American Journal of Engineering Research (AJER)
e-ISSN: 2320-0847 p-ISSN : 2320-0936
Volume-11, Issue-06, pp-125-138
www.ajer.org
Research Paper Open Access

Beta tricalcium phosphate (β-TCP): A scientific and technological mapping

*1Farias, J. R. S.; [1]Rocha, G, M.; [2]Carvalho, G. K. G.; [3]Pereira, G. G. S.; [3]Silva, P. F.; [4]Martins, M. M.; [5]Simões, V. N.; [3,6]Braga, A. N. S

[1]*Degree in materials engineering, CT/UFPI, Av. Universitária, s/n, Teresina, PI, Brasil*
[2]*Postgraduate Program in Materials Science and Engineering, PPGCM/UFPI, Av. Universitária, s/n, Teresina, PI, Brasil*
[3]*Postgraduate Program in Materials Science and Engineering, PPGEM/IFPI, Rua Álvaro Mendes, 94, Teresina, PI, Brasil*
[4]*Civil engineering, Lecturer, Specialist in Concrete Structures and Foundations, Teresina, Piauí*

[5]*Postgraduate Program in Chemical Engineering, Universidade Federal do Rio Grande do Norte, Natal-RN, Brasil*
[6]*Materials Engineering Coordination, CT/UFPI, Av. Universitária, s/n, Teresina, PI, Brasil*

ABSTRACT : *Several researches have been carried out with the aim of developing synthetic materials that can be used as biomaterials in the most diverse applications, such as bone grafts, implants, and in the bone regeneration process, in a safe and satisfactory way without risk to the patient. An alternative is the use of ceramic materials, such as calcium phosphate bioceramics, which are more cost effective, that is, they are highly effective and make the manufacturing process cheaper. Beta tricalcium phosphate (β-TCP) is a calcium phosphate bioceramic widely used because of its excellent biocompatibility, in vivo bioactivity, bioresorbability and osteoconductivity properties. This way, this work consists of presenting data collected from the last six years on β-TCP in scientific articles and patents. The ScienceDirect, Web of Science and Scopus databases were used for scientific articles, and the USPTO, ESPACENET and LENS.ORG databases for patents. The collected results presented the number of published articles, the number of patents, the countries involved in the publications, the main applications, the synthesis methods used, the amount of doping and composites formed as well as the number of publications that synthesized beta tricalcium phosphate in a pure form, with the aim of helping and guiding researchers who use this bioceramic.*

KEYWORDS *Review; Bioceramics; Beta Tricalcium Phosphate*

Date of Submission:01-06-2022 Date of acceptance: 14-06-2022

I. INTRODUCTION

Currently, it is observed that advances in medicine together with the principles of engineering and life sciences have provided the development of natural or synthetic materials, which effectively enable the conservation, repair, regeneration or even the functional replacement of organs or tissues of the body. human beings affected by pathologies, infections and traumas. Such materials are called biomaterials and play an essential role in the replacement/regeneration of injured parts of the human body [1]. These materials must present physicochemical, mechanical and biological properties compatible with the host living tissues, in order to stimulate an adequate response of the same [2]. Biomaterials can be chemically classified, being subdivided into metals, ceramics, polymers and composites, as well as being classified according to the biological response they induce in the tissues to which they are implanted, being biotolerable, bioinert and bioactive [2, 3].

Bioceramics are a class of ceramics used in the repair and reconstruction of diseased or damaged parts of biological systems [4]. The great use of this class of biomaterials is due to the similarity with the basic constituents present in the mineral phase of bones and teeth, which are mainly formed of phosphorus and calcium [5, 6]. Among the most known and used, the following stand out: gypsum ($CaSO_4 \cdot ½H_2O$), dense alumina (α-Al_2O_3), zirconia (ZrO_2), rutile (TiO_2), calcium phosphates such as hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], and tricalcium phosphates as the α-TCP and β-TCP phases [4, 7-12].

Calcium phosphate based bioceramics stand out among the others, mainly due to their chemical and crystallographic similarity to human bone. As a result, in addition to being non-toxic, they are biocompatible, exhibit bioactive behavior and integrate into living tissue through the same processes active in healthy bone remodeling. This leads to an intimate physicochemical bond between implants and bones, called osteointegration. Other main reasons for the successful use of calcium phosphate biomaterials for bone replacement is the ease of handling and molding, without the need for a previous shape to the implant, fully adapting to the shape of the bone cavity and because they do not heat up during implantation. hardening process, avoiding tissue necrosis at the implantation site [13-15].

With chemical formulation $Ca_3(PO_4)_2$, beta tricalcium phosphate (β-TCP) stands out due to its excellent properties of biocompatibility, in vivo bioactivity, bioresorbability and osteoconductivity, releasing calcium and phosphate ions promoting osteogenesis, which can be partially reabsorbed between 6 to 15 weeks after being implanted in the body [16-20]. In this way, this bioceramic has been highlighted in the use in procedures aimed at bone reconstruction due to its lack of local or systemic toxicity, absence of foreign body responses or inflammation and apparent ability to bind to the host tissue, since its chemical nature it is basically formed by calcium and phosphate ions that actively participate in the ionic balance between the biological fluid and the ceramic [2].

In this sense, this research proposes a prospection study of the last six years of patents and articles related to β-TCP, that is, from 2016 to the first six months of 2021. The number of publications per year, the countries that most published, the ions used in the doping process, the materials used to obtain composites, the main applications and the main methods of synthesis.

II. MATERIALS AND METHODS

This research consisted of a prospective technological and scientific study seeking patents and scientific articles through the CAPES journal portal via CAFE (Federated Academic Community) access. The free databases Espacenet (European Patent Office), USPTO (North American Patent and Trademark Office) and LENS.ORG (global patents and academic knowledge) were used to search for patents; and the databases of Web of Science, Scopus and Science Direct journals were used to search for articles.

The following terms were used as keywords in the search field: β-TCP and beta tricalcium phosphate. For technological prospecting, no specific time was defined, the total number of patents being surveyed, while scientific prospecting took place with the survey of the number of scientific articles published from 2016 to July 2021. In addition, the survey of scientific articles was limited only to research articles, excluding review articles.

III. RESULTS AND DISCUSSION

ANALYSIS OF PUBLISHED PATENTS

Table 1 shows the number of patents found in the European (Espacenet), American (USPTO) and Australian (LENS.ORG) databases.

Table 1: Number of patents found with keywords in Espacenet, USPTO and LENS.ORG databases.

Key words	ESPACENET	USPTO	LENS.ORG
Beta tricalcium phosphate	415	56	1559
β-TCP	769	0	71

The Australian base presented the highest number of patents. It is noticed that no results were found with the keyword “β-TCP” in the American database. This fact is possibly due to the insertion of characters that are not allowed in the search fields of the patent database. In general, most patents are focused on the development of biomaterials, such as prostheses, implants, scaffolds and structures aimed at the development and proliferation of osteoblastic cells.

Wuhan University of Science and Technology patent CN110182777A published in 2019 refers to a method for preparing nanosized β-TCP powders. According to the present invention, polyacrylamide is used as a mild shaping agent, microwave assisted co-precipitation is combined, so that the prepared nanometer beta-tricalcium phosphate powder has characteristics of high purity, size of small particle, good crystallinity, good dispersion property, regular and uniform morphology and stable performance, and it can be used in bone transplantation and other biomedical fields and drug loading [21].

The patent US2021023269A1 developed by the company Orthorebirth in 2020 presents the description of a bone regeneration material that has a structure similar to cotton, formed by a plurality of electrospun fibers. After implantation of bone regeneration material at a bone defect site of a human body, the fibers are tied to β-TCP particles on the surface of the bone regeneration material and promote cell proliferation and differentiation at the bone defect site [22].

The patent EP3572102A1 developed by the company Ossdsign in 2019 refers to ready-to use injectable two paste cement-forming compositions based on monocalcium phosphate monohydrate (MCPM) powder oil and an aqueous suspension of beta tricalcium phosphate powder (β-TCP), respectively. In this way, the biphasic system is injectable and can be used for simplified and fast filling of bone defects in a minimally invasive way, greatly facilitating clinical applications, reducing surgery time, reducing the risk of contamination and ensuring repeatable results [23].

