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Bone Cement: A Review

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ABSTRACT

The biomaterials are therefore substances or combination of substances (except drugs) originated from nature or manufactured. Being accepted on a provisional or permanent basis to improve, augment or replace tissues or organs of living beings. This definition has been consolidated in the Consensus Conference on Biomaterials for clinical applications in 1982. The bone cement is a material originated by mixing two or more components, with the purpose of filling the space between the prosthesis and the bone, acting as a fixing of the prosthesis. The use of bone cement began from the decade 60, where their constituents, to the present day, have high biocompatibility with tissue from the living body with and among the various types of bone cements studied, there is poly(methylmethacrylate) (PMMA), which results from the mixing of a polymer (PMMA) powder and a liquid monomer with varying proportions according to the producer.Other elements can be still added, such as antibiotics, to reduce the possibility of infection and colors for better visualization of the cement during surgery. Thus, several studies have been conducted to improve the properties andfind new forms of applications for odontologicals cements.

Keywords: *Odontological cement, biomaterials, PMMA, bone.*

1. INTRODUCTION

The average man'slife expectancy has been expanding (around 80 years); this is due to the progress of technology in all areas and the improvement of biomaterials. However, that increases the rate of the elderly population and consequently increasesdiseases related to old age. Among the many evils, those who affect more the seniors are those that affect the bone structure, such as osteoporosis and bone loss. However, these problems do not affect only the elderly, but also young ones in their most fertile phase have difficulties with bone composition, because of automobile accidents or accidents at work. The scale of these problems has led researchers to search for materials suitable to replace damaged or weakened bones [1].

The most current medical records report the use of adapted materials for medicine without provoking large complications, but they are descriptions of over 2,500 years, showing material applications in medicine by the Egyptians, Romans, Greeks, Incas and Aztecs, in most cases, to make an social distinction between them [2]. Still, eyes, ears, teeth, fingers and artificial noses on Egyptian mummies were found. The Chinese and Indians used glues and waxes for the reconstruction of damaged tissues or body parts that exhibited defects [3].

Fallopius in half century XVIII, made a deployment of a gold plate to restore a cranial defect and from that case, the implants to replace damaged parts of the bone structure were employed [4]. However,the big push for the expansion of Biomaterials Science happened after the mid-twentieth century, especially during World War II, because of the need for palliative care for a multitude of diseases and traumatic injuries caused in people [5].

The biomaterials are therefore substances or combination of substances (except drugs) originated from nature or manufactured. Being accepted on a provisional or permanent basis to improve, augment or replace tissues or organs of living beings [6-7]. This definition has been consolidated in the Consensus Conference on Biomaterials for clinical applications in 1982 [8].

As defined above, the biomaterials are classified as: dentures, lenses, grafts, stents, catheters, tubes bypass and scaffold used in Tissue Engineering [9].

The main function of biomaterials is not only filling in a gap caused by the loss of tissue, but also should provide physical and biological compatible characteristics, i.e. it must be biocompatible with the living tissue of the individuals who will receive the implant or graft.

Biomaterials have a number of important characteristics that should be considered for implantation, such as: low cost, easy fabrication, biocompatibility, non-carcinogenic, appropriate density, mechanical stability, ideal weight, chemically functional, reproducibility, non-toxic, excites biological reactions [10].

It is necessary that the biomaterial presents essential characteristics for the bone regeneration to be accepted without complications, theseare: bioactivity, which is the ability to induce a natural connection with the organs and tissues belonging to the environment in which it was entered; bioreabsorption, the withdrawal process of the material is through dissolution; osseointegration, the material implanted unities with the bone tissue and bone conduction, the process by which bone tissue is transported. These characteristics are essential for bone regeneration to be accepted without complications [6].

Biomaterials can be classified as to their origin, physiological behavior and chemical nature [11-12]. As for their origin, biomaterials can be autologous, allogeneic and alloplastic xenogenous.

Inautogenous, the implanted organic material is derived from the individual himself (for example, the cancellous bone), with the advantage of allowing the maintenance of cell viability [13]. Their major drawback is unsatisfactory in quantity to fill;as a consequence, causes injury to the donor site which increases the risk of infection [14].

When the material is to be deployed from other individuals within the same species, it iscalled halogens. These may be obtained from cadavers, which are processed and leveled. While it is feasible to implement, this process presents risks of contamination and rejection at the time of deployment [15-16].

The xenogenous materials are sourced from individuals of different species,the bone of bovine origin is used as example for implant, being easily obtainable. Alloplastic synthetic biomaterials are found commerciallyas:bioceramics, tricalcium phosphate (TCP), hydroxyapatite, titanium alloys [11].

By interaction with the tissue and the physiological environment, biomaterials are divided into:bioinerts, bioactive, resorbable and biotolerable.

The bioinerts materials are those that are accepted by the body, in which there is virtually no release of any component and they do not react with surrounding tissue [11]. However, in 1986 at the England Conference of the European Society for Biomaterials, in which it was determined that the term bioinerts was no longer to be used, because all materials lead to some type of tissue response from the host. However, the term bioinert is also common in descriptions of biomaterials [6]. The alumina (α - Al_2O_3), zirconia (ZrO_2) and titanium dioxide (TiO_2), ceramics are examples of bioinerts [17].

As for bioactive materials, they are those that allow osteointegration of bone tissue by chemical bond in the absence of fibrous casing. They also allowosteoconduction, by promoting a particular biological response at the interface material that comes from the union between the tissue and the implanted material [18]. Bioactive materials are classified into:osteoinductive and osteoconductive.

The implants that generate an intracellular and extracellular response at the biomaterial interface - tissue, are designated as osteoinductive. The osteoconductive materials promote the development of a biocompatible implant site surface, promoting the formation of bone cells. An example of this group is hydroxyapatite (HA) [19].

The biotolerablematerials are only ones accepted by the body, the surrounding tissues through the development of the fibrous tissue enveloping layer which do not allow the insertion of these materials.The greater the thickness of this layer, the lower the tolerability of the tissues in reaction to the implanted material. Synthetic polymers and most of the metals are consideredbiotolerable materials [20].

