premature fracture of some of the ceramic femoral heads, caused a recall by the Food and Drug Administration. Because of this, Zirconia is used to increase the strength and toughening of Alumina-based composites. For example, Biolox® delta (CeramTec) has received improved FDA certification for utilization in femoral head components [15].

One of the technologies used in recent decades to increase the durability of implants in the body is nanotechnology, which is used to improve the properties of implants that do not require revision surgery later. For this purpose, nanophase Alumina ceramics with a grain size of 23 nm have been synthesized, and it has been able to improve the fracture toughness of Alumina ceramics. Nanophase Alumina has a 70% lower modulus of elasticity and osteoblast cells gave more biological responses to nanophase materials, which indicates the greater osseointegration potential of nanophase Alumina [16].

Titania, with its high biocompatibility and good permeability, as a porous cell carrier material, helps to increase cell vitality. Studies have been conducted on the effectiveness of Titania on cell growth and proliferation, and they were able to increase Young's modulus to a significant amount of attention by incorporating 10 vol% of Titania in HA-TiO_2 coatings, while the integration of 20 vol. % of Titania has resulted in a decrease in Young's modulus. Hydroxyapatite composites with Titania

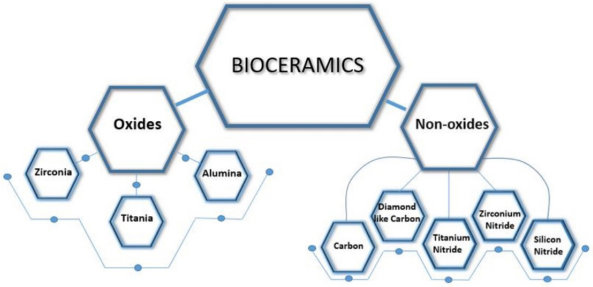

Fig. 1. Classification of bioceramics in two categories bioinert and bioactive.

as the second phase are more researchable due to the high biocompatibility of Titania [17]. Also, hydroxyapatite composites have better mechanical properties compared to their pure ceramics [18, 19].

Carbon and Nitrides are non-oxide bioinert ceramics used as biomaterials. Although carbon and nano carbon tubes have high fracture toughness, excellent strength, and good durability, the use of carbon in orthopedic devices has not been very successful. Using carbon, blood clotting can be prevented at the interface between tissue and material, which covers a coating on the substrates and heart valve prostheses and is used [20].

Carbon nanostructures were considered in implants and soft tissue engineering. For example, graphene and carbon nanotubes were used in served nerves to repair large gaps. Nitrides are also used to increase the wettability and hardness of the surface of metal components. Titanium Nitride (TiN), Niobium Titania Nitride (TiNbN), Zirconia Nitride (ZrN), and Chromium Nitride (CrN) can be used. Silicon Nitride ceramics (Si_3N_4) are used for spine and joint replacement [13, 21].

2.2. Bioactive and bioresorbable

The connection between bioactive substances and tissues is through the biological response that the surface active substance creates at its interface with the tissue. The bioactivity of bioceramics is determined by the formation of an appetite layer on the surface, which is actually the ability of bone grafting [22].

Various models have been proposed to describe the mechanisms underlying apatite layer formation, and Hench's [23] and Ducheyne's [24] are cited the most. The deposition of apatite layer on the bioceramic surface is due to the initial reaction, and then cellular interactions take place with this apatite layer [25].

The rapid absorption of proteins on the ceramic surface may be effective in the first stages [26].

Osteoconductivity is one of the characteristics of all BACs, which is actually the growth of bone tissue along the surface of the implant. The characteristic of osteoinduction means the stimulation of bone growth in non-osseous sites. The presence of nanostructured rough surfaces is important in bone formation and cell differentiation, although osteoinduction is not fully understood. Bioceramics improve osteoinductivity by concentrating bone growth factors circulating in biological fluids [27].

A resorbable biomaterial is decomposed over time, and the host tissue gradually replaces them. Absorbable materials are effective in bone formation and help it. For this reason, the development of these materials has received much attention in recent years [28].