ANALYSIS OF PUBLISHED ARTICLES

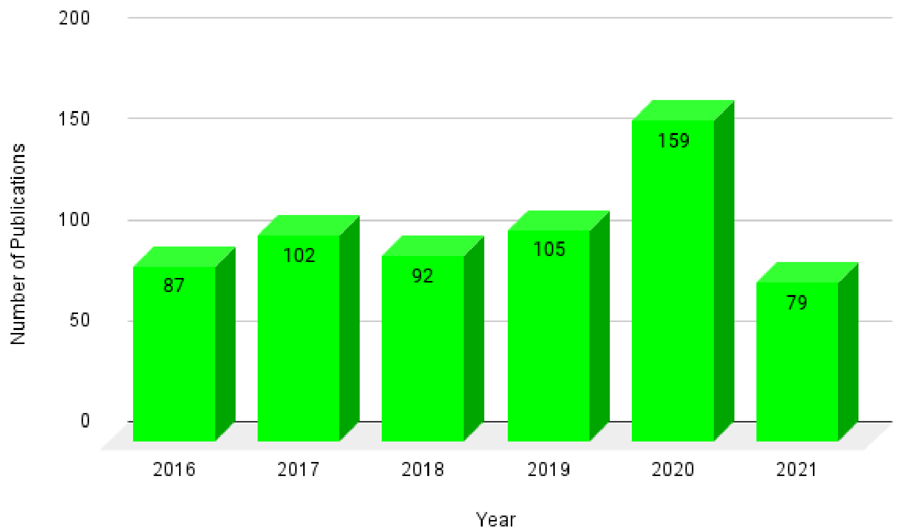
A total of 624 scientific research articles published were obtained during the searches. Table 2 shows the number of articles published in the Web of Science, Scopus and Science Direct databases between January 2016 and July 2021.

Table 2: Number of articles found in the scientific databases Web of Science, Scopus and Science Direct in the last 6 years.

DATA BASE	QUANTITY OF ARTICLES
WEB OF SCIENCE	328
SCIENCE DIRECT	182
SCOPUS	114

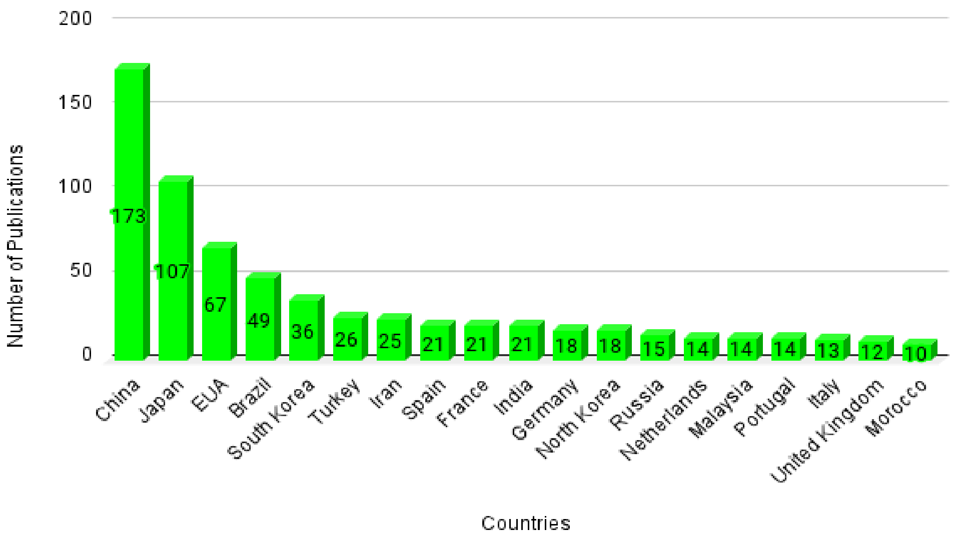
Observing Table 2, it can be seen that the Web of Science database with 328 articles holds the largest number of published articles, corresponding to 52.56% of the total number of articles, followed by the Science Direct database with 182 articles corresponding to at 29.17% and the Scopus base with 114 articles is the base with the lowest number of published articles corresponding to 18.27%. Figure 1 details the annual number of these publications.

Figure 1: Number of articles per year.



Analyzing Figure 1, it can be seen that, in general, there is an increase in the number of publications over the years, probably due to the large number of researches aimed at investigating and improving its excellent properties, which highlights the interest of the academic community for beta tricalcium phosphate. Figure 2 shows in a simplified way the main countries with the respective quantities of publications. A total of 62 different countries were verified, where China with 173 articles is the country that published the most in the last 6 years, followed by Japan and the United States with 107 and 67 publications, respectively.

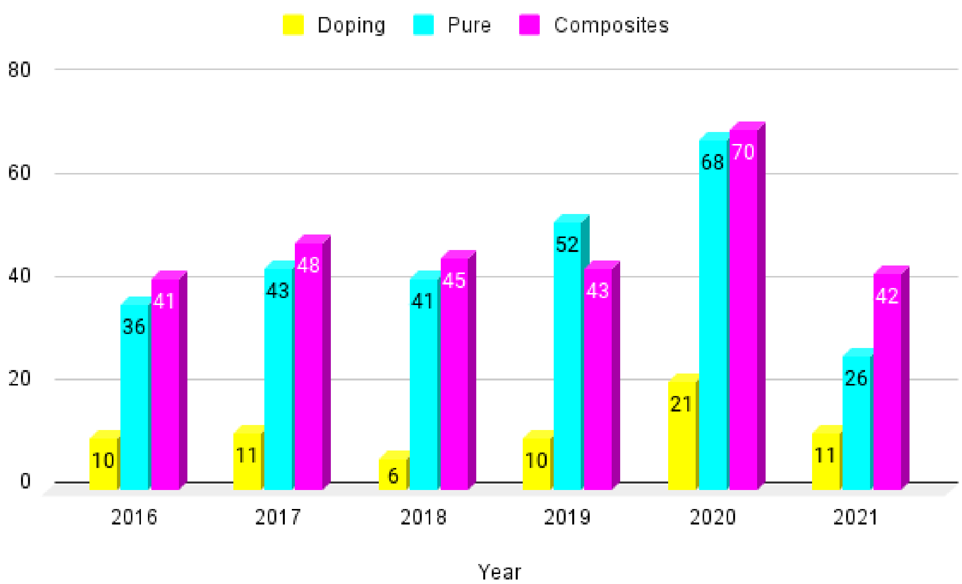
Figure 2: Number of publications by country



B-TCP PURE, DOPED, AND AS A COMPOSITE

The way in which β-TCP was analyzed in research was verified, that is, pure, doped, or as a composite, where it was seen that the synthesis of pure β-TCP concentrates most of the research, corresponding to 45.35% of the syntheses, followed by the formation of composites with 43.59% and doping with ions corresponding to 11.06% of the works. Figure 3 illustrates a graph that illustratively represents this relationship.

Figure 3: Evaluation of the β-TCP phase of the researches that synthesized beta tricalcium phosphate in pure form, from the structural analysis.



There were several research objectives that synthesized beta tricalcium phosphate in pure form, from structural analysis, biodiesel production, synthesis of scaffolds, manufacture of bone cement, among many other applications [24-29].

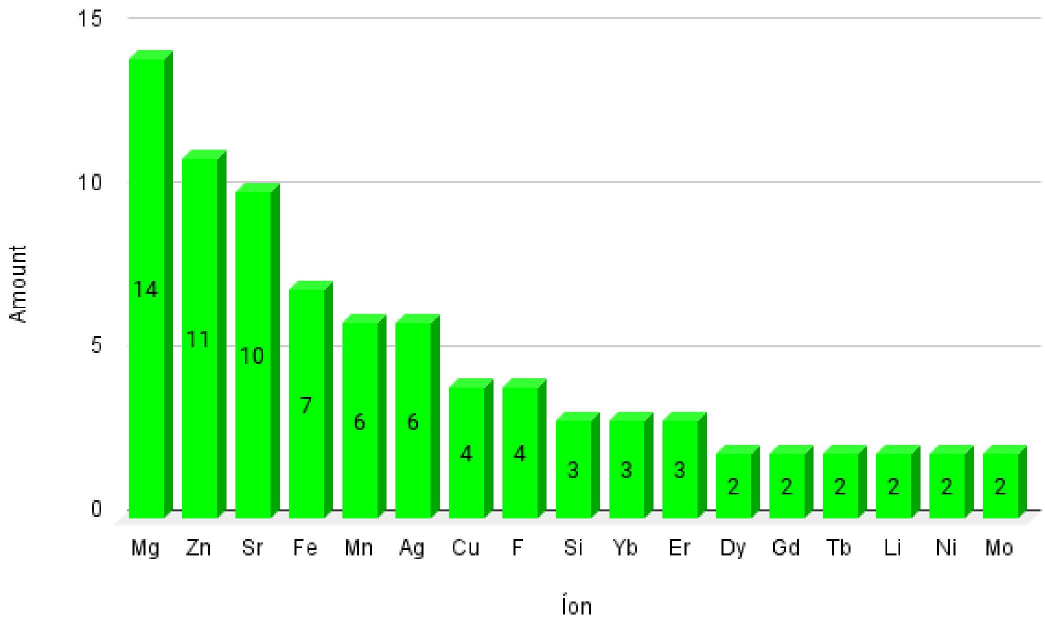
Takeuch et al. [24] synthesized pure porous β-TCP from the carbonate present in starfish, using various conditions of hydrothermal treatments. After removing the organic substances, it was concluded that the starfish structure was formed by calcite granules containing Mg with an interconnected microporous structure of approximately 10−50 μm. After hydrothermal treatment with aqueous ammonium phosphate solutions under various temperature and Ph conditions, the starfish bone structure was converted into Mg-containing β-TCP. After treatment, it was concluded that the temperature and Ph factors affected the morphologies and crystalline phases of the bone structure after treatment, however, it was also found that such changes depended both on the dissolution of calcite and on the rates of formation of calcium phosphate. calcium, which can be applied as a porous bone graft with micro and macropores due to the intergranules of the primitive structure.