In turn, the resorbable materials are those which, after a certain period of timein touch with the fabrics are degraded, solubilized orphagocytosed by the body. They present the role of non-surgical intervention for removal of the material and are of great interest for clinical applications. The main ones are: the α-tricalcium phosphate ceramics (α-TCP), β-tricalcium phosphate (β-TCP), hydroxyapatite (HAP), tetracalcium phosphate (TTCP), octacalciumphosphate (OCP) [20].

Due to their chemical nature, biomaterials can be classified as either natural or synthetic. Pure Collagen or mixed with other compounds;bone removed from the patient or another person or animal sources (such as bovine bone), are considered natural biomaterials.In turn, synthetic biomaterials can be considered as metallic, ceramic, polymeric and composite [11].

Because of the wide diversity of applications of biomaterials,the studiescurrently involvemultidisciplinary areas where it is required knowledge of chemistry, physics, engineering, biology, medicine and dentistry [2].

Its development is dueto great advancement inscience.The availability of new devicesthat allow the ingenuity of new implants whichcan replace not only hard,but alsosotissues.This is due the expansion of medical devices, mobile media creation that assist in bone regeneration and development of devices having controlled resorption in vivo, assuming the gradual release of drugs and bioactive compounds [2].

As earlier described, the search for improved high-related damage to the bones such as bone grafts and facial bone used for bone growth, implants, treatment of bone infection, tissue engineering and other diseases, is brought up to the current knowledge of biomaterials, which can be of natural or synthetic origin. Therefore, among the most important biomaterials is found the Bone Cement.

2. BONE CEMENT

The bone cement is a material originated by mixing two or more components, with the purpose of filling the space between the prosthesis and the bone, acting as a fixing of the prosthesis [21]. The use of bone cement began from the decade 60, where their constituents, to the present day, have high biocompatibility with tissue from the living body.

In 1870, dental cements, zinc phosphate and silicate were developed [22]. Fletcher, in 1879, created silicate cement, with excellent features and anti-cariogenicaction proceeded from fluoride restrained in its formation [23]. However, they present some disadvantages, such as high solubility, disintegration suffered by the oral environment, toxicity and low mechanical resistance [22].

The glass ionomer cements are made by aluminosilicate glass with high content of fluoride, which interacts with the polyalkenoic acid. This type of cement is widely used by dentists [24]. They are classified as: cement for cementation, restoration and liner or base. As disadvantages, delaying the formation and growth of hydroxyapatite crystals (HA) and bone mineral disorder by the presence of aluminum [22].

Bone cements primarily performance is the anchorage of artificial joints and fixation of the implant to the bone. Still acting as transferring load between the implant and the bone, this function is crucial to the stability of the implant in the long term.

The fracture appearance occurs when the external voltage is greater than the capacity of cement to transfer the load. As a result, a basic requirement arose: all bone cements have an excellent distributor of cargoes received [25].

Among the various types of bone cements studied, there is poly(methylmethacrylate) (PMMA), which results from the mixing of a polymer (PMMA) powder and a liquid monomer with varying proportions according to the producer [26]. Other elements can be still added, such as antibiotics, to reduce the possibility of infection and colors for better visualization of the cement during surgery.

Another type of cement prominence and importance are bone cements based calcium phosphate (CPCs). CPCs are materials made of a powder and liquid; the powder may be composed of various calcium phosphates, calcium salt and certain organic additives. In turn, the liquid can be water or aqueous solutions of calcium or phosphate andmay have organic additives [27]. Cements are excellent since there is no immune response, being able to attach directly to the bone, even allowing the development of bone along its surface [28].

Several studies and research on bone cements have been carried out with the purpose of improving their mechanical, thermal and biological properties. Among the various surveys conducted, the addition of small amounts of compounds and / or reagents has gained prominence in improving bone cements [34].

Among the various additives which are inserted into the bone cements, hydroxyapatite (HA) is currently the most widely used; it is biocompatible, resorbable and has osteoconductivity. The addition of HA enhances the biocompatibility of bone cements [34].

2.1 Cement Bone – poly(methylmethacrylate) (PMMA)

2.1.1 History

The poly(methylmethacrylate) (PMMA) is commonly known as bone cement [29]. Was patented in Germany in 1928, being produced by various manufacturers with the name Plexiglas ®, Lucite ® and Perpex ®, among others.Initially, employed as a biomaterial for artificial teeth and dentures format.[30]However, it is still employed in implant fixation, various orthopedic surgery and trauma.

The poly(methylmethacrylate) (PMMA) was developed in 1901 by Otto Rohm. Before that, in 1843, the cement had already been discovered by the chemical industry, called "acrylic acid", because of its strong smell [31]. Otto Rohm later founded Rohm and Haas Company, in which acrylates have been developed [32]. PMMA is an important polymer material with high chemical resistance and corrosion resistance by weathering. Such properties are of paramount importance for applications in coatings, polishing agents, binders, cements, fiber optics, among others [33].

In Germany, in 1902, there were initiated various laboratory studies on polymerization of acrylic acid, the main component of bone cement. But the large-scale production of methyl methacrylate (MMA) only happened in the year 1928 [32].

In 1936, it was discovered by the company Kulzer, a mass would form by the addition of poly(methylmethacrylate) (PMMA) powder with a liquid monomer, the hardening happening when added benzoyl peroxide (BPO) and heated to 100 ºC in a mold stone. Two years later, this mixture was used in monkey's skulls in an attempt to close the cranial defects [25]. The discovery of this experience left surgeons anxious because they wanted to test these materials in humans.

The appearance of the PMMA bone cement, in fact, only occurred by the patent Degussa and Kulzer, where the mechanism polymerization of methyl methacrylate (MMA) at ambient temperature, when added a co-initiator, aromatic tertiary amino groups, was outlined. As a result, in 1943, the companies Degussa and Kulzer established a protocol for the production of PMMA bone cements, suitable process up to this date [25].

The use of Otto Rohnbystudies by the world happened after the end of World War II, as many German patents in the area of methacrylateswere given to the victors, because of the danger of a possible German rearmament [34]. It is noteworthy that the development of the PMMA bone cement happened independently in several countries.

The first use of cement was made by Kiaer (1951), for anchoring acrylic glass capsules on the femoral headby subsequent removal of cartilage [35].

Mendesin 2006 mentioned Judet, were the first to replace articular surfaces by artificial implant (prosthesis) designated as arthroplasty [34].