Table 1.
Table 1. Some important properties of bioinert ceramics

	$T_{Melting}$ (k)	Density ($g.cm^{-3}$)	Thermal conductivity (298K) (W/mK)	Young's modulus (GPa)
Alpha-Alumina	2310	3.98	30	380-420
Zirconia	2790	5.83-6.1-6.06	2.5	150-208
Titania	2116	4.23-3.78	11.8	230-288

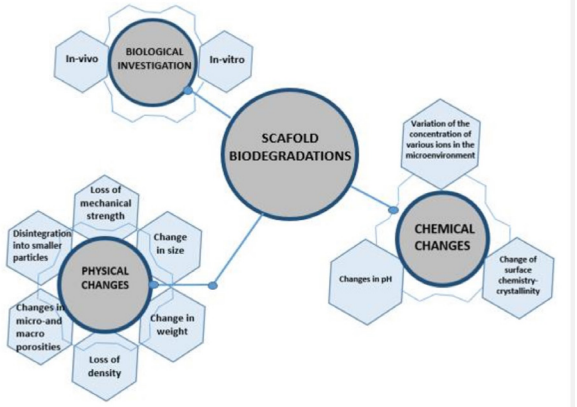

Fig. 2. Types of degradation of bioceramic scaffolds.

Resorption of bioceramics *in-vivo* is done by cellular and physicochemical processes that include dissolution and precipitation steps, which were mentioned in the explanation of bioactivity mechanisms. The function of osteoclasts in the natural resorption of bone and inflammatory multinucleated giant cells that degrade materials by phagocytosis is called cell-mediated resorption. Inflammatory multinucleated cells are formed by the fusion of macrophages. According to the specific function of osteoclasts in hydroxyapatite and TCP, their resorption in the bone is faster than under the skin. Solubility and other properties of bioceramics can affect cell function. Calcium sulfate and some CaPs, which have high solubility and release a large amount of calcium ions, can cause the detachment of osteoclasts from the surface of the material. In this way, chemical dissolution controls the resorption of implants [29].

In order to understand the chemical resorption of bioceramics *in-vivo*, three aspects must be considered: the first aspect is the solubility of bioceramics in the body, and the second is the kinetics of dissolution. Even if dissolution is thermodynamically possible, it is not necessarily observed, and third, the precipitation of other compounds should be considered. The composition of bioceramics and the ratio of calcium to phosphorus have a logical effect on the dissolution and dissolution rate of bioceramics. According to Driessen's [30] work, it has been determined that osteocalcin phosphate (OCP), $Ca_8H_2(PO_4)_6 \cdot 5H_2O$ is the phase that controls the solubility in living bone. The less soluble phases can only be dissolved by the cellular meditative mechanism, while the soluble phases TerOCPs are soluble under physiological conditions [31].

With cellular action, the local pH decreases, which increases the solubility of calcium carbonates and phosphates. Biosoluble is the name given to ceramics that are more soluble in physiological conditions than OCP Ceramics that have less solubility are called bioresorbable. Protein adsorption and geometric factors are among the effective ones for dissolution and precipitation. Protein adsorption, such as dissolved magnesium, which is one of the trace elements in ceramics, can act as a precipitation inhibitor. Surface area and crystal size are also geometric factors that affect the solubility of materials. The difference in the crystal size of CaP and porous hydroxyapatite is the most important factor in the difference in the resorption time of these two materials, which is nanometeric for CaP and micrometric for hydroxyapatite cement. The impact of morphology and porosity on resorption is logical and justifies the use of scaffolds for the possibility of rapid resorption and interaction with the body [32].

2.2.1. Phosphate ceramics

For nearly thirty years, CaP has been used in biomedical fields. CaP, which is an inorganic phase of bone-forming materials, helps the pro-

cess of bone resorption and calcification by improving biological activity and affinity. The material has been used as a substitute for bone tissue (for example: in the construction of coatings, implant fabrication, and clinical settings) for the last three decades. The design of CaP scaffolds should be such that it has a controlled porosity and structure. Organic minerals, inorganic mineral phases, and water make up 15, 60, and 25 percent of natural bone, respectively. CaP can replace about 70% of the inorganic mineral phase. The mechanical properties and porosity of three-dimensional scaffolds are better, and cell proliferation and attachment are enhanced. Using an electron microscope, the microstructure and morphology of the scaffolds are examined. Features such as stability, very good osteoconductivity, and high biocompatibility have expanded the scope of using β- TCP and hydroxyapatite in the field of tissue regeneration [33].

