

Radiopaque Crystalline, Non-Crystalline and Nanostructured Bioceramics

Subjects: [Materials Science, Biomaterials](#) | [Materials Science, Ceramics](#) | [Materials Science, Characterization & Testing](#)

Contributor: Maziar Montazerian , Geovanna V. S. Gonçalves , Maria E. V. Barreto , Eunice P. N. Lima , Glauber R. C. Cerqueira , Julyana A. Sousa , Adrine Malek Khachatourian , Mairly K. S. Souza , Suédina M. L. Silva , Marcus V. L. Fook , Francesco Baino

Radiopacity is sometimes an essential characteristic of biomaterials that can help clinicians perform follow-ups during pre- and post-interventional radiological imaging. Due to their chemical composition and structure, most bioceramics are inherently radiopaque but can still be doped/mixed with radiopacifiers to increase their visualization during or after medical procedures. The radiopacifiers are frequently heavy elements of the periodic table, such as Bi, Zr, Sr, Ba, Ta, Zn, Y, etc., or their relevant compounds that can confer enhanced radiopacity. Radiopaque bioceramics are also intriguing additives for biopolymers and hybrids, which are extensively researched and developed nowadays for various biomedical setups.

[biomaterials](#)[bioactive](#)[bone](#)[glass](#)[ceramic](#)

1. Introduction

Bioceramics have been primarily designed to treat, repair, and/or reconstruct diseased or damaged parts of the musculoskeletal system ^[1]. Depending on the type of interaction that they elicit in/establish with the host tissue, bioceramics can be classified as bioinert or bioactive ^[2]. Bioinert ceramics are passive against the environment in which they are implanted (e.g., alumina and zirconia) ^[3]. On the other hand, bioactive ceramics chemically interact with the surrounding tissue, causing a biological response. They show osteointegrative, osteoconductive, or osteoinductive abilities (e.g., bioactive glasses and calcium phosphates) ^{[4][5][6][7]}. Some bioceramics are also bioabsorbable, i.e., they are capable of being absorbed by the living tissues while being replaced by natural tissue; thus, their rate of dissolution and degradation is close to—and ideally coincides with—the speed of regeneration of the host tissue ^{[2][8][9]}.

The application of bioceramics has proven to be effective in numerous biomedical areas, including tissue engineering ^[10], ophthalmology ^[11], otolaryngology ^[12], cardiology ^{[13][14][15]}, orthopedics ^[16], dentistry ^[17], etc. In orthopedics, bioceramics are used to coat metallic implants ^[14]; as bone cement in arthroplasty, vertebroplasty, and kyphoplasty surgeries ^[18]; bone grafts, bone fillers ^[7]; and so on. ^[16]. In dentistry, bioceramics are used to manufacture prostheses, implants, veneers, orthodontic brackets, dental restorations, endodontic cement, etc. ^[19].

In general, bioceramics must meet some strict requirements considering the complex environment in which they are implanted. They must be biocompatible; possess good physical, chemical, and mechanical properties; be easily processed and sterilized; and be relatively affordable and readily available [20]. However, according to the application, some more specific properties are required. For example, radiopacity is an important physical property that most bioceramics intended for orthopedics and dentistry must have. It enables the clinical evaluation of these materials at the surgical site [21]. The application of radiopaque bioceramics is indispensable in areas where radiographic visualization procedures and detecting medical devices in soft and hard tissues are challenging. Developing highly radiopaque and biocompatible bioceramics is one of the ultimate goals of bio-ceramists. Most bioceramics are intrinsically radiopaque but can still be doped/mixed with radiopacifying elements such as Bi, Zr, Sr, Ba, Ta, Zn, Y, etc., or their relevant compounds (e.g., oxides), to increase their visualization during or after medical procedures. This addition might change the bioceramics' physical, mechanical, and biological properties under investigation.

2. Principle and Physics of Radiopacity

The characteristic of a material absorbing or scattering X-ray photons as they pass through is called attenuation. The attenuation of X-rays by a material mainly depends on electron density, the material's thickness, and specific gravity (i.e., density). Therefore, when a material is irradiated with a parallel beam of X-ray photons, it penetrates the material and is absorbed or scattered after the interaction [22]. For example, the difference in attenuation caused by different tissues and medical devices creates a contrast between them, so greater attenuation creates higher contrast. A material is considered radiopaque if it exhibits good X-ray attenuation and produces positive contrast in the radiographic image [23]. In the diagnostic energy ranges, the photoelectric effect (PEE), Compton effect (CE), and Rayleigh effect (RE) are the three main processes by which X-ray photons can interact with the absorbing material [24].