In 1958, Sir John Charnley, became known among orthopedic surgeons for making use of implants in articular hip replacements [36]. In this process, the bone cement acts as a fixer between the bone and the prosthesis. With the studies of Charnley it was possible to present a new surgical procedure [37].

The bone cement based on PMMA is the material best suited for fixing the artificial joints. However, it can present problems during surgery, accordingly, the biocompatibility of the implant tissue was the prerequisite for the acceptance of PMMA bone cement in surgeries [38].

It is known that surgical operations pose risks of infections, from this perspective, the teacher Buchholz, in 1969, was the first to add antibiotics to bone cement in order to prevent infection at the implant site [25]. By the addition of gentamicin sulfate,Palacos R developed the first antibiotic bone cement, Palacos R Refobacin type, with very satisfactory results [39].

In the 80s, the low viscosity cement was developed, with ease in filling the medullary canal in vertebroplasty surgery, using a pistol injector [34].

In order to designate a basis for reproduction and evaluation of PMMA bone cements, in 1976 started the development of a standard in the United States, in which the American Society for Testing and Materials (ASTM) standard has made public F -451-76-Standard Specifications for Acrylic Bone Cements in 1978 [34]. In 1979, the ISO 5833/1 protocol was developed with the same purpose.

Currently, all bone cements mustmeet the requirements given in ISO 5833/2 protocol developed in 2002. In Brazil, the standards of the cements are represented by the Brazilian Association of Technical Standards and (ABNT) NRB ISO 5833 - Implants for surgery - Acrylic resin cements [30].

2.1.2 Chemical of Cement PMMA

PMMA cements are made by mixing the polymer powder, liquid monomer and some additives. These are usually sold in a 2:1 ratio [31].

2.1.2.1. Polymer Powder

The solid portion is composed of a pre-polymerized PMMA ball, contributing with 83% up to 99% by weight. The other components include a free radical initiator, such as benzoyl peroxide (BPO) required for curing the cement, a radio-opacifier, such as barium sulfate or zirconium dioxide, to facilitate the visibility of the cement on radiographs, antibiotics and coloring agents [31, 33].

Considerable differences are found in the compositions of commercial bone cements.Since these differences cause variations in the properties of bone cements, theyinfluence the performance and success of the arthroplasty. However, not all bone cements are similar [25].

2.1.2.2 LiquidMonomer

The liquid portion typically contains three basic components: the monomer methylmethacrylate(MMA), which comprises 97% up to 99% volume. For the chemical vision, MMA is an ester of methacrylic acid, polarizable in the presence of the double bond in the compound. It displays a boiling point of 100 °C (212 °F) and low solubility in the presence of water. Besides MMA, there are some commercial liquid cements containing butyl methacrylate monomer [25, 31].

The other components are an N,N-dimethyl-p-toluidine (DMPT) that stimulates the polymer and the monomer to polymerize at room temperature (cold-curing) [29]. An inhibitor hydroquinone in about 15 to 75 ppm [31] and itstabilizes the monomer, providing a satisfactory shelf life period and helps prevent premature polymerization of the product during the surgical procedure. Some liquids are still colored by chlorophyll [25, 31].

Table 1. Components of the bone cement base PMMA [40-41].

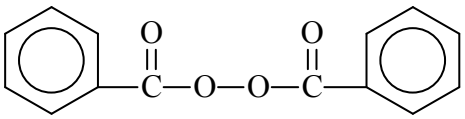
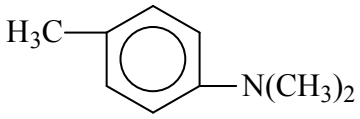
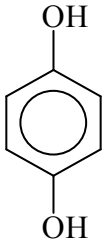
ComponentSolidcomponente	Function	
Polymer	Poly(methylmethacrylate) (PMMA) $(\sim H_2C{-}C(CH_3)(COOOCH_3)\sim)_n$	Altering the physical characteristics of the cement.
Originator	Benzoyl peroxide (BPO) 	Reacts with DMPT to catalyze the polymerization.
Radio-opacifier	Barium Sulfate – $BaSO_4$	• Decreases the mechanical strength of bone cement; • Affectsthepolymerizationtemperature; • Causes an increase in bone resorption.
	ZirconiumDioxide– ZrO_2	• Less soluble than barium sulfate; • Have less effect on the mechanical properties of the cement.
Antibiotics	Gentamicin Vancomycin	Preventsinfection.
Dyes	Chlorophyll	Distinguishethebonecement.

Table 2. Components of the bone cement base PMMA [39-40].

Component	Liquid component	Function
Monomer	Methylmethacrylate (MMA) $H_2C=C(CH_3)(COOCH_3)$	Colorless liquid with a strong smell.
Originator	N, Ndimethyl-p-toluidine (DMPT) 	Favorscold-cure cement.
Inhibitor	Hydroquinone 	Preventsprematurepolymerization.

2.1.3 Curing Cement.

The curing process of the bone cement is divided into four phases: mix, waiting, working and hardening [29].

Mixing can be performed manually with a spatula through a vacuum mixer under centrifugation, ultrasonic agitation or by a combination of systems [41].

The mixing phase is initiated by the addition of liquid to the powder and ends when the mass gets a consistency satisfactory to be manipulated (homogeneous) [25, 30].While the process of the polymerization occurs, there isan increase in viscosity of the mixture [34].

This satisfies the hold phase time of formation of the mass, i.e. the time required for the cement to achieve a non-tacky state. This step may last for several minutes, dependingon the type of cement handling temperature [25].

The next step is the period in whichthe surgeon injects the prosthesis. During this time the temperature of the cement increases, being an exothermic reaction, reaching values between 67 ºC and 124 ºC, with an average value close to 90 °C [41]. The cement viscosity should be low.

However, this viscosity cannot be too low, because the cement applied cannot bear the pressure of the bleeding and the blood will join the cement, causing a decrease in resistance of the inserted material [25].

The curing step is the period that the surgeon waits for the complete hardening of the cement in the body. This time can be short or long, will depend on the P / L ratio, temperature and cement environment [34].

Depending on the trade mark and the environmental conditions the healing process of the conventional cement may remain for 1 to 2 minutes in the pre-dough (mixture).The period of 3 to 7 minutes corresponds to the step of forming and complete hardening of the total mass cement occurs between 8 and 14 minutes [42].

