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Bone Cements

Salma K.Rizk [1]

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[1] *Assistant Lecturer of Dental Materials Science, Dental Biomaterials Department, Faculty of Dentistry, Modern Sciences and Arts University. Egypt.*

* Corresponding author e-mail: *Salma.Rizk @dentistry.cu.edu.eg*

Abstract: The demand for bone substitute materials have grown significantly in the last decade. The increasing size of the elderly population and the number of road traffic accidents could be attributed to this rapid rise. Accidents and trauma may result in bone defects that exceed a critical size, where surgical management is still considered a significant challenge worldwide.

Keywords: Bone cements, bone defect, calcium phosphates,

Introduction:

The demand for bone substitute materials have grown significantly in the last decade. The increasing size of the elderly population and the number of road traffic accidents could be attributed to this rapid rise. Accidents and trauma may result in bone defects that exceed a critical size, where surgical management is still considered a significant challenge worldwide.

When a defect heals only in the presence of bone graft material, it is considered critical-sized defect. A critical-sized defect is defined as the smallest size of a bone wound that does not heal spontaneously during the animal's lifetime. For example, critical-sized defects in a rat calvaria, mandible, and long bone are 8, 4, and 12 mm, respectively. At the same time, those in a rabbit are 15, 5, and 6 mm. In this type of defect, spontaneous healing does not lead to complete bony defect closure. While, on the other hand, formation of connective tissues is faster than the formation of new bone. Therefore, restoring such defects requires an intervening surgical procedure that usually involves bone substitute material. (1, 2)

Terminologies:

Bone graft: is defined as a living tissue capable of promoting bone healing, transplanted into a bony defect, either alone or in combination with other materials.

Bone substitute: is a natural or synthetic material, often containing only a mineralized bone matrix with no viable cells, that can promote healing.

Bone cements: are family of materials that consist of a powder phase and a liquid phase which after mixing form a plastic paste which can self-set once implanted in the body.

Uses of bone cements:

To fill a bony defect.

Mixed with autograft to compensate for its limited availability.

The fixation of screws in mechanically poor bone.

Bone augmentation.

Drug carrier.

Scaffolds.

Ideal properties of a bone cement:(3, 4)

An ideal bone replacement material elicits no adverse reactions following its implantation. It integrates with the host bone to induce the formation of new bone tissue, while being completely resorbed in the process.

Four fundamental biological properties are paramount in performing this role effectively; osseointegration, osteogenesis, osteoconduction, and osteoinduction.

Osseointegration is the ability of a grafting material to chemically bond to the surface of the bone in the absence of an intervening fibrous tissue layer.

Osteogenesis is the formation of new bone via osteoblasts or progenitor cells present within the grafting material.

Osteoconduction is to the ability of a bone grafting material to generate a bioactive scaffold on which host cells can grow.

Osteoinduction is the recruitment of host stem cells into the grafting site, where local proteins and other factors induce the differentiation of stem cells into osteoblasts.

Ease of handling

In vivo setting and hardening with appropriate setting times

Low setting temperature

Near neutral pH during setting

No disintegration in early contact with body fluids

No shrinkage during setting

Appropriate mechanical strength

High radiopacity

No toxicity

Biocompatibility

Bioactivity

Porosity.

- **Classification of bone substitute materials:**

The general classification divides all bone substitute materials into autografts, allografts, xenografts, and alloplasts. **Autografts** are bone grafts obtained from the patients themselves, whereas **allografts** are obtained from donors of the same species. **Xenografts** are bone substitutes derived from animal sources. The remaining nonbiological materials, such as ceramics, metals, alloys, polymers, composites, and hydrogels are listed under **alloplasts** and synthetic materials.

Acrylic bone cements (ABCs):

The term "bone cement" was initially applied to ABCs since the 1960s. ABCs are polymeric materials (polymethyl methacrylate), which cure through a polymerization reaction and produce a stable, nonresorbable material. (3)

Acrylic bone cements are mainly used to achieve mechanical stability by distribution loads evenly and transferring it to bone. ABCs are used for primary fixation of metallic component and for even load distribution.(3)

ABCs have some drawbacks:

- In some cases aseptic **loosening** occurs with time leading to mechanical failure of the cement.
- **Heat** released during the setting stage can induce bone necrosis (50-90°C).
- Wear particles and debris of the bone cement can cause **foreign body reaction** inducing osteolysis.
- **Monomer toxicity**.
- **Non resorbable.**
- **Polymerization shrinkage** of the acrylic cement.