2.1. Photoelectric, Compton, and Rayleigh Effects

The PEE is the emission of electrons when electromagnetic radiation, such as an X-ray, hits a material. Electrons emitted in this manner are called photoelectrons. This happens when the incident radiation's energy reaches the binding energy of the electron in the different shells of an atom (e.g., K and L layers). Subsequently, an electron at a higher energy level (such as those in M and N layers) fills the hole left by the ejected electron, and a characteristic X-ray is emitted with an energy equal to the difference between the binding energies of the two electrons. In general, depending on the atomic number of the atom (occupancy of different shells), photoelectrons can also be emitted from shells other than K and L (i.e., M and N). The body tissues fully absorb these low-energy characteristic X-rays. The linear attenuation coefficient of the photoelectric interaction (mPE) depends entirely on incident beam energy, tissue-effective atomic number, and tissue density. Since the mPE will be higher for materials with high atomic numbers than less dense and low-atomic-number materials, a contrast is generated between high- and low-density materials during imaging. More contrast is obtained between bone with high attenuation and soft tissue with low attenuation capacity [24][25].

In the CE, the photon is scattered by an electron with low binding energy (outer-layer electrons), which receives only part of the X-ray energy, letting it pass inside the material in another direction and with lower energy. As the energy transfer depends on the direction of the ejected electron, which is random, a photon of fixed energy can result in electrons with variable energy, with values from zero to a maximum value [24][26]. The probability of Compton scattering depends primarily on the electron density of the tissues, not on the atomic number of the constituent atoms. Furthermore, it is weakly dependent on the incident energy of X-rays. At low energy X-rays, the PEE is dominant over the CE, whereas with high energy X-rays, increasing the CE reduces the image contrast [27].

The RE is a type of elastic scattering that occurs at very low photon energies. Since diagnostic radiology uses photons above this range, this scattering becomes important only in mammography using low photon energies. In this case, the incident photons are scattered by the atom's electron cloud, causing slight ionization [28].

2.2. Radiopacity Measurement

A radiologically detectable material in the body must have sufficient radiopacity to be differentiated from the anatomical structures surrounding it. In digital and film radiography, radiopacity is measured in terms of the grayscale value, which is calculated from its digital image [29]. Each digital image consists of many pixels—the countable digital units in an image. Each pixel is related to a characteristic brightness value of the material attenuation property. In a grayscale image, since each pixel consists of 8 bits and the image has 28 bits, it reaches 256 shades of gray. Generally, the grayscale value of black and white is 0 and 256, respectively. The grayscale image of any radiodense material tends to have a gray value between 0 and 256 [30].

3. Applications

3.1. Dentistry

Dental restorations, implants, crowns, bridges, dentures, root canal fillings, cavity liners, adhesives/cements, luting agents, and core build-up should be radiopaque in most cases. The adaptation of these materials into the anatomical structure of the mouth is analyzed by X-ray radiography to evaluate their function for long durations. Radiopaque components are usually added to these devices—some are made from bioceramics—to improve their radiopacity without compromising the mechanical properties, biocompatibility, and aesthetics [31].

The derivatives of heavy elements such as Bi, Zr, Sr, Ba, Ta, Ce, etc. are commonly used as opacifiers in dentistry. Their addition to dental ceramics as a dopant or secondary phase should not generate exaggerated radiopacity that can inhibit the dentist's understanding of disease conditions and false-positive errors. Furthermore, the addition of excessive radiopaque fillers either compromises some properties or may cause undesirable tissue inflammations [32][33]. The names, composition, radiopacifier used in the composition.

3.2. Ceramic Bone Cements

Calcium phosphates, calcium sulfate, magnesium phosphate, bioactive glasses, etc., are generally used in bone cements for restoration procedures. For example, they can treat osteoporotic vertebral fractures that require bone cements with radiopaque characteristics. The bone cements can confer radiopacity, but they are further doped with radiodense elements or mixed with relevant oxides. Besides the radiopacity, characteristics such as lower heat release, good shaping ability, and good mechanical and rheological properties are favorable prerequisites [\[34\]](#)[\[35\]](#)[\[36\]](#).