The temperature, moisture and storage conditions affect the curing process of the cement. The higher the temperature and humidity of the airleads to the less healing time of bone cement. The long storage time causes similar effects [31, 41-42].

2.1.4 Free Radical Polymerization via Bone Cement

The polymerization is the process where molecules of long-chain or network are formed from relatively small organic molecules. Therefore, the cements polymerization occurs by mixing their constituents in two steps [43].

In the first stage the absorption of liquid monomer by polymer powder occurs, developing a mass or a more or less viscous fluid. The swelling and dissolution of the monomer and polymer powder are the causes of this procedure, which are important for the properties of bone cements physical processes. In turn, in the second phase a chemical processtakes place, being responsible for the final hardening of bone cement [25].

As shown in Figure 1. The initiator, benzoyl peroxide (PBO) and activator NN dimethyl-p-toluidine (DMPT) interact to produce free radical reaction initiation.

Polymerization of MMA begins by the presence of radicals, linking the molecules of monomer (MMA) for breach of polymerizable double bonds. Consequently, it increases the polymer chain forming macromolecules by addition of monomer molecules.

The polymer chains are formed quickly due to the high number of radicals derived and hence, a rapid conversion of monomer (MMA) occurs in the polymer (PMMA). The termination of the polymer chains occurs when there is a match

between the two chains, resulting in an inactive polymer molecule, i.e. without the presence of free radicals (Figure 2) [25].

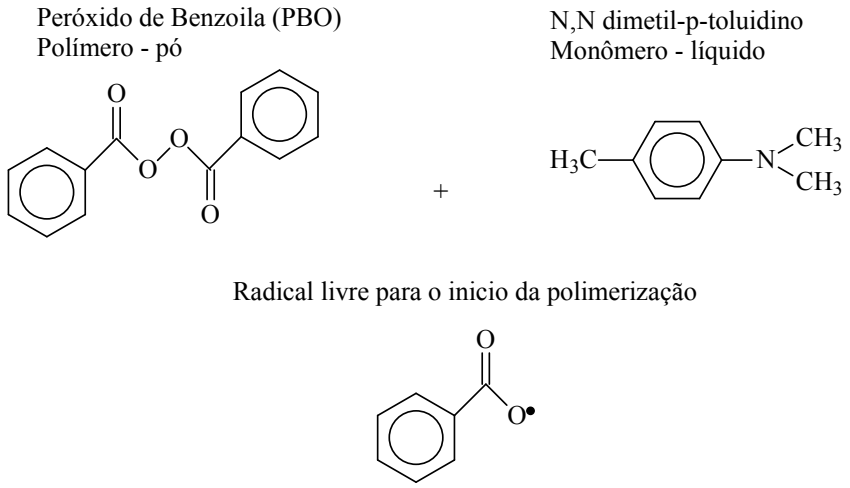


Figure 1. Structure for initiating polymerization of MMA.The benzoyl peroxide component of the solid and N, N-p-toluidine dimetil, the liquid component of bone cement, react to form free radicals, initiating the curing of cement [25].

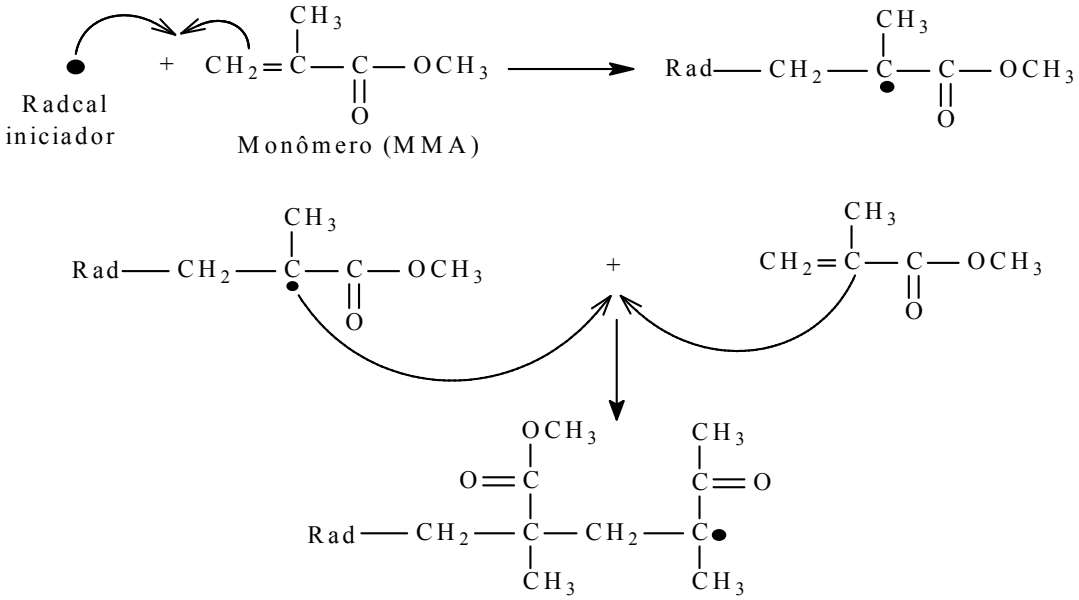


Figure 2. Polymerization of PMMA by an addition reaction.Note that the MMA monomer reacts with a radical to form a secondary radical and can attack the double bond of another monomer MMA. [44].

2.1.5. Methods of Bone Cement Mix

The methods of bone cement mixing may be: Manual mixture by centrifugation, vacuum, by ultrasonic agitation and mechanical combination of the mixtures [45].

2.1.5.1. Manual.

The cement mixture can be accomplished by adding the powder to the liquid in a temperature range between 15ºC and 16 ºC. The mixingof components can be done in a polymer bowl or metal tub with the aid of a propylene spatula or a stainless steel spoon. This requires a speed of 1 to 2 Hz for a period of 45 to 120 seconds [42]. In Brazil, this method is the most widely used in operating rooms.

2.1.5.2. Centrifugation

In this method, the constituents of cement are previously added by hand, then placed in a syringe and taken for a centrifuge at 2300-4000 rpm for a time of 30 to 180 seconds [34, 41].