2.2.2. Hydroxyapatite

Synthetic hydroxyapatite with the chemical formulation of $(Ca_{10}(PO_4)6(OH)_2)$ is a bone-like mineral apatite and broadly employed for bone regeneration applications [17]. It is a biocompatible and alloplastic material with a hexagonal crystalline structure. Hence, it possesses structural composition similar to natural bone and a nominal Ca/P ratio of 1:65. Similar chemistry with the mineralized bone phase is made by hydroxyapatite. It has strong biocompatibility and osteoconductive activity that results in bonding between the tissue and the substance. Despite having constituent, a high similarity to the bone, the mechanical characteristics of hydroxyapatite are much inferior to those of natural bone. Nano-scaled hydroxyapatite has become a research focus for the improvement of mechanical and biological properties. Various methods (including mechanochemical, co-precipitation, sol-gel [34], microemulsion, and hydrothermal) have been employed to synthesize the hydroxyapatite with nano-scale structure [35]. One of the important natural sources for preparing bioceramic powder is biowaste materials [27].

Hydroxyapatite offers a great osteogenic cell and growth factors carrier, making it a promising candidate for delivery carrier application. Inherent brittleness with lower fracture toughness and young modulus are the other characteristics of hydroxyapatite [13]. Because of its good biocompatibility, hydroxyapatite is widely recognized as an implant material. Numerous researchers have thoroughly investigated and stated the biocompatibility of hydroxyapatite. According to studies, the common process of maintaining bone tissue and the hydroxyapatite-bone interface was unaffected by the presence of hydroxyapatite. XRD analysis confirmed hydroxyapatite synthesized by freeze-drying without any contamination. Six different types of hydroxyapatite scaffolds were made by Lee et al. [36]. Without any cracks, and they had no effect on the hydroxyapatite crystallinity. Scaffold porosity changes as hydroxyapatite concentration changes [33].

3. Bioceramics degradation mechanisms

In natural or artificial aqueous environments, bioceramics can be degraded by (1) The mechanisms of solution-mediated resulting in the physicochemical dissolution of the ceramic via changing possibly phase, (2) The mechanisms of cell-mediated with osteoclasts and macrophages, and (3) loss of the entirety of mechanical due to the mechanisms of aforementioned. In systems of biologicals, the degradation of bioceramics can be considered as a combination of non-equilibrium processes. They compete with each other or simultaneously [6, 37, 38]. Fig. 2 shows the types of biodegradation of bioceramic scaffolds and their characteristics.

3.1. Physical degradation

From a mechanical viewpoint, CaP ceramics are fragile polycrystalline materials, and the porosity, grain size, and grain boundaries govern their mechanical properties. They show a compression strength in the range of 80-110 GPa [39]. Under moist conditions, for example, in physiological fluids or liquids, the decrease in mechanical strength and fatigue resistance results from the physiochemical dissolution of phosphate ceramic [16, 40].

Mechanical strength of material is defined as its resistance to failure under acute and specific stress at a point in time, while failure due to fatigue consists of an extra parameter that is long-term strength. Long-duration stress is essential in biomedical applications. For instance, with breaking a ceramic rod in a short time at a specific stress σ, the same rod, after an about 100 times longer period would fracture by applying stress of about 0.75 σ. Commonly, subcritical or slow crack growth may result in decreasing the brittle ceramic materials strength under stress, which is sometimes assisted by environmental parameters [41].

Two factors can affect the mechanical strength of single-phase dense ceramics: grain decohesion due to the higher solubility of nanophases that exist in the grain boundaries and are formed by the processing technique [40]. The second influential factor is the physicochemical dissolution of the grains in a uniform manner, which depends on the solubility product of the CaP phase. Because dense CaP ceramics are multiphase, they have different sensitivities to physicochemical dissolution, affecting mechanical properties after aging in wet conditions. Then the most soluble phase causes the bulk ceramic to become destabilized, and the mechanical strength decreases [42]. The densification of grains can cause mechanical stabilization of ceramics, which may be caused by the addition of fluoride to the hydroxyapatite lattice or the presence of phases such as hydroxyapatite combined with TCP [42, 43].