DOPING

The doping process is the addition of a very low concentration of an element, which typically ranges from a few parts per million (ppm) to a percentage fraction of the composition of the main material [27, 28]. The addition of dopants can have a significant impact on the synthesis and processing of materials, leading to the obtaining of nanostructures with different morphologies and, consequently, different physical and chemical properties. In this sense, the doping process can affect the synthesis process in a positive way, such as by decreasing the temperature and reaction time, inhibiting the growth of grains or the development of crystal growth in certain faces or directions [29].

When an ion is incorporated into the structure of a bioceramic such as β-TCP, a new category of material is created, where numerous unique properties that overcome the disadvantages of the primitive material favor its use in different biological applications. In this sense, the doping process can improve handling properties, angiogenic and osteogenic performance, antimicrobial activity, among other properties [31, 33-35]. Figure 4 presents the main ions used in the β-TCP doping process.

Figure 4: Ions used in the doping process



Analyzing the data regarding the ions used in the doping process, it was found that there are a total of 69 articles that synthesized β-TCP doped with ions, where there is a variety of 29 different dopants. Among the ions used in the doping process, magnesium (Mg) was the most used, corresponding to 14.74% of the total dopings, followed by zinc (Zn), representing 11.58% of the total and strontium (Sr), representing 10.53% of the total doping.

Magnesium is the fourth most abundant trace element in the human body whose presence is essential for more than 100 enzymes by virtue of its catalytic activity [36]. Thus, the insertion of Mg in the β-TCP crystal structure is of great interest, as it plays an important role in tissue regeneration, conferring an advantage both for the osteogenesis process and for the angiogenesis process [36-38]. In this sense, the incorporation of Mg significantly improves the adhesion, propagation and alkaline phosphatase activity of osteoblastic cells, reducing the risk of osteoporosis [39, 40]. Furthermore, the presence of magnesium within the β-TCP crystal lattice strongly influences the transformation kinetics of the β-TCP phase to α-TCP, slowing it down during heating, as well as promoting the reconversion of the α-TCP phase to β phase. -TCP spontaneously even after rapid cooling, or in sintered TCP components by optimized annealing treatment at 850 °C, and can also increase the phase transformation temperature sequentially, improving sintering density and mechanical properties [40, 41].

Guo et al. [36] analyzed the influence of irradiation time and temperature on the synthesis of β-TCP doped with different Mg substitution contents (0, 5, 10 and 14 mol%) (Mg-TCP) by the microwave-assisted hydrothermal method. It was found that smaller and more homogeneous particles were obtained after microwave irradiation. Microwave irradiation increased defects in crystalline grains causing particle agglomeration. Furthermore, Mg was incorporated into β-TCP as designed and the replacement did not change the phase structure notably, except for the reduction of cellular parameters and lattice volume. Using mesenchymal stem cells from the bone marrow of rats to discuss the influence of Mg-TCP on cell proliferation and differentiation, it was also concluded that the proportion of 14 mol% presented the best facilitation in proliferation and differentiation, while the proportions of 5 and 10 mol% had their effects suppressed by the deposition of ions dissolved in the medium in ceramic samples.

Zinc (Zn) is known to play crucial roles in the formation, mineralization, development and maintenance of healthy bones [42, 43]. Zn^{2+} ions are part of the process of angiogenesis [43], homeostasis [44], have antibacterial action [45], act as a cofactor in several transcription factors and enzymes [46], wound healing processes, increasing fibroblast proliferation [47], being widely used in tissue engineering applications [48].

Boanini et al. [49] applied the Matrix Assisted Pulsed Laser Combinatorial Evaporation (C-MAPLE) technique to deposit gradient thin films with varying compositions of Sr-substituted hydroxyapatite (SrHA) and Zn-substituted beta tricalcium phosphate (ZnTCP) on substrates. titanium, investigating how the compositional mixture of two calcium phosphates that differ in several aspects can be used to modulate the bone cell response. To complement the process, a co-culture model of osteoblasts and osteoclasts was created to reproduce the in vivo microenvironment in which different cells interact with each other and with possible biomaterials that may be present. The study concluded that the presence of SrHA inhibits osteoclast viability and differentiation, while ZnTCP exhibits a beneficial action in the mineralization process promoting osteoblast proliferation and osteocalcin production. Furthermore, intermediate compositions, containing SrHA and ZnTCP, coupled positive effects on osteoblasts with inhibitory action on osteoclasts, providing materials with tailored capacity, via laser processing, in order to improve and accelerate bone repair.

Strontium (Sr) is an alkaline earth metal considered an effective and safe doping element whose effect on bone formation and remodeling becomes more noticeable and different over time depending on the applied concentration [48, 49]. Currently, Sr is used for the treatment of osteoporosis, forming part of the composition of biomaterials, aiming at bone formation and/or remodeling [49, 50]. Furthermore, it accelerates the osteogenesis and mineralization process, where its effects in vivo and in vitro have been studied aiming at bone consolidation and regeneration [51-53].

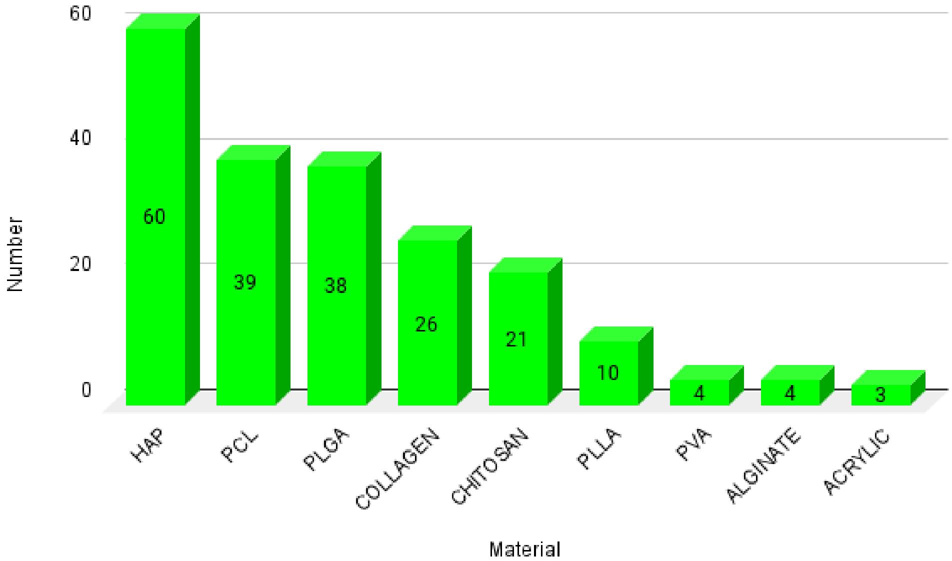
Tohidnezhad et al. [54] investigated the potential of using pure or strontium-doped beta tricalcium phosphate (β-TCP) scaffolds in the process of bone regeneration in mouse femur fractures, evaluating the process of angiogenesis, as well as possible inflammation in the process of bone regeneration. healing. The study concluded that pure β-TCP scaffolds favored the formation of a large percentage of bone tissue in fracture healing, however, the addition of strontium to the scaffolds influenced the inflammatory response at various stages of the healing process, which may have affected regeneration bone. In this way, the study concluded that an extended period of inflammation caused by the addition of strontium accelerates the formation of bone tissue, also accelerating the filling of the fracture, which can help in the treatment of patients suffering from osteoporosis.

COMPOSITES

Composite materials emerged in the mid-20th century as a promising class of engineering materials, providing new perspectives for modern technology. Generally speaking, any material that consists of two or more components with different properties and distinct boundaries between the components can be referred to as a composite material. Furthermore, the idea of combining several components to produce a material with properties that are not attainable with the individual components has been used by man for thousands of years. Correspondingly, most natural materials that emerged as a result of a prolonged process of evolution can be treated as composite materials [55, 56].

There are several studies dedicated to the formation of composite materials together with β-TCP, aiming to increase, improve and incorporate new properties to the conjugated material, where the possibilities of applications are numerous [57]. Figure 5 presents the main materials used to form composites together with β-TCP.

Figure 5: Materials used to manufacture composites.



Analyzing the data regarding the materials used for the formation of composite materials, it was found that there are a total of 272 articles where β-TCP was used for this purpose and a very large variety of different materials used, reaching to exceed the order of 100 different materials. Among the materials used, hydroxyapatite (Hap) was the most used, corresponding to 22.06% of the total composites, followed by Polycaprolactone (PCL), representing 14.34% of the total and polylactic acid-co-glycolic acid. (PLGA), representing 13.97% of total composites.