3.3. Bone Grafts and Scaffolds

With the primary goal of fixing, repairing, and regenerating bone defects, synthetic bone grafts/scaffolds are increasingly employed in modern reconstructive surgery due to the complications of using autografts or allografts. Radiopaque bone grafts, scaffolds, and implants enhance their visibility during medical imaging. Many researchers are convincingly considering the application of 3D scaffolds in regenerative medicine [\[37\]](#) and, specifically, bioceramics such as wollastonite, calcium phosphates, silicates, HAp, glasses, and glass-ceramics are mostly investigated to prepare scaffolds [\[38\]](#)[\[39\]](#).

3.4. Composites

Polymeric composite materials are a unique class of biomaterials with important properties in engineering and biomedicine. A polymeric composite typically comprises bioceramics or other inorganic materials dispersed within a polymer matrix at micron- or nano-sizes. The radiopaque composite concept highlights the unique properties of the base polymer while improving the radiopacity of the composite device through the addition of radiopaque bioceramics [\[40\]](#). Bioceramics can add additional properties to polymers generally unavailable in the polymeric matrices, such as bioactivity, osteointegration, controlled drug delivery, and many other functionalities discussed in [Section 6](#) [\[41\]](#)[\[42\]](#)[\[43\]](#).

4. Radiopacifiers in Crystalline Bioceramics

There are generally two types of bioceramics: crystalline and non-crystalline (or partially-crystalline) materials. Most crystalline bioceramics are oxide or non-oxide powders that are shaped and sintered to form a solid product. Non-crystalline and partially-crystalline ceramics include glasses and glass-ceramics, respectively, that are usually synthesized through melting–casting or sol-gel routes and subsequently are subjected to controlled heat treatment or powder sintering [\[44\]](#)[\[45\]](#)[\[46\]](#)[\[47\]](#)[\[48\]](#)[\[49\]](#)[\[50\]](#)[\[51\]](#). Specific mechanical and biological properties should be engineered in bioceramics. The mechanical properties mainly include elasticity, hardness, compressive strength, and fracture toughness. The biological properties involve apatite-forming ability (i.e., bioactivity in osseous applications), biocompatibility, biodegradability, cytotoxicity, antibacterial properties, angiogenesis, etc. [\[16\]](#)[\[52\]](#)[\[53\]](#)[\[54\]](#)[\[55\]](#)[\[56\]](#)[\[57\]](#). As discussed earlier, radiopacity is another essential characteristic of bioceramics that deserves to be highly considered in modern applications.

Adding some constituents with a high atomic number is the most commonly used technique to increase bioceramics' radiopacity. This can be executed by the incorporation of substances such as bismuth oxide (Bi_2O_3)

[58][59][60][61], zirconium dioxide (ZrO_2) [58][60][61][62][63], strontium carbonate (SrCO_3) [50][51][52], barium sulfate (BaSO_4) [58][60], iron oxides (Fe_2O_3 e Fe_3O_4) [64], calcium tungstate (CaWO_4) [59][61][65], ytterbium trifluoride (YbF_3) [60][66][67], and titanium dioxide (TiO_2) [60][68]. Doping bioceramics with heavy elements can also confer radiopacity. This table summarizes the radiopacity values of different bioceramics incorporated with various radiopacifying agents.

Bismuth (Bi), a metallic element with a high atomic number ($Z = 83$), is known for its relatively low toxicity and high stability when compared to other neighboring metals in the periodic table, such as lead (Pb), thallium (Tl), and antimony (Sb) [58][63][69]. Doping crystalline ceramics with bismuth ions increases radiopacity without significantly deteriorating mechanical properties, usually after adding radiopacifying microparticles to a ceramic matrix. Unlike ions such as barium (Ba, atomic radius (AR) = 253 pm), zirconium (Zr, AR = 216 pm), and strontium (Sr, AR = 219 pm), which are generally larger than the host lattice, the Bi (AR = 143 pm) ion does not tend to cause distortions in the crystal structure, which are responsible for changes in material properties [70].

Zirconium has been widely used in orthopedics and orthodontics due to its chemical and physical stability as well as biocompatibility in the physiological environment [71]. Bi_2O_3 can be replaced with zirconium dioxide (ZrO_2 , zirconia) on some occasions, such as in dental cements, as it does not cause problems such as dentin discoloration [72].