2.1.5.3. Vacuum

Themixture of the components are placed under vacuum, in which is applied pressures ranging from 5 up to 100 kPa, a frequency of 1 to 2 Hz for a period of 15 to 150 seconds. The porosity of the cement can be decreased by using an atmospheric pressure between 400 and 730 mmHg [42].

2.1.5.4. Ultrasonic Agitation

In this process, the constituents are placed into a vat, after they are taken to a vibrating plate with 50 vibrations per second and homogenized with a propylene spatula [42].

All of these methods have been developed to reduce the porosity of the bone cement, which is caused by the air between the polymer chains. The porosity occupied by air spaces isclassified in microporosity with diameters between 0.1 to 1 mm and macroporosity with a diameter greater than 1 mm [41].

The literature values of porosity are ranging from 5% to 16% [46] and 9% to 27% [47] in the hand blended cements.

2.1.6. Evolution of Cementation Techniques

The cementing techniques can be classified into first, second and third generation [29].

2.1.6.1. Cementation of First Generation

In this technique, the introduction of the cement happens manually, in slurry phase, with no bone preparation, i.e. without the need for washing or drying the cement insertion. This technique allowed the formation of a potential cement that provided lamination, including blood or void and inadequate cement mantles, as well as poor penetration of the cement into the interstices of the bone [48].

In the beginning, the technique produced satisfactory results, however, over time it began showing high incidence of complications, such as acetabular and femoral loosening and increased surgery revisions, especially in younger patients [49].

2.1.6.2. Cementation Second Generation

In 1972 starts thesecond generation techniques with the insertion of the cement by gun retrograde injection and the use of buffers for thespinal pathway, while the acetabular bone was compressed by other instruments.The cements used were of low viscosity. The cement was injected immediately after the bone preparation(cleaning). This procedure was necessary to reduce the lamination and vacuum blood of the femoral loosening [49, 50].

2.1.6.3. Cementation Third Generation

Other technical improvements led to third generation. The insertion of the femoral stem was maintained by pressurization, this was achieved by placing a rubber seal around the mouthpiece of the cement gun, which effectively sealed the femoral artery proximal to the termination, resulting in increased pressure and forcing the interstices of the surrounding bone due to increase of the amount of cement added [50]. The mixture was vacuum, also of great importance to reduce the porosity of the cement [31].

2.1.7. Applications

Bone cement based on PMMA has many surgical applications, such as [34, 52]:

- Fixation of implants in the hip, knee and shoulder (arthroplasty);
- Anchoring prosthesis and reconstruction of bone and facial deformation (plastic surgery);
- In the dental field;
- Fill gaps in coverage of head and cranial aneurysms (cranial surgeries);
- As domestic support the spine (vertebraplasty);
- Completingthebone cavity;
- OrthopedicSurgeries.

The bone cements applied in orthopedic surgeries have three basic functions. The first is the mass modeling, subject to a minimum voltage. The second is filling bone cavities and third is the fixation of prostheses.In the latter function the cement forms an interface between the prosthesis and the bone, acting as a strain, homogenizing and buffer [41, 53].

2.1.8. Advantages

In this review we describe some of the large advantages of using bone cement [22, 32, 54]:

- Easytohandle;
- Easy to access;
- Quickhardening;
- Excellent aggregation of the prosthesis;
- Short durationofsurgery;
- Easy to homogeneously fill the empty spaces, adapting an excellent distribution of loads and stresses incidents prosthesis;
- Decreased fatigue and wear of the prosthesis;
- Adjustable snap in fixing the prosthesis;
- Lack of striking the prosthesis when placed in the correct position, in that way likely preventing fractures;
- Reducing stress in the case of cement and reduction in the development of prosthetic failure due to accommodation of the bone cement;
- Increased ability to resist to excessive loads.

2.1.9. Disadvantages

Problems such as fractures, fatigue or failure of implant fixation, occur when the bone cement is exposed to forces beyond resistance [36].

The decrease in resistance of the cement over time with the addition of antibiotics and the problems associated with poor homogenization during the preparation cause problems in the mechanical properties of bone cements [55].As a consequence, this disadvantages cause failures that can promote the release of the prosthesis [56]. These failures cause the needof new surgery to replace the implant, which can lead to surgical risks forthe patient [57].

The use of cements with viscosity less than ideal can cause the extravasation of the cement by the surrounding fields, neurological damage and pulmonary embolism. In turn, the use of cement with very high viscosity requires application of high pressure, usually preventing the surgeon to make a good penetration and homogeneous filling of cement. [58]

High temperatures contribute to the development of fibrous tissue around the cement-bone interface leading to laxation of the prosthesis, caused by the thermal necrosis of bone tissue [59].

Low temperatures weaken the cement-prosthesis interfaces due to the existence of porosity in cement by weak polymerization [60].

Other problems in the application of bone cement are aseptic loosening. This loosening is initiated by the fragmentation of the cement leading to osteolysis[36], resulting in loss of bone density and consequent displacement of the prosthesis [60] and infections in the implant.

Due to the various problems associated with the use of poly(methylmethacrylate) bone cement (PMMA), we sought to develop a cement withminimum disadvantages of use.Wetherefore developed, for this purpose, the calcium phosphate cement (CPC), which exhibits similar behavior to bioceramics of calcium phosphate, or are reabsorbed due to osteoclast activity, forming new bone tissue at the bone implant interface, thereby not acting

as a permanent replacements, [61] still providing excellent biocompatibility and bioactivity.

2.2. Cements based on Calcium Phosphate

The bioceramics of calcium phosphate appeared on the market in the early 80s.Since then they are considered excellent materials due to their properties of biocompatibility, bioactivity and osteoconductivitywhen implanted in the bone. They do not induce immune response, allowing further growth of bone along its surface to bind directly to bone [22, 62]. However, bioceramics have a significant disadvantage, they are only available to the surgeon in pre-fabricated format, sold in standard sizes or granules in which migration of materials occurs at the implant site [63]. Therefore, the search for improving these materials is to create a calcium phosphate cement, with almost the same characteristics of bioceramics, but without the need of pre-fabricated or granular forms during surgery, because they are employeesin the form of self-curable paste [64] and do not act as permanent bone substitutes, since they are slowly replaced by new bone [22, 65].