Regarding the dependence of mechanical strength failure on total porosity, the dependency between mechanical strength failure and micro and macro porosity is clear [40, 44]. With the increase of these pores, the surface exposed to fluids takes more, and the intensity of propagating of failures and cracks though ceramic increases. The 1920s can be considered the beginning of the investigation of CaP ceramics from a mechanical point of view. Based on the studies conducted since then, it has been determined that these ceramics are not suitable for permanent skeleton repair if loading other than compressive happens. In order to combine the biological properties of CaP with the mechanical properties of other biological materials, metal composites with CaP coating or its polymer mixtures have been developed [45].

The parameters which are effective on physicochemical dissolution have a direct relationship with the parameters which are effective on the degradation of mechanical strength (whether *in-vitro* or *in-vivo.*

3.2. Chemical degradation

The exchanges at a liquid-solid interface leads to a dissolution-reprecipitation cascade, describing the dissolution or physicochemical degradation of CaP ceramics. Dissolving these bioceramics occurs in natural or artificial aqueous ambiances. This physicochemical process has predominant ionic features and is an example of inorganic substrates. It results from a multi-component dynamic process, which cannot be imitated *in-vitro*. Nonetheless, the simplified biological environment *in-vitro* studies have provided conclusions fitted with *in-vivo* observations.

All CaPs are thermodynamically soluble in acid, but most of them dissolve sparingly in water. The dissolved solute amount present in the saturated solution describes their solubility when the continuous passing of solute particles into the solution along with returning of other particles to the solid soluble phase is occurring simultaneously. An increase in pH is accompanied by decreasing solubility. Supersaturation is

a solution state that can be either metastable or unstable. The concertation of dissolved substance in supersaturated solutions is more than the concentration that can dissolve in water under an equilibrium condition. Crystals have not yet grown, however, introducing seeds can initiate that [46-48].

3.3. Biological degradation

In bioceramics, the osteoclasts mediate their typical cellular degradation. Hematopoietic stem cells, differentiating along the macrophage/monocyte lineage, induce osteoclasts. They lead to bone resorption through the acidity of bone mineral, which causes it to dissolve, and through the enzymatic breakdown of demineralized extracellular bone matrix. The apical pole of the functionally polarized osteoclast cell results in its attachment to the mineralized bone matrix through the formation of the sealing zone (a tight ring-like adhesion zone). Transmembrane adhesion proteins, integrins, which mediate cell-cell and cell-substratum interactions, induce specific interaction between some proteins of bone matrix and cell membrane, resulting in this attachment. Osteoclasts create an acidic environment in the resorbing compartment underneath the cell and within the sealing zone, which causes the bone mineral to dissolve. Extruding water, carbon dioxide, and protons generated from the action of Carbonic anhydrase through the membrane of a cell into the resorbing compartment mediates this osteoclastic acidification [49].

In-vitro and *in-vivo* cellular breakdowns of CaP ceramics have been widely studied. Osteoclasts are in charge of bone resorption after substrate colonization via macrophages/monocytes, recruiting during the inflammatory response over surgery. *In-vitro* and *in-vivo* investigations have proved that similar to the bone mineral, firm attachment of osteoclasts to the sealing zone of substrate results in the degradation of CaP ceramics. Afterward, secreting H^+ in the center of the sealing zone provides a local pH in the range of 4 to. *In-vivo*, osteoclasts get partially involved in CaP degradation. At the surface of the bioceramics, resorbing osteoclasts have been discovered alongside newly created bone. However, there is also a dissolution phenomenon connected to the *in-vivo* degradation of CaP ceramics [50-53].

The CaP nature (sparingly soluble hydroxyapatite, highly soluble TCP, particles, bulk ceramic, cement, etc.) determines the degree of its dissolution process and osteoclastic activity. It has been demonstrated that the physicochemical dissolution degree in the instance of the *in-vivo* degradation of highly soluble TCP ceramics was greater than osteoclastic resorption. Osteoclasts can also phagocytose the particles of CaP, which incorporates them into the cytoplasm and afterward dissolves them through enzymatic action or acid attack. Mechanical stress-induced debris or local dissolution at grain boundaries generate these phagocytosed particles. The intrinsic features of the CaP materials are what determine osteoclastic activity. Nonetheless, the following trends might be noted [50, 53]:

1. The kinetics of physicochemical dissolution of biomaterial: Not all CaP ceramics interact with osteoclasts in the similar manner. The osteoclastic activity appears to be significantly influenced by the calcium ions released from the biomaterial; osteoclastic resorption is prevented from exceeding a certain level of calcium ions. The structure of the ceramic of CaP affects the osteoclastic activity and crystallinity, in addition to the dissolving behavior [54].