The use of β-TCP together with hydroxyapatite aiming at the formation of biphasic calcium phosphate ceramics (BCP ceramics), either by mechanical mixing of the two components or by the synthesis itself, aims to improve the biological properties of bioceramics, such as bioactivity, bioresorbability , osteoconductivity and osteoinductivity, in order to increase the formation of bone tissue and manipulate the proportion of the composition of Hap, which is the most stable phase, and β-TCP, which is the most biodegradable phase, seeking to optimize the biodegradation rate and improve the process of bone repair for specific applications [58, 59].

Prezas et al. [60] analyzed the electrical polarization characteristics of pure hydroxyapatite (Hap), and pure beta tricalcium phosphate (β-TCP), as well as the composites formed by the junction of Hap and β-TCP, measuring the thermally stimulated depolarization currents (TSDC). The samples were thermoelectrically polarized at 500 °C under an electric field with a magnitude of 5 kV/cm. The biphasic samples were also polarized under electric fields with different magnitudes: 2, 3, 4 and 5 kV/cm. The results indicate that the β-TCP crystalline phase has a considerably higher capacity to store electrical charge compared to the Hap phase. This indicates that it has a composition and structure suitable for ionic conduction and establishment of high electrical charge density, presenting great potential for orthopedic applications.

Poly(ε-caprolactone) (PCL) is a semi-crystalline, linear-chain synthetic polymer belonging to the class of biodegradable polyesters. Its excellent viscoelasticity properties, adequate degradation kinetics, high flexibility, biodegradability, biocompatibility, non-toxicity, pore sizes and mechanical properties favorable to conduct tissue in growth give this biopolymer the characteristic of being the most attractive and useful class of polyesters. biodegradable, especially when used in resorbable sutures, in scaffolds together with other materials such as β-TCP and in long-term drug/vaccine delivery devices [61-63].

Lowe et al. [64] created a new process for the fabrication of three-dimensional (3D) polycaprolactone (PCL) and beta tricalcium phosphate (β-TCP) scaffolds, evaluating the scaffold behavior under physiological oral conditions, as new bone growth, to establish the relationship between applied physical stresses associated with mandibular function at the bone scaffold interface, seeking to overcome the limits of the proportion of ceramic materials that can be integrated into synthetic polymeric materials for 3D printing. The study concluded that a 50:50 ratio of PCL/β-TCP yields scaffolds capable of sustaining loading as new bone forms, however, it cannot fully replicate bone stiffness. Thus, additional mechanical support would be needed to support the surgical site and compensate for changes in the scaffold due to degradation, where further studies in animal models are needed to verify the suitability for clinical application.

Poly (lactic-co-glycolic acid) (PLGA) is a synthetic, biodegradable, biocompatible copolymer, formed through condensation reactions between lactic acid and glycolic acid monomers, in different proportions. Due to its excellent properties of short time for degradation by hydrolysis, regular chain geometry, mechanical resistance, sustained and appreciable release and safety profile, this biopolymer has a multitude of applications such as: material for biodegradable sutures, production of devices such as implants, tissue grafts, prostheses, therapeutic devices, encapsulation and drug delivery [65-67].

Zheng et al. [68] analyzed the effect of a scaffold composed of beta tricalcium phosphate and polylactic acid-co-glycolic acid β-TCP/PLGA, printed in 3D technology, loaded with osteogenesis-promoting drug (HA15), performing implantation in a model of rabbit radial bone defect. The biomechanical properties of the scaffold were studied by compressive tests, as well as the microstructure, pore morphology, drug release concentration and the scaffold's ability to repair defects were studied. The study concluded that the scaffold loaded with the HA15 delivery system has favorable biomechanical properties comparable to cancellous bone tissue and can promote cell differentiation in osteoblasts in vitro, promoting bone regeneration in a rabbit bone defect model. Furthermore, this framework can enhance angiogenesis, which plays a significant role in more effective bone repair and regeneration.

SYNTHESIS METHOD

Basically, the synthesis of β-TCP can be carried out by the thermal conversion of a precursor with a Ca/P molar ratio ≈ 1.5 such as calcium-deficient hydroxyapatite (CDHA), or amorphous calcium phosphate (ACP), in a range temperature ranging from 650 to 750 °C, or by solid-state reaction of a mixture of solid precursors at high temperatures [69]. However, several other synthesis routes can be used for the synthesis of beta tricalcium phosphate, where the characteristics of the material produced will depend on the type of synthesis used [70].

Table 3 presents the synthesis methods used reported in the literature for the manufacture of beta tricalcium phosphate. It is worth mentioning that only 141 of the total of all articles surveyed described the synthesis methods used, that is, only 22.60% of the total of articles, which indicates that most articles do not report the synthesis route described for manufacturing β-TCP powders, or even, many of the articles use ready-made β-TCP samples from other previous studies.

Table 3: Synthesis methods used to manufacture β-TCP powders

SYNTHESIS METHOD	QUANTITY OF ARTICLES
CHEMICAL PRECIPITATION	49
SOLID STATE REACTION	39
CO - PRECIPITATION	15
SUN - GEL	13
NATURAL SOURCES	13
MICROWAVE ASSISTED HYDROTHERMAL METHOD	4
SPRAY - DRYING	3

SYNTHESIS BY COMBUSTION REACTION	2
MECHANOCHEMICAL SYNTHESIS	2
PYROLYSIS SPRAY	1

Analyzing Table 3, it can be seen that 10 different synthesis routes were described for the manufacture of β-TCP, where the most used synthesis route was the chemical precipitation method, corresponding to 45.39% of the total of articles, followed by the method solid state reaction with 27.66% of the total articles and the co-precipitation method with 10.64% of the total.

Called wet, chemical or aqueous precipitation the method of chemical precipitation is the process by which a soluble substance is converted to an insoluble form either by chemical reaction or by changes in the composition of the solvent to decrease the solubility of the substance contained therein presenting the advantage of the ease in controlling the process parameters, obtaining powders with fine particles, high specific surface area, chemical homogeneity and the use of low-cost reagents, allowing the production of dense ceramics at sintering temperatures lower than the temperatures required for powders obtained by others methods [71, 72].

The method consists of dissolving a solid in a solution, with the formation of ionic species, in sequence the ionic species formed will give rise to precursors when they are again precipitated in the ideal form and quantity. Such a synthesis route consists of two processes: nucleation (growth and formation of the nucleation center) and the subsequent growth of the particles [73].

Such a method must be quantitative and simultaneous, aiming at efficiency, without the preferential separation of some of the constituents of the formed precipitates. Furthermore, it is necessary to strictly control parameters such as pH of the solution, viscosity, temperature and concentration of the reagents, in order to obtain powders with the desired characteristics [73].

Pang et al. [74] coated beta tricalcium phosphate synthesized by the chemical precipitation method on a gold (Au) surface, using the electrophoretic deposition (EPD) method, investigating the adsorption behavior of bovine serum albumin (BSA) and lysozyme (LSZ) on Au/β-TCP surfaces in real time by the dissipation technique using a quartz crystal microbalance (QCM-D). The experiments showed that with increasing electric field strength, more β-TCP nanoparticles with large dimensions could be deposited on a golden surface, where the quantity, dimension and surface roughness of the coatings increased with increasing electrophoresis time. In this way, the study deepened the understanding of the interaction mechanism between biomaterials and proteins, being useful for the design of biomaterials.

The solid state reaction method involves chemical decomposition reactions, in which a mixture of solid reactants is heated to produce a new solid composition and gases. This method is commonly used for the production of complex oxides from simple oxides, carbonates, nitrates, hydroxides, oxalates, alkoxides and other metal salts [75].

Typically, the procedure includes several annealing steps with several intervening grinding steps to increase the homogeneity of the mixture and to decrease the particle size of the powder. Such a method is relatively inexpensive and requires a simple apparatus. Furthermore, large volumes of powder can be prepared relatively simply. However, compared to other methods, the powder obtained shows relatively high agglomeration and therefore relatively large particle size as well as relatively limited homogeneity [75].

Vahabzadeh et al. [76] evaluated the effect of adding different concentrations of Lithium (Li) on the sintering temperature, phase composition, density and compressive strength of beta tricalcium phosphate (β-TCP) synthesized by the solid-state reaction method. For this, concentrations of 0.15, 0.65 and 1% by weight of β-TCP were added, and temperatures of 1150 and 1250°C were used for sintering. The study concluded that the addition of Li at concentrations of 0.65 and 1% by weight inhibited the formation of the β-TCP phase to the α-TCP phase at both sintering temperatures, accompanied by grain growth and extensive formation of grains. liquid phase. The addition of 0.15% by weight of Li at the temperature of 1150°C increased the compressive strength of β-TCP, where the presence of Li increased the apparent density of β-TCP. In addition, greater cell proliferation along with the formation of multilayered cells were found in all doped samples after 3, 7 and 11 days of cell culture, proving the effective role of ion release in the interaction of osteoblastic cells with β-TCP.

