Orthopedic Bone Cements

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"Cement", a word comes from the domain of architecture construction. It consists of a system of powder/liquid materials which, when mixed to a paste, set to a hard mass. "Bone cement" is to benefit this system for an application in medicine, for example: filling of bone defects and fixation of surgical prosthesis etc.

The history of the application of bone cement dates to more than 100 years. In 1890, Dr. Gluck described the use of the ivory ball-and-socket joints which were especially useful in the treatment of diseases of the hip joint. These joints were stabilised in the bone with a cement composed of colophony, pumice powder and plaster. He stated that the cement remained walled off in the marrow cavity in the same way as a bullet, the marrow cavity appearing to have almost unlimited tolerance to aseptic implantation [1]. In 1951, Dr. Haboush used self-curing acrylic dental cement to secure a total hip replacement [2]. Also at this time similar resins were being used to repair defects in the skull after brain surgery. Polymethylmethacrylate (PMMA) cement was used primarily in dentistry to fabricate partial dentures. orthodontic retainers, artificial teeth, denture repair resins, and an all-acrylic dental restorative. Dr. Charnely had used a cold-cured acrylic as a possible luting cement to retain the femoral shaft in total hip arthroplasty [3].

From 1950s to 1970s numerous studies and tong-term clinical trials exposed the biological disadvantages of PMMA cement: (1) the release of monomer toxicity; (2) the high temperature of the cement polymerisation; (3) osteonecrosis mediated by inflammatory reaction; (4) osteolysis caused by wear debris formation or (5) impairment of blood circulation in the bone caused by reaming, then, plug of cement [4]. Moreover, this cement is neither biodegradable nor colonisable by bone tissue. Therefore, surgeons sought to ameliorate the PMMA cement looking for new cement to replace it. Brown and Chow [5] were the first to develop and patent a calcium orthophosphate cement. Different formulations of the calcium phosphate cement have since been developed by various research groups [5–10]. The studies *in vitro* and *in vivo* have shown that the calcium phosphate cement (CPC) was an excellent biocompatibility, a good bioresorption, an osteoconducteur, and a less exothermic, but weaker mechanical properties than PMMA cement.

This paper provides a general regulatory background, chemical composition information, mechanical and biological properties as well as a discussion of the mechanisms of the risks and failures of bone cements. We present

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principally two bone cements; polymethylmethacrylate cement (PMMA) and calcium phosphate cement (CPC).

Polymethylmethacrylate Cement (PMMA)

Chemical Composition and Polymerisation of the PMMA

PMMA bone cement has remained largely unchanged over the years consisting of preformed PMMA beads mixed with methylmethacrylate (MMA) monomers. PMMA cements include: (1) the weight ratio of powder to the liquid monomer; (2) the use of PMMA or copolymers thereof; and (3) the use of benzoyl peroxide as initiator in the powder and MMA; (4) the use of MMA as the monomer in the liquid component; (5) the use of a radio-opaque filler (e.g. barium sulphate or zirconium dioxide). Differences include: (1) the amount of the initiator (benzoyl peroxide) in the powder; (2) the amount of accelerator (*N*,*N*-dimethyl-*p*-toluidine) in the liquid component; (3) the amount and type of stabilisers (e.g. hydroquinone) in the liquid component; and (4) the addition of chlorophyll used to colour the cement green. The chemical composition of the commercially available bone cements is similar, with the minor differences described in Table 10.1.

The polymerising process of the cement occurs as a result of the reaction between the initiator in the polymer powder and accelerator in the monomer. These act together to form a complex which produces benzoate and amine radicals. These two radicals then initiate polymerisation of the monomer [11]. A radiopacifier, added to the powder component, enables the surgeon to view the cement *in vivo*. This process transforms the initial thick liquid to a soft deformable material and finally to a rapidly hardening cement with an associated increase in temperature due the exothermic polymerisation which can exceed 80 °C. The cement sets through the polymerisation of the monomer, which concurrently dissolves and softens the polymer particles. The set mass consists of the polymer matrix uniting the undissolved but swollen original polymer granules. The degree of polymerisation is affected by the following: (1) the amount of accelerator and initiator in the powder and liquid monomer; (2) wetting caused by the monomer mixing with the powder; (3) the type of mixing used, (4) the pro-chilling of the monomer; and the presence of oxygen.