2. Carbonates and some other mineral ions: Osteoclasts reabsorb calcium carbonate structures like calcite and aragonite, as well as carbonated apatitic salts like synthetic carbonated apatite, bone mineral, and dentine. It has been suggested that carbonic anhydrase activity, known to increase osteoclastic acid production in-vitro, can be stimulated by carbonate content. However, when added at a particular concentration to CaP biomaterials, fluoride and zinc have also demonstrated an inhibitory effect on the resorption of osteoclastic both *in-vitro* and *in-vivo* [55].

3. The calcium phosphate's surface energy: it was realized that the osteoclastic adhesion is modulated by the polar part of surface energy *in-vivo*. Nonetheless, the differences in surface energy between the substrates did not impact the subsequent spreading and resorption [56].

4. The surface roughness: recognized generally to affect the attachment of cells *in-vitro*, particularly osteoclasts. Compared to smooth apatitic surfaces, rough ones appear to promote osteoclastic adhesion [57].

2. Study of bioceramics degradation in-vitro and in-vivo

The processes of biological degradation are investigated in two ways: either with laboratory processes of cell culture (*in-vitro*) or by clinical applications and experimenting inside the body of animals (*in-vivo*) [58].

4.1. in-vitro degradation

Investigating the effect of zinc on magnesium phosphate bioceramics degradation was studied by Kaushik Sarkar et al. [59]. The result of their research showed that after 8 weeks of immersion in simulated body fluid, Zn-doped MgP (0.5 wt. %) showed up to 50% less degradation compared to pure MgP. According to their findings in laboratory conditions (*in-vitro*), the reduction of degradation by adding zinc to bioceramics is caused by changes in the kinetics of degradation and sintering, while the implantation of magnesium phosphate bioceramics doped with zinc inside the rabbit's body (*in-vivo*) had different results due to the reduction of The concentration of magnesium ions in the degradation media leads to an increase in degradability.

Examining the dissolution behaviors of $CaSiO_3$ (CS), Mg_2SiO_4 (M_2S), and beta-$Ca_2(PO_4)_2$ (β-TCP) ceramics in Tris-HCl solution during 28 days has shown that the dissolution of all samples continued after immersion and pure CS ceramics due to their weight reduction compared to other samples showed the highest dissolution rate in the entire immersion period. Comparing the weight loss of CS ceramics that were sintered at different temperatures did not show a significant difference. The following results were obtained after 28 days: 27.8% (1100 °C), 27.5% (1250 °C), and 24.4% (1350 °C). At the end of the immersion time, the weight loss reached 2.5% and 1.2% for β-TCP and M2S ceramics, respectively, and it showed that β-TCP and M2S ceramics have a lower dissolution rate than CS ceramics. At the end of the immersion time, the weight loss of 2.5% and 1.2% was obtained for β-TCP and M2S ceramics, respectively, and it showed that β-TCP and M2S ceramics have a lower dissolution rate than CS ceramics [60].

Ammar z. alshemary et al. [61] by microwave radiation, incorporated different fractions of chromium into β-TCP through the process of wet precipitation. SBF solution was used for a bioactivity test at 37 degrees Celsius and 14 days. Their findings showed that the rate of degradation of βTCP and the rate of degradation of the apatite layer also increased by adding Cr^{3+} ions. After soaking βTCP and Cr-TCP samples in SBF solution, the dissolution started quickly. In the first hours of the experiment, the amount of Ca^{2+} and Cr^{3+} ions released in the SBF solution increased. After 8 hours, the release of Ca^{2+} ions reached its maximum value, and after 3 days of incubation, the maximum release of Cr^{3+} ions was observed. After a long period of incubation, the concentration of Ca^{2+} and Cr^{3+} ions in the SBF solution has decreased, which is caused by their consumption to create the apatite layer.