Chemical coprecipitation is a method of synthesis where soluble substances are incorporated into the precipitates during formation. This method consists of mixing cations and anions in proportions that exceed the solubility product, causing a change in the pH of the solution, which can be aqueous or not, when the anion responsible for the formation of the insoluble salt is added. At this time, the precipitation phenomenon occurs and the nucleation phase predominates, where a large number of small particles are produced [77, 78].

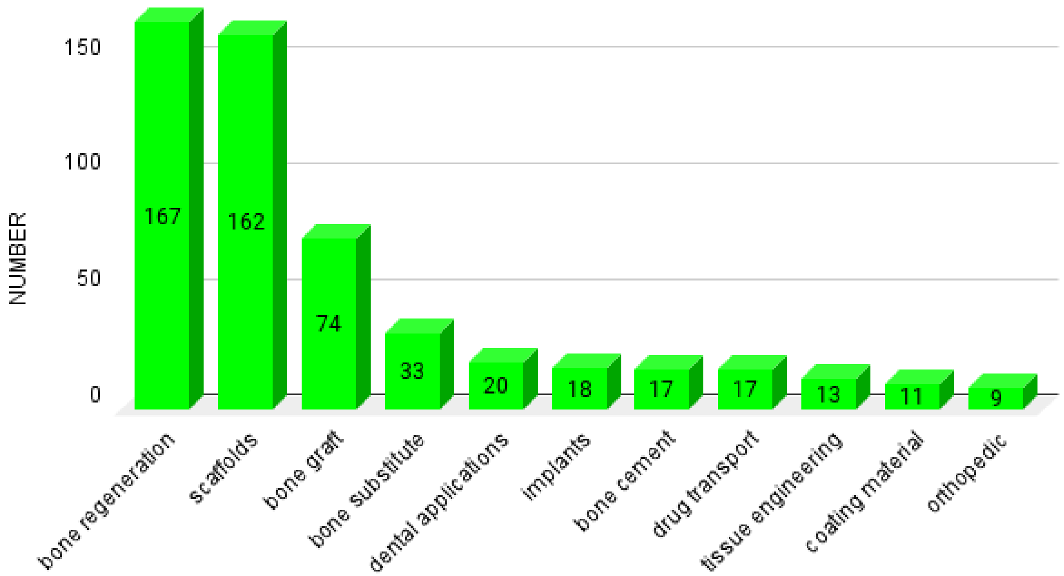
This method is described in the literature as one of the most effective in controlling the properties of materials, combined with operational simplicity and low cost of synthesis, which makes it one of the most used methods. In this sense, the term co-precipitation refers to precipitation reactions in which, in complex systems, the various species involved must be precipitated simultaneously. It is worth mentioning that at the time of synthesis, a solution of cations is mixed with another solution containing the precipitating agent, where the co-precipitate is separated from the supernatant liquid by filtration, washed, dried and calcined to obtain the oxide corresponding to the cations [77, 78].

Yoo et al. [79] investigated the effects of silicon addition on the mechanical properties of β-TCP synthesized via chemical co-precipitation method, used in the production of biocomposites prepared with PLA. The flexural and tensile properties of PLA/Si/β-TCP biocomposites were improved by the substitution of Si ions in β-TCP, especially at 20 wt% filler content. Such results concluded that the internal change such as the substitution of Si ions can improve the mechanical properties of the organic/inorganic composite.

APPLICATIONS

Analyzing the applications, it was found that 541 articles aim at applications in the field of biomaterials, which corresponds to 86.70% of the total of articles, and the remaining 83 articles aim at other distinct and varied applications such as heterogeneous catalysis [80], production of biodegradable batteries [81], production of interference screws (biodegradable screws) [82], magnetic resonance [83] and computed tomography [83]. Figure 6 details the applications aimed at the field of biomaterials.

Figure 6: Applications of β-TCP



It can be seen that there are 11 different applications in the field of biomaterials, where 167 articles applied β-TCP in guided bone regeneration, which corresponds to 30.87% of applications in biomaterials, followed by applications in scaffolds with 162 articles, corresponding to 29 94% and to bone grafts, with 74 articles, corresponding to 13.68%.

Guided bone regeneration (GBR) is a surgical procedure that uses graft materials and barrier membranes to stimulate and guide the growth of new bone in defects. In this technique, an autogenous bone and/or a biomaterial is placed in the deficient bone area, maintaining the space and stimulating the formation of new bone, where membranes are used above the filled defect to prevent soft tissue permeation. This technique is used, for example, to restore bone in case of fenestration-like defects or dehiscence around the implant, to compensate for major maxillary deficiencies, or to prevent bone resorption after tooth extraction in deficient sockets [84, 85].

Santos et al. [86] developed PLGA membranes together with hydroxyapatite and beta tricalcium phosphate, evaluating the mechanical, morphological and in vitro properties, trying to overcome the limitations of bone regenerative capacity, adequate mechanical behavior or adequate degradation profile. The analysis of the results concluded that the membranes produced showed adequate interlayer adhesion, a pore size of the dense layer of 4.20 μm and an electrospun layer with a degree of porosity of 38.2%, being able to prevent the infiltration of fibroblasts at the same time as allows, the migration of osteoblasts and the permeation of nutrients. In addition, they presented a glass transition temperature of 82 °C and a superior storage module, which remained constant up to 54.6 °C, important characteristics for membrane implantation and use without mechanical compromise, where they also presented excellent fixation, proliferation and migration. of osteoblasts, confirming the great potential of the membranes in bone reconstruction with an adequate profile of degradation, morphology, mechanical behavior and bone regenerative capacity.

Scaffolds are three-dimensional structures that have a porous three-dimensional framework, bioactive and biodegradable properties, which promote cell proliferation, or cell colonization, providing a stable environment, serving as a template for the formation of new tissue. The mechanical and degradation properties are directly related to the material that makes up the scaffold. Thus, the main biological interactions, such as adhesion between proteins and peptides, cell adhesion, migration, proliferation and differentiation, are primary functions of the surface properties of the material in question [87-89].

Rajabi and Esmaelli [90] synthesized scaffolds composed of biphasic calcium phosphate ceramics (BCP ceramics) composed of hydroxyapatite and beta tricalcium phosphate, in addition to gelatin and bioglass, which were used in the drug transport process, aiming at guided bone regeneration. The study concluded that the biocompatibility and mechanical strength of this scaffold was adequate and resembled natural bone structure materials. In addition, the use as drug transport had an efficiency of 80% for a concentration of 5mg/l, all the properties of the nanoparticles in vitro were formed based on the three phases of the biocomposite, where it was concluded that, after 8 weeks, the in vitro experiment vivo led to the formation of bone and collagen sheets and connective tissue layer.

Bone graft is the name used for bone tissue transplanted from a donor area to another recipient area. When it belongs to the same individual, it is called an autogenous graft, when the bone originates from another person, it is called a homogenous graft, and when the bone originates from a donor of another species (non-human) it is called a heterogenous graft. In this sense, the autogenous graft is the only one that provides live, immunocompatible and indispensable bone cells for osteogenesis. In its various forms and applications, bone grafts represent one of the most important methods for the reconstruction of the musculoskeletal system and are the most used technique in orthopedic procedures, being used as an adjunct in fracture repair and replacement of skeletal defects [91].

Song et al. [92] proposed a bone graft support model to increase the mechanical strength of bioprinted 3D constructs. The 3D constructs were bioprinted using polycaprolactone (PCL) ink for the external support in extrusion mode and cell-loaded tricalcium phosphate (TCP)/alginate bioink for the internal fill in air pressure delivery mode. The relationship of bioink viscosity, 3D bioprint pressure, TCP/alginate ratio, and cell survival were investigated by shear viscosities, live/dead cell analysis and testing, and cell count kit measurement. In this way, the study allowed low viscosity bioinks to be bioprinted for manufacturing 3D constructions, providing sufficient mechanical strength for 3D units. In this sense, it was found that the printing pressure was closely associated with the viscosity of the bioinks, affecting the survival of cells after printing, where when the bioink viscosity was in the range of 3.86 to 61.65 Pas, the 3D bioprinting process could achieve good printability and higher cell survival rate, concluding that the combination of the use of 3D bioprinting technique and support was viable to obtain personalized substitutes.

IV. CONCLUSION

In the last 6 years, the number of scientific research related to beta tricalcium phosphate has been increasing. The results presented with the technological mapping revealed that there are a total of 624 scientific articles on β-TCP indexed in the journal databases, and 2870 registered patents, of which 1184 belong to the ESPACENET database, 56 to the USPTO and 1630 to the LENS.ORG. Analyzing the countries involved in the publications, it was found that China is the country that has the most scientific articles published in the area, totaling 173 publications. Most of the applications are focused on the field of biomaterials, where the field of guided bone regeneration is the main bioapplication. The main method of synthesis is the chemical precipitation method, where there are 272 publications involving the formation of composites, 69 publications involving doping with metal ions and 283 publications that synthesized β-TCP in a pure form.