The first studies of calcium phosphate cements (CPCs) were performed by Gruninger and colleagues [66]. However, the first CPC was developed by Brown and Chow, 1985, by mixing the powders oftetracalcium phosphate [$Ca_4O(PO_4)_2$ - TTCP] and anhydrous calcium hydrogen phosphate [Ca_2HPO_4 - DCPA] resulting in a grip to be added to water [63, 67]. The calcium phosphate dissipated and formed a plastic paste, which after a few minutes lostplasticity and fine crystals of hydroxyapatite precipitated. The mechanical strength is provided by the entanglement of the crystals [67, 68].

The calcium phosphate cements are composed of two phases: a solid and a liquid. The components of the solid phase are salts of calcium phosphates and the liquid phase comprising water or aqueous phosphate salts.Thehardening of the mixture occurs at room temperature or body due to developing a precipitate containing one or more calcium phosphate wherein the intercrossing of these crystals give rise to the hold of the mixture [69].

As mentioned above, CPCs are formed by direct crystallization of hydroxyapatite *in vivo*, without heat generation in the development of a stable scaffold implant (not exothermic reaction). The reaction that happens in the course of mixing components (solid and liquid) is complex and can be synthesized in solution, precipitation and phase transformation [70].

CPCs are osteoconductive, because they have chemical and morphological similarity to the mineral part of bone tissue, thus, over time, the cement is replaced by a newly formed bone. One advantage of this cement is that it does not trigger inflammatory processes by the eventual expulsion of the inserted material [71].

Partial resorption of CPCs can occur in two ways; the solution process, in which the implant is dissolved in the physiological environment and osteoclast absorbing cement through phagocytosis [72].

Due to the properties of CPCs reported above, the rate of extrusion is lower when compared to other alloplastic materials, making, therefore, the CPC suitable for the repair of bone defects and craniofacial contours failures [73].

The compressive strength is characterized by the end of the handle of the reaction mixture, in which variations in the crystallinity of the apatite or the particle size used in the solid phase may affect the compressive strength of CPCs. The porosity also alters the compression resistance and is determined by the ratio powder / liquid mixture used in the beginning, so the more porous the cement, the lower the compression strength will be[70].

In general, the properties of the CPCs, such as the initial plasticity, hardening time and ultimate strength are controlled by intrinsic factors ofthe constituents of the mixture, as shown in the following table [74]:

Table 3. Factors affecting the properties of the folders of CPCs [75].

Powder	Nature and purity of the solid components. Mixing ratio of the solid components. Additives (accelerated retardants). Particle size.
Liquid	Additives (accelerators and retarders). pH.
Mixture	Liquid / solidratio (L / P).
Maturation	Temperature. Humidity. pH.

CPCs are presented in seven different types, depending on the amount of calcium phosphate precipitatedas ternary system $Ca(OH)_2$-H_3PO_4-H_2O [76]. However, these types of CPCsare reduced by offering some requirements on their clinical use and bone repair.The requirements for CPCs for clinical application are: absence of toxicity, perfect adhesion to hard tissue, not halogen or carcinogenic properties, easy handling, to handle and harden *in vivo* in a reasonable period of time, degradability, be carrier and stimulating formation of new bone and controllable time setting and hardening [76].

In turn, the ideas of a CPC requirements for bone repair are: short time for the completion of the mixture (1 minute or less); setting time needed for the handling of the material occurs appropriately (the handle begins around 5 minutes and is finished between 15 up to 20 minutes); dough preparation time should be close to the time of initial setting, about 5 minutes; cohesion time (the time at which the cement does not swell or disintegrate in contact with body fluids) is shorter than the time of preparation and initial setting; the end compression resistance similar to the repaired tissue; not generate heat during setting and display a

neutral pH (6.5 to 8.5) during and after for preventing cytotoxiceffects [75].

Table 4. Calcium phosphate in biological systems [28].

Calciumphosphate		Chemical formula	Reason Ca / P molar	Occurrence
Hydroxyapatite, Fluorapatite, Cloroapatite		$Ca_{10}(PO_4)_6X_2$ where X = OH, F, Cl	1.67	Enamel, dentin, bone, dental calculus, rocks, kidney stones, calcification in soft tissue.
Octacalcium Phosphate(OCP)		$Ca_8H_2(PO_4)_6.5H_2O$	1.33	Dental calculus (tartar) and renal
Brushite	Dicalciumphosphatedihydrate (DCPD);	$CaHPO_4.2H_2O$	1.00	Tartarus, decomposedbones
	Dicalciumphosphateanhydrous (DCPA).	$CaHPO_4$		
Whitlockita	Tricalcium Phosphate (β-TCP) Tricalcium Phosphate Modified Mg, Mg-TCP	$(Ca, Mg)_9(PO_4)_6$	1.50	Renal calculusandtartar, salivarias stones, dentine caries, cartilage.
Calcium Pyrophosphate Dihydrate		$Ca_2P_2O_7.2H_2O$	1.00	Pseudodeposits in synovialfluid.

Not all calcium phosphates system can be achieved at room or body temperature, therefor being another factor that limits the number of types of calcium phosphate cements, thus existing CPC formulations are divided into two groups: cement apatite and brushite cement [77] and can be grouped into three categories [74]:

- Based on β-tricalcium phosphate (β-TCP, $Ca_3(PO_4)_2$) and phosphoric acid (H_3PO_4) or calcium phosphate (DCP, $CaHPO_4$) that react to form a phase of dicalcium phosphate dihydrate (DCPD, $CaHPO_4.2H_2O$);
- Based on α-tricalcium phosphate (α-TCP) phase forming a calcium deficient hydroxyapatite (CDHA, $CA_9(HPO_4)(PO_4)_5(OH)$, with excellent biocompatibility, bioactivity and osteointegrabily;
- Based on tetracalcium phosphate (TetCP, $Ca_4O(PO_4)_2$), and dicalcium phosphate, which also form an apatite phase.

CPCs precipitates in the form of octacalciumphosphate and deficient in calcium hydroxyapatite are preferred for reasons of cytotoxicity and does not modify the physiological pH as precipitate and do not cause damage to the tissue around the implant [78].

In the recent years, CPCs have been materials of intense study, due to their wideuse in biomedical applications, biocompatibility and the fact that they harden at the implantation site [75, 79].