Due to the biocompatibility of forsterite (Mg_2SiO_4), it has been used as a bioceramic. Forsterite has shown better fracture toughness and bending strength than hydroxyapatite. The powder of Talc and magnesium carbonate for various times were mechanically activated and used for synthesis. The powder was blended with ammonium chloride catalyst and annealed at various temperatures to synthesize forsterite powder.

The provided forsterite powders were immersed in the body simulation solution in the form of compressed tablets and their bioactivity was evaluated. Their results showed that the forsterite ceramic is biodegradable. The magnesium ions of the ceramic nanostructure were released in the SBF solution [62]. Some recent *in-vitro* degradation investigations of bioceramics are shown in Table 2.

4.2. in-vivo degradation

UweKlammert et al. [70] investigated different phosphate and calcium ceramics and the effect of the regime of long-term muscle implantation on the low-temperature dissolution of these ceramics *in-vivo*.

After 15 months, the studied materials incuding hydroxyapatite ($Ca_9(PO_4)5HPO_4OH$), struvite ($MgNH_4PO_4{\cdot}6H_2O$), newberyite ($MgHPO_4{\cdot}3H_2O$), , and brushite ($CaHPO_4{\cdot}2H_2O$) revealed considerable differences in terms of changes of their features.

The mechanical performance loss for struvite, brushite, and newberyite was 95%, 41%, and 67%, respectively.

This resulted in dissolution a certain amount of cement and the phase composition changes in the retrieved cement implants.

Octacalcium phosphate and whitlockite re-precipitates were created in either whisker or particulate morphology, while the secondary phosphate phases including struvite, newberyite, brushite dissolved entirely.

It was proved that the volume degradation mechanism without macropore was possible for these bioceramics.

Zn-doped MgP bioceramics were prepared from $Mg(OH)_2$ and magnesium trihydrogen phosphate using a method of conventional solid-state sintering by Kaushik Sarkar and colleagues.

Then bone regeneration and degradability *in-vivo* were evaluated. The samples were implanted in the rabbit femur in the size of the critical defect. Examination of histological samples in 30 and 90 days showed that the number of osteoclast cells in MgP-0.5Zn ceramic was more than that of undoped MgP, and due to the increase of these cells and their greater activity, bone formation, osteointegration. SEM imaging of the samples also confirmed their results. Zn-doped samples showed higher bone regeneration according to fluorochrome labeling, which may be related to the control degradation kinetics. MgP-0.5Zn showed much higher *in-vivo* degradability than MgP-0.25Zn and pure MgP [59].

To modify the biosafety, bioactivity, and degradability of silicocarnotite (CPS), Kerong Dai et al. [71] incorporated copper (Cu) and cerium (Ce) into CPS structure. Throughout implantation *in-vivo*, potential stress fracture would happen.

0.5Ce0·5Cu-CPS bioceramics containing 0.5 wt. % CuO and 0.5 wt. % CeO_2 and CPS-Cex (x= 0, 0.5, 1.0, 1.5 wt. %) were subjected to the sintering at various temperatures, and their influence on degradability, microstructure, sinterability, and phase composition of CPS were studied.

It was reported a gradual degradation in different Ce-CPSs during immersion and increasing the CeO_2 content of specimens resulted in the decrease of degradation rate.

Micro-CT scanning was used to evaluate *in-vivo* degradation of material qualitatively. The gradual degradation of all groups occurred after 6 or 12 weeks of implantation in rats.Ce-CPS displayed slower degrading rates with CeO_2 addition increase, especially at early 6 weeks. 0.5Ce0·5Cu group exhibited the smallest residual volume at both time points, which suggested that it had superior degrading activity to all other groups *in-vivo*.

MgP scaffolds doped with 2 wt. % Strontium, 0.5 wt. % Silicon, and 0.5 wt. % zinc with a porosity of up to 47% were prepared and implanted in the femur of rabbits. After two months, the doped MgP scaffolds showed major degradation. Among the implanted bioceramics, according to the results of Micro-T (μ-CT), the sample doped with strontium showed the least degradation, and the sample doped with zinc showed the most degradation. Strontium ions had a dual action, which led to a decrease in osteoclastic resorption, and the proliferation of osteoblast cells was increased. As a result, the sample doped with strontium showed less biodegradability and more bone formation [72].