REFERENCES

[1]. Barrere, F; Mahmood, T. A; Groot, K; Blitterswijk, C. A. V. Advanced biomaterials for skeletal tissue regeneration: instructive and smart functions. Materials Science and Engineering, v. 59, p.38-71, 2008.

[2]. Sinhoreti, M. A. C.; Vitti, R. P.; Correr-Sobrinho, L. Biomaterials in Dentistry: current view and future perspectives. Revista da Associação Paulista de Cirurgiões Dentistas, vol.67, n°4, p.178-86, 2013.

[3]. Pires, A. L. R.; Bierhalz, A. C. K.; Moraes, A. M. Biomateriais: tipos, aplicações e mercado. Química Nova, vol.38, n°7, p.957-971, 2015.

[4]. Kawachi, E. Y.; Bertran, C. A.; Reis, R. R.; Alves, O. L. Biocerâmicas: tendências e perspectivas de uma área interdisciplinar. Química Nova, vol.23, n°4, p.518-522, 2000.

[5]. Oréfice, R. L; Pereira, M. M.; Mansur, H. S. Biomateriais: fundamentos e aplicações. Rio de Janeiro: Cultura Médica, 2006.

[6]. Oliveira, S. V; Medeiros, K. M; Araújo, E. P; Braga, C. R. C; Araújo, E. M; Fook, M. V. L. Caracterização química e morfológica do pirofosfato de cálcio obtido por via úmida. Revista Eletrônica de Materiais e Processos, v. 4.3, p. 11-20, 2009.

[7]. Prakash, C.; Singh, S. On the characterization of functionally graded biomaterial primed through a novel plaster mold casting process. Materials Science & Engineering C, v.110, p.110654, 2020.

[8]. Rodríguez, A. K. M.; Alvarado, J. A. G.; Requena, C. L. V.; López, S. Y. R. In vitro evaluation of poly-ε-caprolactone-hydroxypatite-alumina electrospun fibers on the fibroblast's proliferation. Results in Materials, vol.6, p.100091, 2020.

[9]. Faria, D.; Henriques, B.; Souza, A. C.; Silva, F. S.; Carvalho, O. Laser-assisted production of HAp-coated zirconia structured surfaces for biomedical applications. Journal of the Mechanical Behavior of Biomedical Materials, vol.112, p.104049, 2020.

[10]. Wagstaffe, M.; Hussain, H.; Taylor, M.; Murphy, M.; Silikas, N.; Thomas, A. G. Interaction of a tripeptide with titania surfaces: RGD adsorption on rutile TiO2(110) and model dental implant surfaces. Materials Science & Engineering C, vol. 105, p.110030, 2019.

[11]. Sebastiammal, S.; Fathima, A. S. L.; Devanesan, S.; AlSalhi, M. S.; Henry, J.; Govindarajan, M.; Vaseeharan, B. Curcumin-encased hydroxyapatite nanoparticles as novel biomaterials for antimicrobial, antioxidant and anticancer applications: A perspective of nano-based drug delivery. Journal of Drug Delivery Science and Technology, vol.57, p.101752, 2020.

[12]. Rad, M. R.; Fahimipour, F.; Dashtimoghadam, E.; Nokhbatolfoghahaei, H.; Tayebi, L.; Khojasteh, A. Osteogenic differentiation of adipose-derived mesenchymal stem cells using 3D-Printed PDLLA/ β-TCP nanocomposite scaffolds. Bioprinting, vol.21, p.e00117, 2021.

[13]. Farias, J. R. S.; Carvalho, G. K. G.; Braga, A. N. S. Cerâmicas de fosfatos de cálcio bifásicas: uma revisão. Revista Eletrônica de Materiais e Processos, v. 15, n°2, p.54-70, 2020.

[14]. Moraes, P. C.; Filho, J. G. P.; Canola, J. C.; Santos, L. A.; Macoris, D.Graça.; Alessi, A. C.; Castro, M. B.; Neto, F. A. D. Biocompatibilidade do cimento de fosfato de cálcio implantado no rádio de coelhos. Acta Cir Bras, vol.19, n°4, p.351-359, 2004.

[15]. Dorozhkin, S. V. Bioceramics of calcium orthophosphates. Biomaterials, vol.31, n°7, p.1465- 1485, 2010.

[16]. Eslaminejad, M. B.; Bordbar, S.; Nazarian, H. Odontogenic differentiation of dental pulp- derived stem cells on tricalcium phosphate scaffolds. Journal of Dental Sciences, v. 8, n. 3, p. 306–313, 2013.

[17]. Leucht, P.; Castillo, A. B.; Bellino, M. J. Comparison of tricalcium phosphate cement and cancellous autograft as bone void filler in acetabular fractures with marginal impaction. Injury, v. 44, n. 7, p. 969–74, 2013.

[18]. Stefanic, M.; Krnel, K.; Kosmac, T. Novel method for the synthesis of a âtricalcium phosphate coating on a zirconia implant. Journal of the European Ceramic Society, v. 33, p. 3455–3465, 2013.

[19]. Wang, L., Ma, X., Zhang, Y., Feng, Y., Li, X., Hu, Y., Wang, Z., Ma, Z., Lei, W. Repair of Segmental Bone Defect Using Totally Vitalized Tissue Engineered Bone Graft by a Combined Perfusion Seeding and Culture System. Plos One, vol.9, n°4, p.e94276, 2014.

[20]. Hench, L. L.; Wilson, J. An introduction to bioceramics. 1. ed. Singapore: World Scientific Publishing Company, 1993.

[21]. Xinyu, W.; Fei, S. Beta-tricalcium phosphate nanometer powder preparation method. Depósito: 22 abr. 2022. Concessão: 30 ago. 2019. Acesso em: 16 abr. 2022.

[22]. Hiroyuki, T.; Alvarez, L. bone regeneration material having a cotton-wool like structure formed of a plurality of electrospun fibers. depositante: taira hiroyuki. us2021023269a1. depósito: 6 out. 2020. concessão: 28 jan. 2021. acesso em: 16 abr. 2022.

[23]. Luo, J.; engqvist, h.; persson, c. two-paste cement-forming compositions. depositante: luo jun. ep3572102a1. depósito: 21 mai. 2019. concessão: 27 nov. 2019. acesso em: 16 abr. 2022.

[24]. Takeuch, A.; Tsuge, T.; Kikuch, M. Preparation of porous β-tricalcium phosphate using starfish-derived calcium carbonate as a precursor. Ceramics International, vol.42, p.15376-15382, 2016.

[25]. Madhu, D.; Sharma, Y. C. Synthesis of a reusable novel catalyst (β-tricalcium phosphate) for biodiesel production from a common Indian tribal feedstock. Resource-Efficient Technologies, vol.3, n°2, p.144-157, 2017.

[26]. Fukuda, N.; Tsuru, K.; Mori, Y.; Ishikawa, K. Fabrication of self-setting b-tricalcium phosphate granular cement. Journal of Biomedical Materials Research, vol.106, n°2, p.800-807, 2017.

[27]. Putri, T. S.; Sugiura, Y.; Tsuru, K.; Ishikawa, K. Fabrication of an interconnected porous β-tricalcium phosphate structure by polyacrylic acid-mediated setting reaction and sintering. Journal of the Ceramic Society of Japan, vol.128, n°8, p.555-559, 2020.

[28]. Wang, X.; Lin, M.; Kang, Y. Engineering Porous β- Tricalcium Phosphate (β-TCP) Scaffolds with Multiple Channels to Promote Cell Migration, Proliferation, and Angiogenesis. ACS Applied Materials & Interfaces, vol.11, n°9, p.9223-9232, 2019.

[29]. Bovand, D; Arabi, A. M; Bovand, M. Microwave assisted solution combustion synthesis of β-tricalcium phosphate nano-powders. Boletín de la Sociedad Española de Cerámica y Vidrio, vol. 57, p.240-246, 2018.

[30]. Nedelec, J. M.; Courtheoux, L.; Jallot, E.; Kinowski, C.; Lao, J.; Laquerriere, P.; Mansuy, C.; Renaudin, G.; Turrell, S. Materials doping through sol–gel chemistry: a little something can make a big difference. Journal of Sol-Gel Science and Technology, v. 46, p.259–271, 2008.

[31]. Schatkoski, V. M.; Montanheiro, T. L. A.; Menezes, B. R. C.; Pereira, R. M.; Rodrigues, K. F.; Ribas, R. G.; Silva, D. M.; Thim, G. P. Current advances concerning the most cited metal ions doped bioceramics and silicate-based bioactive glasses for bone tissue engineering. Ceramics International, vol. 47, p.2999-3012, 2021.

[32]. Kolar, D. Chemical research needed to improve high-temperature processing of advanced ceramic materials (Technical report). Pure and Applied Chemistry, v. 72, n. 8, p. 1425-1448, 2000.