Strontium is a trace element in the human body [73]. It belongs to group II on the periodic table, like calcium; in fact, they respond similarly in the body. Among the bioactive metals, strontium ions (Sr^{2+}) offer the best responses to the body in terms of bone regeneration [74]. Strontium's application as an additive in bone cements is recommended because it is a therapeutic component for treating osteoporosis [75], in addition to absorbing greater amounts of X-rays than Ca, making the material more radiopaque [24][73].

Barium sulfate is routinely used in gastroenterology as a contrast medium [76] and is among one of the most researched effective radiopacifiers, together with zirconium oxide (ZrO_2) and bismuth oxide (Bi_2O_3), to improve the visualization of non-radiopaque materials due to its high atomic number ($Z = 56$) [70][77][78]. It is a white element and, therefore, should not cause color changes in dentistry [79].

5. Radiopacifiers in Glasses and Glass-Ceramics

Bioactive glasses (BGs) and glass-ceramics (BGCs) belong to the third generation of biomaterials that, once implanted, can help the body heal itself [80]. BGs were first introduced in 1969 by Larry L. Hench in the USA [81]. They offered great versatility for bone and tissue engineering/regeneration [82]. Furthermore, through a controlled heat treatment of bioactive glasses, an internally nucleated monolithic sample or a sintered/partially-crystallized glass powder compact, called glass-ceramic, was made [83][84][85]. BGCs are, in principle, tougher and stronger than BGs. BGs are developed by melting–quenching or sol-gel methods, and in some cases, BGCs can also be obtained without the need for any post-synthesis thermal treatment. Sol-gel glasses are promising in developing modern bioactive glasses, i.e., nanoporous powders and even small monoliths [86]. They offer higher purity and

homogeneity than melt-derived glasses and exhibit faster bioactivity over a broader compositional range due to their high surface areas [87][88][89][90]. Mesoporous bioactive glasses (MBGs) are the latest generation of BGs developed by Yan et al. [91] through the application of the surfactant-induced self-assembly of the inorganic constituent of bioactive glasses. MBGs are mesostructured materials with a well-ordered pore arrangement, a high surface area, and an average porosity in the range of 2 to 50 μm . They are highly reactive and show drug-delivery ability.

Many BGs and BGCs that host unique structural modifiers such as strontium (Sr) have been studied, considering that Sr is a radiopacifier and plays a vital role in the human body. For example, in some cases, Sr can replace Ca in the physiological pathway or be deposited in the bone mineral structure [92][93][94].

The presence of Sr in MBGs and BGs shows promise due to its high radiopacity and degradation rate. High levels of radiopacity can also be achieved by incorporating very high levels of strontium (equivalent to 40 mol% SrO) in the glass composition. Studies show that considerable amounts of Sr can also decrease the dissolution rate of the material [95][96][97].

Bi has emerged as a new element to be included in MBG and glass-ceramics due to its favorable properties such as biocompatibility and low toxicity. In addition, Bi's inclusion can increase these materials' mechanical, biological, and osteogenesis properties. The radiopacity of the materials with the presence of Bi improves the image contrast of the treated area by X-ray radiography and computed tomography [77][98].

Zr-containing BGs and BGCs have constituted an active field of research for over 20 years. This element can be added to glasses or ceramics for at least three distinct purposes: (1) to develop radiopaque bioactive powders and mix such powders with bone cements or bone fillers to improve contrast during a radiological follow-up, (2) to develop inert and durable glass-ceramics for dental restoration, and (3) to reinforce BGs or BGCs. For example, the use of $\text{SiO}_2\text{-ZrO}_2$ glasses as adjuvant radiopacity fillers has been suggested for light-cured dental composites, bone graft substitutes, and bone cement.

Barium and barium compounds are valuable candidates for medical applications due to their unique properties, such as their high density, high polarizability, and radiopacity. As briefly mentioned, the radiopacity of barium sulfate and other barium-containing compounds enables the detection of body vessels and implants [99]. This feature helps radiologists determine the orientation and status of body ducts (e.g., angiography to examine cardiovascular channels and barium swallow studies to examine the gastrointestinal tract).

Magnesium (Mg) is an important mineral of the bone matrix that is contained in enamel, dentin, and bone structure. Magnesium oxide (MgO) has also been considered a substitute for CaO in BG and BGC compositions to modify their biological characteristics and mechanical properties [94].