Considering that the degradability inside the human body within a reasonable time frame is an important criterion for absorbable bioceramics, agents that reduce the degradation time are desirable. The release of strontium from the bioceramic during degradation may shorten the recovery time. Ying-Cen Chen's [73] studies showed that calcium sulfate bioceramic containing strontium has this capability. The prepared porous bioceramic was implanted in the distal femur of rats. The degradation rate of the implanted discs was dependent on the strontium content of the discs. In 12 weeks for the (3.8%Sr, Ca)SO_4 disc sample, a relative volume of 40% of new bone was formed, and about 25% of the implanted bioceramics volume remained [73].

β-TCP/Calcium silicate porous composite bioceramics were prepared by Shen Liu et al. [74]. The bioceramics were prepared with ratios of 50% calcium silicate, 80% calcium silicate, β-TCP, and pure calcium silicate. The samples were kept for 26 weeks. They were implanted in the femur defect of rats. All the implanted samples had degradation, and among them, pure calcium silicate had the highest amount of degradation, which was reported as 97.17%. The rate of degradation of materials has increased with the increase of calcium silicate content. Also for the sample containing 50% calcium silicate, the rate of degradation was much lower compared to the sample containing 80%.

Fe-bioceramic composites were prepared from iron powder, hydroxyapatite, and TCP. Hermawan and his colleagues prepared TCP and hydroxyapatite nanopowders by microwave irradiation and sintering methods and obtained iron-based bioceramic composites by sintering and mechanical mixing. Three different pure iron iron-based bioceramic composite samples were used for *in-vivo* investigation. The samples implanted in the bone defects of the radial forelegs of male sheep, below the radial periosteum membrane, and in the middle-proximal region. Biodegradation was investigated by non-invasive x-ray radiography. Relative to pure iron, iron-based bioceramic composite due to the addition of degradable ceramics was biodegraded at a relatively higher rate.

The degradation of all implant samples was confirmed by X-ray radiography. Therefore, according to the obtained results, iron-based bioceramic composites can be used as biodegradable bone implants. Based on the weight loss data, the activity of cells inhibited the dissolution of bioceramics phases. In the culture medium, the direct contact between the samples and the cells induced more release of Fe [67].

Zinc-containing silicocornite ($Ca_5(PO_4)2SiO_4$, CPS) scaffolds with amounts of 0, 1, 3, and 5 w% zinc oxide were studied by Fanyan Deng et al. [68]. The samples were implanted in rats' skulls and bones and examined after 12 weeks. The results revealed that with the increase of zinc oxide, the residual amount of the implanted scaffolds decreased, which means that with the increase of zinc oxide content, the *in-vivo* biodegradation of the silicocarnovite scaffolds increased.

The percentage of biodegradation of the samples CPS,1Zn-CPS, 3Zn-CPS, and 5Zn-CPS was 22.9%, 32.0%, 39.6%, and 50.9%, respectively. According to the results of proteomics of proteins adsorbed on bioceramics, there is the possibility of PI3K-Akt signaling pathway activation for promoting osteogenesis by addition of zinc oxide to CPS, and considering that *in-vitro* and *in-vivo* results were contradictory, enzymes, cells, and proteins are very effective *in-vivo* degradation.

Calcium silicate bioceramic scaffolds doped with magnesium (CSM) and titanium alloy were prepared by chemical method and printed by DIW technique by Su Wang et al. [75]. The prepared bioceramic scaffolds had the same pore structure and their osteogenic properties were investigated *in-vivo* after implantation in the rabbit skull bone. Over time, the amount of CSM bioceramic scaffold decreased significantly *in-vivo* and the amount of new bone increased. *In-vivo* degradation of the scaffold re-