[33]. Pan, X.; Huang, J.; Zhang, K.; Pei, Z.; Ding, Z.; Liang, Y.; Gu, Z.; Li, G.; Xie, H. Iron-doped brushite bone cement scaffold with enhanced osteoconductivity and antimicrobial properties for jaw regeneration. Ceramics International, vol. 47, p.25810-25820, 2021.

[34]. Kulanthaivel, S.; Mishra, U.; Agarwal, T.; Giri, S.; Pal, K.; Pramanik, K.; Banerjee, I. Improving the osteogenic and angiogenic properties of synthetic hydroxyapatite by dual doping of bivalent cobalt and magnesium ion. Ceramics International, vol. 41, p.11323-11333, 2015.
[35]. Almeida, C. M.; Ribeiro, J. S.; Meereis, C. T. W.; Ogliari, A. O.; Noremberg, B. S.; Ogliari, F. A.; Michelon, D.; Lund, R. G. β-TCP nanoparticles doped with antimicrobial agents as an orthodontic adhesive component. International Journal of Adhesion and Adhesives, vol. 110, p.102896, 2021.
[36]. Guo, X.; Long, Y.; Li, W.; Dai, H. Osteogenic effects of magnesium substitution in nano-structured β-tricalcium phosphate produced by microwave synthesis. Osteogenic effects of magnesium substitution in nano-structured β-tricalcium phosphate produced by microwave synthesis. Journal of Materials Science, vol.54, n°16, p.11197–11212, 2019.
[37]. Banerjee, S.S.; Tarafder, S.; Davies, N. M.; Bandyopadhyay, A.; Bose, S. Understanding the influence of MgO and SrO binary doping on the mechanical and biological properties of beta-TCP ceramics. Acta Biomaterialia, vol.6, n°10, p.4167–4174, 2010.
[38]. Bose, S.; Tarafder, S.; Bandyopadhyay, A. Effect of chemistry on osteogenesis and angiogenesis towards bone tissue engineering using 3D printed scaffolds. Annals of Biomedical Engineering, vol.45, n°1, p.261–272, 2017.
[39]. Landi, E.; Logroscino, G.; Proietti, L.; Tampieri, A.; Sandri, M.; Sprio, S. Biomimetic Mg-substituted hydroxyapatite: from synthesis to in vivo behaviour. Journal of Materials Science: Materials in Medicine, vol.19, n°1, p.239–247, 2008.
[40]. Ryu, H. S.; Hong, K. S.; Lee, J. K.; Kim, D. J.; Lee, J. H.; Chang, B. S.; Lee, D. H.; Lee, C. K.; Chung, S. S. Magnesia-doped HA/beta-TCP ceramics and evaluation of their biocompatibility. Magnesia-doped HA/β-TCP ceramics and evaluation of their biocompatibility. Biomaterials, vol.25, n°3, p.393-401, 2004.
[41]. Frasnelli, M.; Sglavo, V. M. Effect of Mg2+ doping on beta–alpha phase transition in tricalcium phosphate (TCP) bioceramics. Acta Biomaterialia, vol.33, p.283-289, 2016.
[42]. Neščákováa, Z.; Zheng, K.; Liverani, L.; Nawaz, Q.; Galusková, D.; Kaňková, H.; Michálek, M.; Galusek, D.; Boccaccini, A. R. Multifunctional zinc ion doped sol – gel derived mesoporous bioactive glass nanoparticles for biomedical applications. Bioactive Materials, vol.4, p.312-321, 2019.
[43]. Balasubramanian, P.; Strobel, L. A.; Kneser, U.; Boccaccini, A. R. Zinc-containing bioactive glasses for bone regeneration, dental and orthopedic applications. Biomedical glasses, vol.1, n°1, p. 51-69, 2015.
[44]. Pérez, R.; Sanchez-Salcedo, S.; Lozano, D.; Heras, C.; Esbrit, P.; Vallet-Regí, M.; Salinas, A. J. Osteogenic Effect of ZnO-Mesoporous Glasses Loaded with Osteostatin. Nanomaterials, vol.8, n°8, p. 592, 2018.
[45]. Chasapis, C. T.; Spiliopoulou, C. A.; Loutsidou, A. C.; Stefanidou, M. E. Zinc and human health: an update. Archives of Toxicology, vol.86, n°4, p. 521-534, 2012.
[46]. Stubbs, N.; Lansdown, A. B. G.; Ågren, M. S.; Mirastschijski, U.; Scanlon, E. Zinc in wound healing: theoretical, experimental, and clinical aspects. Wound Repair Regen, vol.15, n°1, p. 2-16, 2007.
[47]. Stefanidou, M.; Maravelias, C.; Dona, A.; Spiliopoulou, C. Zinc: a multipurpose trace element. Archives of Toxicology, vol.80, n°1, p. 1-9, 2006.
[48]. Wu, C.; Chang, J. Multifunctional mesoporous bioactive glasses for effective delivery of therapeutic ions and drug/growth factors. Journal of Controlled Release, vol.193, p. 282-295, 2014.
[49]. Boanini, E.; Torricelli, P.; Sima, F.; Axente, E.; Fini, M.; Mihailescu, I. N.; Bigi, A. Gradient coatings of strontium hydroxyapatite/zinc β-tricalcium phosphate as a tool to modulate osteoblast/osteoclast response. Journal of Inorganic Biochemistry, vol.183, p.1-8, 2018.
[50]. Baheiraei, N., Eyni, H., Bakhshi, B.; Najafloo, R.; Rabiee, N. Effects of strontium ions with potential antibacterial activity on in vivo bone regeneration. Scientific Reports, vol.11, n°8745, 2021.
[51]. Neves, N., Linhares, D., Costa, G., Ribeiro, C.; Barbosa, M. In vivo and clinical application of strontium-enriched biomaterials for bone regeneration: a systematic review. Bone & Joint Research, vol.6, p.366-375, 2017.
[52]. O'Donnell, S., Cranney, A., Wells, G. A., Adachi, J. D. & Reginster, J. Y. Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database of Systematic Reviews, vol.19, n°3, 2006.
[53]. Pilmane, M., Salma-Ancane, K., Loca, D., Locs, J.; Berzina-Cimdina, L. Strontium and strontium ranelate: historical review of some of their functions. Materials Science And Engineering: C, vol.1, n°78, p.1222-1230, 2017.
[54]. Molino, G., Bari, A., Baino, F., Fiorilli, S.; Vitale-Brovarone, C. Electrophoretic deposition of spray-dried Sr-containing mesoporous bioactive glass spheres on glass–ceramic scaffolds for bone tissue regeneration. Journal of Materials Science, vol.52, p.9103- 9114, 2017.
[55]. Jalise, S. Z., Baheiraei, N.; Bagheri, F. The effects of strontium incorporation on a novel gelatin/bioactive glass bone graft: In vitro and in vivo characterization. Ceramics International, vol.44, p.14217- 14227, 2018.
[56]. Vasiliev, V. V.; Morozov. E. V. Advanced Mechanics of Composite Materials and Structures, Chapter 1 - Mechanics of a Unidirectional Ply, 2018.
[57]. Bohner, M.; Santoni, B. G.; Döbelin, N. β-tricalcium phosphate for bone substitution: Synthesis and properties. Acta Biomaterialia, vol.113, p.23-41, 2020.
[58]. Ebrahimi. M.; Botelho, M. G.; Dorozhkin, S. V. Biphasic calcium phosphates bioceramics (HA/TCP): Concept, physicochemical properties and the impact of standardization of study protocols in biomaterials research. Materials Science and Engineering: C, vol.71, p.1293-1312, 2017.
[59]. Mano. J. F.; Silva, G. A.; Azevedo, H. S.; Malafaya, P. B.; Sousa, R. A.; Silva, S. S.; Boesel, L. F.; Oliveira, J. M.; Santos, T. C.; Marques, A. P.; Neves, N. M.; Reis, R. L. Natural origin biodegradable systems in tissue engineering and regenerative medicine: present status and some moving trends. Journal of the Royal Society Interface, vol.4, p. 999-1030, 2007.
[60]. Prezas, P. R.; Melo, B. M. G.; Costa, L. C.; Valente, M. A.; Lança, M. C.; Ventura, J. M. G.; Pinto, L. F. V.; Graça, M. P. F. TSDC and impedance spectroscopy measurements on hydroxyapatite, β-tricalcium phosphate and hydroxyapatite/-tricalcium phosphate biphasic bioceramics. Applied Surface Science, vol.424, p.28-38, 2017.
[61]. Dwivedi, R.; Kumar, S.; Pandey, R.; Mahajan, A.; Nandana, D.; Katti, D. S.; Mehrotra, D. Polycaprolactone as biomaterial for bone scaffolds: Review of literature. Journal of Oral Biology and Craniofacial Research, vol.10, n°1, p.381-388, 2020.
[62]. Woodruff, M. A.; Hutmacher, D. W. The return of a forgotten polymer—Polycaprolactone in the 21st century. Progress in Polymer Science, vol.35, p.1217-1256, 2010.
[63]. Sinha, V. R.; Bansal, K.; Kaushik, R.; Kumria, R.; Trehan. A Poly-Ɛ-caprolactone microspheres and nanospheres: an overview. International Journal of Pharmaceutics, vol.278, p.1-23, 2004.