Modifications of the formulation of ABCs are being investigated, aiming to improve their biological properties as: (3)

- The substitution of initiators, accelerators or radiopacifying agents by more biocompatible compounds,
- The addition of other monomers to the liquid phase that improve the biological performance of ABCs.

Bone Minerals' content:

The mineral phase of bone has an apatite crystalline structure which can exist in a range of compositions. So called **non-stoichiometric** or **calcium deficient hydroxyapatite (CDHA).** For stoichiometric hydroxyapatite with molar Ca/P ratio is 1.67 and for CDHA the molar Ca/P ratio is nearly 1.50. In fact, biological apatite is a carbonate containing CDHA, which in addition, contains several other ionic substitutions such as Na^+, K^+, Mg^{2+}, F^- and Cl^-. (3)

Calcium Phosphate Cements (CPCs):

CPCs were discovered by Legeros and (Brown and Chow) in the early 1980s [5]. This was an important break through as it supplied a **moldable material** which can adapt to the shape of the bone cavity, presenting a **good fixation** and providing **optimum tissue–biomaterial** contact to stimulate the bone ingrowth, thus providing osteo-integration and osteo-conduction. Moreover, CPCs are **resorbable,** with a resorption rate that depends on their composition and microstructural features. The properties mentioned give CPCs high bone regeneration potential. On the other hand, they have some limitations related to their **poor mechanical properties**. Thus used in non-load bearing application as cavity filling and enhancement of bone regeneration. [3]

CPCs are formed by a combination of one or more calcium phosphates, which upon mixing with a liquid phase (water or an aqueous solution) form a paste which is able to set and harden after being implanted within the body. The cement sets as a result of a **dissolution and precipitation** process. The entanglement of the precipitated crystals is responsible for cement hardening. [3]

Classification of calcium phosphates:

- **According to the end product (Hydroxyapatite, brushite & monetite in few cases).**

Hydroxyapatite is precipitated when the pH value of the paste is **above 4.2.** Apatite cements have higher mechanical strength than brushite. Yet, it has slow rate of resorption in vivo that interferes with the bone regeneration process.

Some CPCs have been designed to form **brushite** as the end product. Brushite is an acidic calcium orthophosphate, which is metastable under physiological conditions. For this reason, brushite CPCs are much more quickly resorbable than apatite CPCs and may convert into HA. All brushite CPCs are obtained because of an acid–base reaction. The paste of brushite CPCs is acidic during setting because brushite can only precipitate at a pH **lower than 4.2**. After setting, the pH of the cement paste slowly changes toward the equilibrium pH. The setting reaction is more exothermic than apatite forming cements. [3]

- **According to the setting reaction (Acid-base reaction & hydrolysis).**

CPCs can also be formed by two reactants, one of them an acidic calcium orthophosphate and the other a basic calcium orthophosphate, which set following an **acid– base reaction**. The most widely studied combinations are tetra-calcium phosphate TTCP (basic) + dicalcium phosphate dihydrate DCPD (acidic) and TTCP (basic) + dicalcium phosphate DCP(acidic) mixtures that form HA or CDHA.

In **hydrolysis** of a metastable calcium orthophosphate in aqueous media, CPCs are formed of only one calcium orthophosphate. The solid part of such formulation is called single phase cement powder. Thus, the cement is made of one type of calcium phosphate (ACP) and aqueous solution. (3)

- **According to the temperature at which precipitation occurs (CP obtained at high temp, & CP obtained at ambient temperature)**.

Setting time:

The setting time of a CPC can be defined as the time required for the initial setting of the cement paste, which is reflected in loss of plasticity.

Ideally, the initial setting time should allow sufficient time for shaping and filling. After filling, the set cement should not be disturbed till hardening occur as any mechanical strain during this period can adversely affect the strength.