2.2.1. Systems based Cements Calcium Phosphate

The main systems of calcium phosphate cements are: system tricalcium phosphate / dihydrogen calcium monohydrate (β-TCP/MCPM), tricalcium phosphate system / calcium hydrogen phosphate dihydrate / calcium carbonate (β-TCP/DCPD/CC) system hydroxyapatite / calcium sulfate hemihydrate of (HA / CSH) system, tetracalcium phosphate / hydrogen phosphate (TTCP / DCPA) and (α-TCP) system tricalcium phosphate.

2.2.1.1. System β-TCP/MCPM

Lemaitre and colleagues were the first to develop based cement β-TCP [76]. The mixture of β-TCP with MCPM forms a handle when water is added in a very short time interval (about 30 seconds) and harden similar to conventional hydraulic cements. The system hasthefollowingcharacteristics [22]:

- The process handle occurs in the first stage of mixing because of the rapid development of DCPD, showing the proportional amounts to MCPM, in which the DCPD crystals formed have the function of bridging the β-TCP particles. In this sense, the β-TCP/MCPM system behaves as a hydraulic binder, substance or mixture;
- In this system technique, a handle is formed by dissolving the MCPM accompanied by a progressive crystallization of DCPD throughout the folder;
- Various additives are used in the purpose of delaying the setting time of the cements formed by β-TCP/MCPM;
- Additives such as calcium pyrophosphate, calcium sulfate hemihydrate and of dihydrated calcium sulfate increases the setting time of 30 seconds to 10 minutes;
- The addition of calcium sulfatedihydrate also results in increased resistance to diametral compression cement (an increase of 1 MPa to 3 MPa);
- The final resistance of cement is increased by β-TCP powder with a high particle size, obtained by sintering at high temperatures. This process is inconsistent since increasing the particle size decreases the resistance of the cement.

2.2.1.2. β-TCP/DCPD/CC System

This system has also been developed by Lemaitre and collaborators [66], which describes that [22]:

- By adding hydroxyapatite (HA) to β-TCP/DCPD/CC, the system decreases the setting time of 5 hours to 20 minutes (time of onset of the handle) and 18 to 11 am, the time to complete hardening;
- By replacing demineralized water by a saturated solution in HA and DCPD (mixture of the two solutions) increases the strength of the mixture;
- The rapid hardening occurs by precipitation of HA crystals, acting as a binder between the particles of β-TCP;
- When fluoride ions are added, the homogenization increases the setting time of 5 to 1 hour [68]. This relationship is due to the increase of DCPD and CC in the formation of apatite.

2.2.1.3. System HA / CSH

Hemihydratecalcium sulfate (CHS) is one of the oldest resorbable materials. In 1961, Peltier published experimental work with CSH in the form of pressed pellets.

In 1984, Hanker et al, patented that a blend of particles of calcium phosphate with CSH [80] have the disadvantage of rapid dissolution of the material.

In an attempt to increase the alveolar Bill C. Terry and colleagues used blends of 70% of HA with 30% CSH, obtaining satisfactory results [81].

2.2.1.4. TTCP / DCPA System

Brown and Chow in 1985 developed the first system based on calcium phosphate cement-system TTCP / DCPA [82].

This cement is obtained by mixing the powders of tetracalcium phosphate (TTCP) and dicalcium phosphate (DCPA) giving handle when mixed with water. The reaction setting this system uses 25 mmol / L solution of H_3PO_4; the reaction takes around 4 hours to complete processing, in which virtually all DCPA and TTCP turns into HA [22].

This system shows some properties, such as increased mechanical strength by the addition of HA, the compression resistance comprises a value of approximately 36 MPa, the final cement composition can reach 40% of hydroxyapatite crystal growth dependingon the HA specific surface area of raw materials during the development of the cement, increasing the mechanical strength depends on the expansion of the specific surface area of DCPA; when the particle size is large, mechanical resistance of all CPCs decreases the dissolution rate of the calcium phosphates, which is controlled by the solubility and surface area of the solid. [22].

Due to the extensive development of the properties of CPCs, this phosphate system is the most studied, with numerous published works.

2.2.1.5.α-TCP System

Major systems studied calcium phosphate, this is the one that carries the requirement for the pH (6.5 to 8.5) [75].

Driessens and colleagues conducted studies on the effect of temperature and of various additives on the properties of cement α-TCP [83].

The powder of the cement comprises 98% of α-TCP (15% β-TCP as impurities) and 2% HA precipitated.In turn, it consists of a aqueous Na_2PO_4, 2.5%, as compared with liquid / powder (L / P) of 0.32 ml / g.The dwell time of the mixture remains for 1 minute, molding time occurs in a period of 4 minutes and the handle body temperature lasts about 6 minutes. During the handle cement:does not retract, dosen't expand and releases no heat [75, 82]. The compressive strength is improved by 4% by the addition of precipitated hydroxyapatite [84].

The final compressive strength is 40 MPa, the pH remains nearly neutral during the setting time. Cement is not cytotoxic, showing excellent biocompatibility and stimulation for bone formation [85].

Table 5. Additives which can be used in the CFC formulations.Accelerators, retarders, promoters of bioactivity, among others [86].

Components	Compounds
Sodium	NaF, $NaCO_3$, $NaHCO_3$, Na_2SO_4, Na_2SiO_3, Na_2HPO_4, NaH_2PO_4, Na_3PO_4.
Potassium	KF, K_2CO_3, K_2SO_4, K_2SiO_3, K_2HPO_4, KH_2PO_4, K_3PO_4
Magnesium	$MgHPO_4$, $Mg_3(PO_4)_2xH_2O$, $Mg(OH)_2$, $MgSO_4$, MgF_2, $MgCO_3$, MgO, $CaMg(CO_3)_2$.
Zinc	$Zn_3(PO_4)_2.4H_2O$, ZnF_2, $ZnCO_3$, $ZnSO_4$, ZnO, $Zn(OH)_2$.
Calcium	$CaSO_4$, $CaSO_4.1/2H_2O$, $CaSO_4.2H_2O$, caF_2, $CaCO_3$.
Biopolymers	Proteins, peptides, proteoglycans, glycosaminoglycan, carbohydrates.
Organicacids	Citric acid, malonic acid, pyruvic acid, tartaric acid.
Inorganicacids	Phosphoricacid.
Syntheticpolymers	Poly(lactic acid, poly (glycolic acid)
Antibiotics	Gentamicin.
Growthfactors	TGF-β,osteocalcine, GLA proteins BMP.