Zinc-doped glass-ceramics and glasses have been shown to stimulate wound healing by increasing osteoblast differentiation and osteoblast DNA content. Zn-doped biomaterials have also shown antibacterial efficacy by killing

many bacterial strains commonly associated with infection after orthopedic surgery [95]. However, Sharifianjazi, Moradi [94], emphasized the importance of controlling the Zn content, as the glass transition temperatures can be reduced with the increase in Zn and can also deteriorate the bioactivity of glass or glass-ceramics.

6. Polymer-Based Composites/Hybrids

The application of different composite/hybrid materials in medicine and dentistry has been growing. One interdisciplinary approach that has been investigated for a long time is the treatment of various types of bone- and tooth-related diseases and disorders by utilizing biopolymer–ceramic composites or organic–inorganic hybrids, which combine the properties of two materials and achieve enhanced biological and biomechanical properties along with radiopacity. They show appropriate properties for applications that require strength, durability, and biocompatibility. Recently, a wide range of biopolymers, such as poly(L-lactic acid), poly(L-lactide-co-glycolide), poly(methyl methacrylate) (PMMA), poly(ε-caprolactone), etc., have been studied for different biomedical procedures because of their good biodegradability and biocompatibility. They can be processed by advanced additive manufacturing techniques for the fabrication of custom-made prostheses. Radiopaque bioceramics or heavy inorganic elements can contribute significantly to the medical success and evaluation of these biomaterials as they improve radiopacity and biocompatibility similar to the degrees found in natural bone and teeth [100][101][102][103]. Most of the bioceramics discussed in the previous sections can infer radiopacity from the polymeric matrix composites. In addition, the heavy inorganic elements mentioned above can contribute at a molecular scale to the formation of radiopaque polymeric hybrids.

Nowadays, the harnessing of nanotechnology and the chemistry-based synthesis of materials at molecular scales are recommended as solutions for overcoming several drawbacks related to conventional polymer–ceramic composites. For example, nano-fillers/opacifiers can contribute significantly to increasing materials' homogeneity and degradation, improving the modulus of elasticity and strength and, if needed, delivering drugs or therapeutic ions. On the other hand, inorganic–organic hybrids are relatively new materials and show low polymerization shrinkage, improved wear resistance, and biocompatibility. They are synthesized through sol-gel processing, in which a polymeric molecular precursor as a starting material is combined with metallic oxide frameworks during hydrolysis and condensation at low temperatures [87][104][105][106].

7. Nanostructured Bioceramics

Intrinsically radiopaque nano-bioceramics are extensively researched as theranostic biomaterials. In this application, they can eliminate the need for two distinct biomaterials that serve cancer therapy and diagnostics/imaging. Modern theranostic bioceramics enable simultaneous diagnostic imaging, drug delivery, or other adjuvant treatments [107]. The nano-bioceramics employed for such applications include superparamagnetic iron oxide nanoparticles (SPIONs), carbon nanotubes (CNTs), and quantum dots (QDs), among others [108][109][110]. The therapeutic methods in nano-theranostics are chemotherapy, thermal ablation, photoablation, radiation therapy, and magnetic hyperthermia.

Magnetic bioceramics are widely studied for several applications, whereas their eligibility for theranostic applications has been proved just recently. Enormous research interest in bioceramics for magnetic hyperthermia has been reported in the past decade with respect to bypassing the drawbacks of conventional cancer treatments. Designing multifunctional materials for delivering therapeutic drugs together with providing diagnostic potentials and additional therapies (e.g., magnetic hyperthermia, photothermal therapy, and radiotherapy) is at the center of current attention.

MBGs have also recently emerged with distinguished capabilities in cancer imaging and therapy ^[111]. For example, recently, a theranostic multifunctional radiopaque Eu-Gd-doped MBG decorated with alendronate and folate, loaded with doxorubicin (DOX), was thoroughly studied for skin cancer therapy, imaging, and regeneration. An ultrahigh amount of DOX (600 mg g⁻¹) could be loaded in the nano-MBG, which presented a burst release up to 24 h followed by a sustained release up to 120 h. An increased release at pH = 5.5 up to 24 h evidenced the pH-sensitive nature of the MBG ^[112]. The synthesis, multifunctional nature, drug release profiles.

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