Table 2.
Some recent in-vitro degradation investigations of bioceramics

Bioceramic	Synthesis method	Characterization	Time	Result	Solution	Ref.
Forsterite nanopowder with 31 nm crystallite size	Wet chemistry	-Study of apatite formation using: 1.Fourier transitioned-infrared spectroscopy (FTIR), 2.scanning electron microscopy (SEM) 3.energy dispersive X-ray (EDX). -Determination of released ions concentration uing atomic absorption spectrometer -Measurement of pH changes over immersion using pH meter	4 week	-Possessing the apatite formation ability and biodegradability.	SBF	[62]
Porous biphasic α/β-TCP with various α- and β-TCP phase ratios.	Wet-synthesis.	-Study of dissolution behavior of samples in dynamic and static SBF using 1.FTIR 2.XRD 3.FE-SEM -Quantification of ions concentrations by atomic absorption spectrophotometer -Monitoring the pH solution over immersion using pH meter	12 day	-Great bioactivity and controlled degradability of dual α/β-TCP bioceramics. - Facilitating the degradation of bioceramics in dynamic environment. -Increasing the dissolution rate of α/β-TCP bioceramics with increasing α-TCP phase.	SBF	[63]
Porous CSi-Mgx scaffolds (x = 0, 4, 10)	Co- precipitation procedure.	-Mechanical testing using mechanical test machin - Degradation evaluation by 1. Inductively coupled plasma-optical emission spectrometry (ICP-OES) 2. Weighing the scaffolds before and after immersion	6 weeks	-Inhibiting both mechanical deca and material biodegradation by Mg substitution in CSi	Tris buffer	[64]
Zn doped Forsterite (Mg_2SiO_4)	Solid state synthesis.	-Determination of the Si and Mg ions concentrations using Inductively coupled plasma mass spectrometry (ICP-MS) -The morphological and compositional studies by SEM/EDS	8 weeks	-Enhancing the degradation of Forsterite by Zn addition	SBF	[65]
A composite coating made from fluoridated hydroxyapatite, brediglite, and diopside on the AZ91 Mg alloy	Wet chemistry.	-Degradation evaluation by 1. ICP 2. Weighing the samples before and after immersion	4 week	-Notable decrease in degradation rate of AZ91 Mg alloy modified with composite bioceramic coating	SBF	[66]
Iron-based bioceramic (BCP, TCP, and HA) composites	Powder sintering process.	-Study of degradation behavior of composites using 1. Electrochemical impedance spectroscopy (EIS) 2. Potentiodynamic polarization 3. Weight loss measurements	2 week	-Greater biodegradability of composites rellativr to pure Fe due to the incorporation of degradable ceramics	SBF	[67]
Silicocarnotite ($Ca_5(PO_4)_2SiO_4$, CPS) scaffolds containing zinc (Zn-CPS)	Sol-gel method and mechanical mixing method.	-Measurment of ions concentrations using ICP-AES	4 week	-Inhibiting the degradation of CPS bioceramics by the addition of ZnO.	Phosphate buffer saline (PBS)	[68]
Mg-Zn/x β-TCP (x = 5, 10, and 15 wt.%) composite scaffolds	Wet chemistry.	-Degradation evaluation by X-ray micro-computed tomography. - Analysis of chemical elements in their compositions and the degradation products usinf EDS	4 week	-A reduced biodegradability of Mg-Zn/5TCP samples (0.5 mm/y) relative to Mg-Zn, being in the range of ideal degradation rates for bone substitute materials. -Deterioration of biodegradation behavior of Mg-Zn/15TCP samples due to the heterogeneous dispersion of β-TCP particles.	SBF	[69]

duced the mechanical properties, which is not favorable for bone defect repair applications that require mechanical strength. The titanium alloy scaffold had a stable bearing capacity, and with the organic combination of these two scaffolds, it is possible to make progress in the field of BTE

4. Conclusions and future insights

Bone tissue substitutes, considering their need in the healing process, deserve attention and are susceptible to progress. Among these materials, biodegradable materials are necessary because of eliminating the requirement for revision surgery to remove implants from the body. In the discussion of BTE, biodegradability is one of the most important effective factors in evaluating implant performance. Bioceramics are an important class of these materials because of their biocompatibility and mechanical properties.

Degradation types and mechanisms of bioceramics were reviewed. The effect of the composition of different bioceramics on their biodegradability was also reviewed. Considering that the investigation of the biological degradation of these materials *in-vivo* and *in-vitro* does not necessarily show the same results, an attempt was made to provide a point of view for the reader to better understand the difference between them. It was showed that further research is needed for *in-vivo* studies of bioceramics which makes them good candidates for human applications.

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