2.3. Chemistry of cements calcium phosphates

The components of the solid phase are responsible for setting the reaction handleof CPCs.When these components come in contact with the liquid phase, they dissolve until the liquid locates an invariant point (intersection of the solubility isotherms constituents) or a saturation point, in the case of a single type of calcium phosphate salt [22].

Solubility is one of the most important features of CPCs, theisallows the determination of the direction of almost all chemical reactions that interfere with calcium phosphates at room

temperature (dissolution, precipitation or phase transformations) [22].

2.3.1. Solid Phase

The composition of the solid phase depends on the final cement product, which is desired after the handle [63].

Among metaphosphates, polyphosphates and orthophosphates, only the latter offers importanceas solid components of cement.In addition, they are of great interest when substituted with biocompatible ions such as Na^+, K^+, Mg^{2+}, CO_3^{2-}, SO_4^{2-}, Cl^-, since they allow to obtain a precipitate hydroxyapatite with characteristics more similar to the biological hydroxylapatite [63].

When the cement provides adequate setting time and good mechanical characteristics, similar CDHA or HA can be added to the solid phase acting as nuclei for precipitation [63].

2.3.2. Liquid Phase

In the liquid phase, the components used can be distilled water or aqueous solutions of phosphate salts. The liquid phase acts as a transport for the dissolution of the reactants and products of precipitation [63].

For the broad versatility of CPCs systems, various additives can be incorporated both in the liquid phase and the solid phase acting as accelerated, retarders, promoters of bioactivity, among others, as can be seen in the table below [63].

2.4. Times Handle and Behaviors in Physiological Environment

Two types of reactions are possible handle. The first type is an acid-base reaction, i.e. a relatively acidic calcium phosphate reacts with a relatively basic calcium phosphate, forming a relatively neutral calcium phosphate [82]. In turn, the second reaction occurs when the initial and final phosphate calcium has the same Ca / P ratio [87].

The initial setting time can be between 4 to 8 minutes and the final time 10 to 15 minutes. However, there are no specific criteria and standards that can determine the exact setting time of cement. Therefore, it is appropriate that cements harden in short time and suitable for both to handle the mixture as to give time for the surgeon to shape and deploy the cement [63].

The curing rate of the handle and final properties of the cement depends the initial particle size of the powder, because the smaller the particles will be, the faster the cure rate of the handle [63].

For biomedical applications, it is necessary that not only handle deem cements under physiological conditions, but under atmospheric conditions, in contact with the blood and physiological fluids, occurs without the decohesionor disintegration of the material occurs [88].

2.5. Advantages

The calcium phosphate cements main advantages are [75, 79, 89]:

- No need to shape the cavity;
- Their preparation can be carried out during surgery;
- MinimumCavity;
- Excellent contact between the bone and the implant;
- Shows excellent biocompatibility and bioactivity;
- Ability to spontaneously heal *in vivo*;
- Achievementnoninvasivesurgicalinterventions via injection;
- Providessatisfactoryosteoconductive properties;
- Allows the cement replacement by a new bone after a significant period of time (degradability);
- They are moldable;
- They are nontoxic;
- Low cost of production and application;
- Easypreparationandimplementation;
- The healing happens atbody temperature;
- They form chemical bonds with bone tissue;
- It can also be used for the controlled release of drugs (in this case requires further study).

2.6. Disadvantages

The main disadvantages of the use of calcium phosphate cements are [89]:

- Low mechanical resistance, which limits application of CPCs in places that do not receive high mechanical stresses;
- Once deployed, leaching may suffer if there is an excess of fluid and blood;
- Difficulty in the rapid growth of the new tissue and degradation of the material inside out, due to lack of interconnected macroporosity;
- Showing higher resorption rate than the rate of new tissue growth.

2.7. Applications

Due to its excellent biocompatibility and osteoconductive capacity, CPCs offer a range of applications, among these are [89, 90, 91-92]:

- Orthopaedics;
- Dentistry;
- Maxillofacial Surgeries;
- PlasticSurgeries;
- Periodontics;
- Oral Implantology;
- Cranioplasty;
- Vertebroplasty;
- Tissueengineering;
- Drug delivery system.

3. CONCLUSIONS

Bone cements are materials realized from the mixture of two or more components in order to fill the space between the prosthesis and the bone, acting as a fastener. The use of bone cements happened around the 60's, whose constituents have high biocompatibility with tissue from the living body.

Since its discovery to the present day, many types of bone cements were developed with specific purposes. However, most cements had some drawbacks that could compromise the patient. Therefore, in order to mitigate these problems, several studies were conducted and other cements developed. Among the various types of cement developed, the acrylic cement and calcium phosphate cements stood out for presenting non-committal properties during surgery.

Acrylic cements are made by mixing a powdered polymer and liquid monomer,then other constituents are added in order to improve the properties of the cements.

The healing process is divided into four stages: mixing, waiting, working and hardening. These cements can be mixed manually by vacuum centrifugation, by ultrasonic agitation and the combination of mechanical mixtures.

Its applications are diverse because they offer several advantages, such as easy handling, easy access, quick hardening, less surgery time, good aggregation of the prosthesis, among others. But some disadvantagesare: fractures, fatigue or failure of the prosthesis and high temperature can cause laxation of the prosthesis, causing thermal necrosis in bone tissue, which is one of the biggest problems of acrylic cements.

Accordingly, in recent years began thedevelopment in the cement market whichreduced the disadvantages presented in acrylic cements.

The calcium phosphate cements offers remodeling and bone reconstruction due to certain advantages: easy handling, flexibility, non-toxic, excellent biocompatibility, easy preparation and healing happens atbody temperature.

CPCs have a solid phase of calcium phosphate salts and a liquid phase which may be water or an aqueous solution of phosphate salts, when water is added,the mixture forms a gum and various substitutes, additives, retarders, among others, can be inserted to enhance the characteristics of cement.

CPCs are still reabsorbed and replaced by newly formed bone; the expulsion of the material does not cause infection in the living organism. However, it has low mechanical strength, limiting its application in places that do not receive high mechanical stresses. Thus, several studies have been conducted to improve the properties andfind new forms of applications for CPCs.

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