[64]. Lowe, B.; Huotilainen, E.; Laitinen, M.; Henell, A. M.; Ye, Q.; Troulis, M. J.; Walsh, L. J. FEA evaluation of material stiffness changes for a polymer assisted 3D polycaprolactone/β-tricalcium phosphate scaffold in a mandibular defect reconstruction model. Ceramics International, vol.47, p.8075-8081, 2021.

[65]. Zhao, D.; Zhu, T.; Li, J.; Cui, L.; Zhang, Z.; Zhuang, X.; Ding, J. Poly(lactic-co-glycolic acid)-based composite bone-substitute materials. Bioactive Materials, vol.6, n°2, p.346-360, 2021.

[66]. Swider, E.; Koshkina, O.; Tel, J.; Cruz, L. J.; Vries, J. M.; Srinivas, M. Customizing poly(lactic-co-glycolic acid) particles for biomedical applications. Acta Biomaterialia, vol.73, p.38-51, 2018.

[67]. Erbetta, C. D. C.; Alves, R. J.; Resende, J. M.; Freitas, R. F. S.; Sousa, R. G. Synthesis and characterization of poly (D,L-lactide-co-glycolide) copolymer. Journal of Biomaterials and Nanobiotechnology, vol.3, p. 208-225, 2012.

[68]. Zheng, X.; Attarilar, S.; Li, K.; Wang, X.; Liu, J.; Wang, L.; Yang, J.; Tang, Y. 3D-printed HA15-loaded β-Tricalcium Phosphate/Poly (Lactic-co-glycolic acid) Bone Tissue Scaffold Promotes Bone Regeneration in Rabbit Radial Defects. International Journal of bioprinting, vol.7, n°1, 2021.

[69]. Bohner, M.; Santoni, B. L. G.; Döbelin, N. β-tricalcium phosphate for bone substitution: Synthesis and properties. Acta Biomaterialia, vol..113, p.23-41, 2020.

[70]. Chaair, H.; Labjar, H.; Britel, O. Synthesis of β-tricalcium phosphate Synthèse du phosphate tricalcique-β. Morphologie, vol.101, n°334, p.120-124, 2017.

[71]. Liang, L. Filtration and Separation. In: Standard handbook of hazardous waste treatment and disposal. FREEMAN, H Ed. McGraw-Hill, 2ed., 1997.

[72]. Mazumder, S.; Nayak, A. K.; Ara, T. J.; Hasnain, M. S. Hydroxyapatite composites for dentistry. Applications of Nanocomposite Materials in Dentistry. 2019, Pages 123-143.

[73]. Kakihana, M.; Okubo, T.; Arima, M.; Nakamura, Y.; Yashima, M.; Yoshimura, M. Polymerized complex route to the synthesis of pure SrTiO3 at reduced temperatures: implication for formation of Sr-Ti heterometallic citric acid complex. Journal of Sol-Gel Science and Technology, v. 12, 1998.

[74]. Pang, D.; He, L.; Wei, L.; Zheng, H.; Deng, C. Preparation of a beta-tricalcium phosphate nanocoating and its protein adsorption behaviour by quartz crystal microbalance with dissipation technique. Colloids and Surfaces B: Biointerfaces, vol.162, p.1-7, 2018.

[75]. Buekenhoudt, A.; Kovalevsky, A.; Luyten, Ir J., Snijkers, F. Basic Aspects in Inorganic Membrane Preparation. Comprehensive Membrane Science and Engineering, Volume 1, 2010, Pages 217-252.

[76]. Vahabzadeh, S.; Hack, V. K.; Bose, S. Lithium-doped b-tricalcium phosphate: Effects on physical, mechanical and in vitro osteoblast cell–material interactions. Journal of Biomedical Materials Research, vol.105, n°2, p.391-399, 2015.

[77]. Wang, F.; Liu, X. Rare-Earth Doped Upconversion Nanophosphors. Comprehensive Nanoscience and Technology, Volume 1, 2011, Pages 607-635.

[78]. Bellardita, M.; Di Paola, A.; Yurdakai, S.; Palmisano, L. Preparation of Catalysts and Photocatalysts Used for Similar Processes. Heterogeneous Photocatalysis, 2019, Pages 25-56.

[79]. Yoo, K. H.; Cho, H. S.; Kim, D. H.; Lee, J. K.; Yong-Il, K.; Hwang, K. H.; Yoon, S. Y. Polylactic Acid/Nanostructured Si-Substituted β-Tricalcium Phosphate Composites for Biodegradable Fixation Medical Devices. Journal of Nanoscience and Nanotechnology, vol.18, p.856–860, 2018.

[80]. Bitire, S. O.; Jen, T. C.; Belaid, M. Synthesis of beta-tricalcium phosphate catalyst from Herring fishbone for the transesterification of parsley seed oil. Environmental Technology, vol.2, p.1-13, 2021.

[81]. Xia, J.; Yuan, Z.; Cai, F. Toward a Biocompatible and Degradable Battery Using a Mg-Zn-Zr Alloy with β-Tricalcium Phosphate Nanocoating as Anode. Journal of Materials Engineering and Performance, vol.27, p.4005–4009, 2018.

[82]. Santos, A. E.; Braccialli, A. L.; Vilela, J.; Foschini, C. E.; Sanchez, L. E. A. Poly L, DL-lactic acid, and composite poly l, DL-lactic acid/β-tricalcium phosphate-based bioabsorbable interference screw. Polymer Composites, vol.40, n°6, p.2197-2207, 2019.

[83]. Meenambal, R.; Sanjeevi, K.; Geethanath, S.; Poojar, P. Structural insights in Dy 3+ -doped b-Tricalcium phosphate and its multimodal imaging characteristics. Journal of the American Ceramic Society, vol.1, n°11, 2017.

[84]. Jensen, T.; Schou, S.; Svendsen, P. A.; Forman, J. L.; Gundersen, H. J. G.; Terheyden, H.; Holmstrup, P. Volumetric changes of the graft after maxillary sinus floor augmentation with Bio-Oss and autogenous bone in different ratios: a radiographic study in minipigs. Clinical Oral Implants Research, vol.23, n°8, p.902-10, 2012.

[85]. Orsini, G.; Scarano, A.; Degidi, M.; Caputi, S.; Iezzi, G.; Piattelli, A. Histological and ultrastructural evaluation of bone around Bio-Oss particles in sinus augmentation. Oral Diseases, vol.13, n°6, p.586-93, 2007.

[86]. Santos, V. I.; Merlini, C.; Aragones, A.; Cesca, K.; Fredel, M. C. In vitro evaluation of bilayer membranes of PLGA/hydroxyapatite/β-tricalcium phosphate for guided bone regeneration. Materials Science and Engineering: C, vol.112, 2020.

[87]. Hutmacher, D. W.; Schantz, J. T.; Lam, C. X. F.; Tan, K. G.; Lim, T. C. State of the art and future directions of scaffold-based bone engineering from a biomaterials perspective. Journal of Tissue Engineering and Regenerative Medicine, vol.1, n°4, p.245-260, 2007.

[88]. Liu, X; Ma, P. X. Polymeric Scaffolds for Bone Tissue Engineering. Ann. Biomed. Eng, vol. 32, p.477-486, 2004.

[89]. Oliveira, L. S. A. F; Oliveira, C. S; Machado, A. P. L; Rosa, F. P. Biomateriais com aplicação na regeneração óssea – método de análise e perspectivas futuras. Revista de Ciências Médicas e Biológicas, vol. 9, p.37-44, 2010.

[90]. Rajabi, A.; Esmaelli, A. Preparation of three-phase nanocomposite antimicrobial scaffold BCP/Gelatin/45S5 glass with drug vancomycin and BMP-2 loading for bone regeneration. Colloids and Surfaces A: Physicochemical and Engineering Aspects, vol.606, 2020.

[91]. Puricelli, E.; Baraldi, C. E. E.; Cardoso, C. F. R. Princípios cirurgicos para enxertos ósseos nas reconstruções alveolares. In: Atualização clínica em odontologia. São Paulo: Artes Médicas: APCD, 2004. Cap. 2, p.13-35.

[92]. Song, J. L.; Fu, X. Y.; Raza, A.; Shen, N. A.; Xue, Y. Q.; Wang, H. J.; Wang, J. Y. Enhancement of mechanical strength of TCP-alginate based bioprinted constructs. Journal of the Mechanical Behavior of Biomedical Materials, vol.103, 2020.

Farias, J. R. S, et. al. "Beta tricalcium phosphate (β-TCP): A scientific and technological mapping."*American Journal of Engineering Research (AJER)*, vol. 11(06), 2022, pp. 125-138.