The proposed ranges for the initial and final setting time were $\mathbf{4 < \mathit{I} < 8\ min}$ for the initial setting time and $\mathbf{10 < \mathit{F} < 15\ min}$ for the final setting time. Thus, providing enough time for filling and shaping of the cement in the bony defect. Then hardening of the cement occurs. (6)

Setting times of **apatite CPCs** are too long and several strategies can be applied to reach the clinical requirements as:

- The liquid-to-powder ratio (a smaller amount of liquid reduces the setting time),
- The reduction of the powder size (smaller size shorter setting time),
- The addition of calcium or orthophosphate ions either predissolved in the liquid phase or as highly soluble salt (common ion effect: the higher the concentration, the shorter the setting time),
- The addition of seed materials, which act as crystal nuclei (the more the nuclei, the shorter the setting time).

On the other hand, brushite CPCs tend to set too quickly. The setting time of brushite CPCs is controlled by the solubility of the basic phase: the higher the solubility, the faster the setting time. In brushite CPCs, setting retarders are often used as an approach to increase the setting time. (3)

Microstructure and porosity

The setting reaction of a CPC consists of the dissolution of one or more constituents of the cement powder and the precipitation of a different calcium orthophosphate. Physically, it takes place by the entanglement of the crystals of the precipitating calcium orthophosphate.

In cements that set by acid base reaction, liquid is required only to make the reactants workable and to allow homogeneous reaction. In other cases, when a hydration reaction takes place, some water is consumed, but much less than the total amount added to make a workable paste.

Water is a major contributor to the origin of porosity in this system and therefore CPCs are intrinsically porous materials. The porosity of the set CPC is closely related to the **liquid-to-powder ratio** used and it normally varies between 30% and 50%. although even higher values can be reached. The pores are normally micro- or nanometric in size and **the particle size** of the starting powder can modify the size of the precipitated crystals and also the pore size distribution. [3]

Porosity is an important factor for the cement degradability. It allows proliferation, migration, and invasion of cells into the cement. Moreover, it provides space for the newly formed bone to grow in.

Several different aspects of the porosity are important for the osteoconductive properties:

- Pore size
- Total porous volume, (the relationship between pore volume and specimen volume)
- Interconnectivity of the pores.

Pore size can be divided in two different groups:

- **Microporous** (<5-μm pores)
  Important for the bioresorbability of the material.
- **Macroporous** (>100-μm pores).
  Large macroporosity (i.e., 400–600 μm) facilitates infiltration by fibrovascular tissue and revascularization, allowing bone reconstruction. The optimal macroporosity for the ingrowth of bone tissue ranges between 150 and 500 μm. [7]

Total pore volume

Porous materials have the advantage of allowing circulation of body fluids and increasing the potential for firm attachment of body tissue. However, the disadvantage of a larger total porous volume is a decrease in mechanical strength. For example, an increase of the total porous volume from 10 to 20% results in a decrease in mechanical strength four folds. [7]

Interconnectivity

The pores may either be interconnecting or they con- tain “dead-ends.”

Biomaterials with interconnective pores are superior to biomaterials containing dead-end pores because a spatial continuous connection of the pore system allow the ingrowth of new bone. [7]

Strength of CPCs:

Since these materials are used as bone substitutes, it is important to keep in mind the reference values of the compressive strength of human cortical bone that ranges between 90 and 209 MPa and that of the cancellous bone between 1.5 and 45 MPa.

Factors that affect the strength of the CPC:

- The chemical composition
- The liquid-to-powder ratio
- The particle size of the reactants
- The crystallinity
- The use of liquid accelerators

Different studies reported that the compressive strength of apatite cements normally ranges between 20 and 50 MPa. Brushite CPCs are in general weaker than apatite CPCs and compressive strengths of 25 MPa have been reported. . [3]

Solubility

- Calcium phosphate ceramics can dissolve in basic, neutral, or acid solutions depending on their chemical composition.
- In **acidic environments** calcium phosphate ceramics dissolve **rapidly**.
- Ca/P ratio of the CPC is important for the dissolution process. TCP (Ca/P <1.67) dissolves 12.3 times faster than HA (Ca/P = 1.7). [7]
- Other properties of the biomaterial influence its solubility:
  - ⇒ Porosity
  - ⇒ Crystallinity
  - ⟹ Presence of impurities

Biocompatibility

Biocompatibility can be defined as the ability of a material to perform with an appropriate response in a specific application.