Table 10.1 General chemical compositions of various commercially available bone cements

	Brand 1	Brand 2	Brand 3	Brand 4
Powder components	***40 g***	***40 g***	***40 g***	***40 g***
PMMA (polymer)	88.85 %(w/w)		15.00 %(w/w)	89.25 %(w/w)
Polystyrene/MMA copolymer			75.00 %(w/w)	
MMA/PMMA copolymer		83.55 %(w/w)		
Benzoyl peroxide (initiator)	2.00 %(w/w)	0.5–1.6 %(w/w)		0.75 %(w/w)
Sulphate barium (radio-opacifier)	9.10 %(w/w)		10.00 %(w/w)	10.0 %(w/w)
Zirconium dioxide (radio-opacifier)		15.00 %(w/w)		
Liquid components	***18.37 g***	***20 ml***	***20 ml***	***20 ml***
MMA (monomer)	98.215 %(w/w)	99.26 %(w/w)	97.40 %(v/v)	97.25 %(v/v)
N,*N*-dimethyl-*p*-toluidine	0.816 %(w/w)	1.96 %(w/w)	2.62 %(v/v)	2.75 %(v/v)
(accelerator)	0.002 %(w/w)		75 ± 15 ppm	75 ± 10 ppm
Hydroquinone (stabilizer)	15–20 ppm			
Other monomeric additives				
Ethyl alcohol	0.945 %(w/w)			
Ascorbic acid	0.022 %(w/w)			
Chlorophyll (colour additive)		0.002 %(w/w)		

Table 10.2 Physical and mechanical properties

	ISO-5833
Dough time	5 ± 1.5 min
Setting time	3–15 min
Exothermic temperature	<90 °C
Compression strength	70 MPa
Tensile strength	50 MPa
Tensile modulus	1.8 GPa

Physical and Mechanical Properties of the PMMA

The physical and mechanical characteristics of the acrylic bone cement were determined by the ISO 5833–1992 standard [12] (Table 10.2). The liquid and powder mixing procedure should be influenced by various factors in order to modifier the properties. These factors include the amount of the ingredient, the temperature and humidity of the mixing environment, the type of sterilisation used and the type of mixing (hand, centrifugation, or vacuum mixing) used to prepare the cement; as well as the surgical installation used in the mixing process.

Physical Properties

Cement viscosity is increased by the addition of fibres, greater molecular weight of the polymer, solubility of the polymer in the monomer, variation in the powder composition or bead size distribution, and the temperature of the cement components. Pre-chilling the cement components increases the setting time and reduces the viscosity of the cement, as compared to cement components which are stored at room temperature prior to mixing. In contrast, mixing of bone cement under vacuum generally decreases the setting time. At the time mixing, the components are usually hand mixed in a bowl. However, with the use of vacuum mixing or centrifugation after mixing, the cement porosity and pore size can be reduced to improve the mechanical properties of the cured cement [13–16]. Greater monomer evaporation may occur if the applied vacuum is too great during vacuum mixing.

Poor monomer wetting in the powder can occur if: (1) the powder is insoluble or only partially soluble in the liquid MMA monomer; (2) an inadequate amount of MMA monomer is mixed into the powder; or (3) the free volume is lowered due to tighter packing of powder. On the other hand, styrene copolymers may have better wetting properties due to a higher free volume which allows for faster monomer diffusion rates [17].