Three different levels of biocompatibility can be distinguished: inert, bioactive, or biodegradable

- **Bioinertness**

Bioinertness means that no chemical interaction takes place between the implant material and host tissue.

- **Bioactivity**

Bioactivity can be described as the occurrence of an interaction between a biomaterial and the surrounding tissue.

The interaction consists mainly of the formation of a layer of hydroxyapatite on the surface, whereas the bulk of the material remains unchanged. This layer of hydroxyapatite increases integration

- **Bioresorption**

Bioresorption is a biological mechanism by which certain ceramic materials resorb partially or completely and thereby disappear partially or completely over a period of time. Ideally, the rate of resorption is similar to the rate of formation of new bone. . [7]

In vivo resorption and remodeling

⇒ CPCs are highly biocompatible osteoconductive materials and can stimulate tissue regeneration.

⇒ Brushite CPCs are resorbed in vivo much faster than apatitic cements because brushite is metastable in physiological conditions. However, it has been reported that brushite CPCs tend to transform to HA in vivo, this transformation reducing its overall degradation rate. The addition of magnesium salts can be used to avoid or at least delay this transformation.

Factors affecting the degradation rate of CPCs:

- Chemical composition
- Crystallinity of the final product
- Porosity of the set cement

To accelerate the resorption of apatite CPCs incorporation of **macroporosity** is done, which is a method used to facilitate bone ingrowth, not only from the external surface, but throughout the whole bulk of the material. This would accelerate its resorption and its transformation in newly formed bone tissue.

Two different strategies have been adopted to introduce macroporosity in CPCs:

- The first approach: aims to produce the macropores **after the cement set**. by adding different porogenic agents such as sugars, PLA fibers or particles to the CPC paste. After setting, the porogenic agents degrade faster than the cement itself, creating the macroporosity.

Disadvantage: It is necessary to add a large amount of porogenic agent to guarantee interconnectivity of the macroporosity, thus compromising the excellent bioactivity and biocompatibility of CPCs.

- The second approach: cement paste is foamed **while it has a viscous consistency** and its setting creates a solid macroporous construct. This could be done by the addition of some gas-generating compounds, such as hydrogen peroxide.

Disadvantage: the liberation of gas after the implantation of the cement paste could have harmful effects on the organism. (3)

Modifications in CPCs

HA-based bone substitute materials:

Producing nano-sized HA, which showed enhanced biomechanical properties and mimicing the composition of natural bone. (4)

The rationale for development of these nanosized materials include:

- Much closer resemblance to bone extracellular matrix.
- Nanocrystalline HA exhibits improved biological performance and dissolution compared with its conventional forms of HA.
- Enhanced delivery and controlled release of bioactive molecules, such as growth factors, allowing for
  nced osteo-regenerative properties.
  nanostructure allows for a larger surface to volume ratio, promoting more effective adhesion, proliferation, and differentiation of osteogenic progenitor cells , enhancing new bone formation, resulting in improved fracture toughness and other mechanical properties. (4)

Biphasic Calcium Phosphate Ceramics (HA and β-TCP Ceramics)

- This combination resulted in more rapid and higher bone regeneration rates seen compared with the use of HA alone and the greater mechanical properties than β-TCP alone. Additionally, the resorption and osteoconductivity of biphasic calcium phosphate ceramics can be controlled by altering the ratio of HA/β-TCP.
- Despite the improvements in mechanical strength compared with β-TCP alone, biphasic CP ceramics still possess compressive strengths lower than that of cortical bone. The use of biphasic CP ceramics has been indicated as a bone substitute in periapical surgery and showed complete alveolar bone healing over a two year period. (4)

Combination with osteogenic substances

Bioactive molecules such as bone morphogenetic proteins (BMPs) play an important role in the process of differentiation.

Despite the osteogenic capacity of bone marrow, it cannot be used as a spatial filler.

Therefore, when used in combination with bone replacement materials such as calcium phosphates the later can supply the matrix, osteoconductivity, and a bioactive surface for the osteogenic bone marrow. [7]

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