High temperatures of the polymerisation process can cause evaporation of the monomer leading to microporosity in the curing cement. There are a number of factors that affect the maximum exothermic temperature. The following may contribute to a higher cement polymerisation temperature: (1) a large cement mass; (2) a cemented device with a low conduction heat;(3) a cemented device that is not cooled before implantation; (4) lack of irrigation at the implant site; (5) a greater amount of monomer mixed into the powder; or (6) increased levels of accelerators or initiators which may form radicals initiating rapid polymerisation [18].

Microporosity in the bulk cement may result form the following: (1) monomer evaporation during the exothermic reaction and/or leaching of the unreacted monomer [19]; (2) flow and wetting during mixing with the beads leading to air entrapment; (3) CO_2 formation due to a benzoyl peroxide reaction with the accelerator; (4) turbulent cement flow during the insertion of the implant into the cement; (5) the mixing method used to assemble the bone cement components.

Mechanical Properties

The implant-cement-bone interfacial strengths are also considered risk factors [20]. Implant-cement interfacial loosening may result from: (1) cement fracture or poor implant-cement bonding due to foreign matter; (2) inadequate coverage at the implant-cement interface [21]; (3) amount of mechanical interlocking; or (4) a lack of chemical bonding at this interface. More specifically, the inadequate cement coverage at the interface may be caused by: (1) shrinkage of the cement due to polymerisation; (2) poor mechanical interlocking strength between the implant and cured bone cement [22]; or (3) an increase in the bone cement viscosity over time leading to poor contact between the cement and implant.

Cement-bone loosening may result from: (1) cement fracture; (2) formation of gaps at the

interface; or (3) tissue failure. More specifically, the gaps may form due to: (1) bone resorption; (2) foreign material at the cement-bone interface such as bone particles or blood [23]; (3) shrinkage of the cement after implantation; (4) low cement pressurisation during implantation [24]; or (5) movement of the implant before hardening of the cement. For gaps caused by shrinkage, the shrinkage is greater as the porosity is decreased.

A fatigue fracture of the cement is a result of a cement stress which exceeds the fatigue limit of the bone cement. High cement stress may be due to an applied stress or a residual stress, cement modulus, implant loosening or poor cement bonding with the implant or with the bone. Other causes of cement fracture include; fibrous membrane formation between the bone and cement, improper cement mantle thickness (a layer too thin or too thick), lamination of the cement due to the presence of blood or other body fluids, poor canal preparation or areas of increased stress (e.g. the presence of a pore or a sharp corner of an implant). High stress applied to the bone cement may be caused by: (1) Increased patient weight or activity; (2) lack of constraint; (3) adverse implant size and orientation; or (4) inadequate bone cement mantle. The latter three are related to the quality of the tissue and the applied surgical technique. A weakness may also be caused by bone resorption or by disease.

Cement mechanical properties are affected by the level of stress at a specific site. This is influenced by: (1) irregular trabecular bone; (2) porous implant coatings; (3) sharp edges on the implant; or (4) a defect in the bulk cement such as a pore or additives. More specifically, localized stress caused by porosity and inclusions (e.g. additive agglomeration, redio-opacifiers and antibiotics) are perhaps the greatest factor affecting cement fatigue properties. The addition of agglomerates (e.g. redio-opacifiers) may also play a similar and significant role in cement fracture.

Biological Properties of the PMMA

All biomaterials must be biocompatible. PMMA cements are considered biocompatible despite the toxic potential of the bone cement monomer and the heat generated during the exothermic polymerisation.

Cellular Reactions

Initially, the major problems of PMMA bone cement are related to the temperature increase during the polymerisation and the release of residual monomer after polymerisation. PMMA is non toxic, but the residual monomer (MMA) can cause an irreversible deterioration of the cells [25, 26]. After 15 min of polymerisation, there is a residual monomer of approximately 3–5 %. This percentage may decrease up to 1–2 % with time [25]. Haas et al. [19] measured the residual MMA content to be 3.3 % after 1 h, 2.7 % after 24 h and 2.4 % after 215 days under storage in an ambient air environment. According to Schoenfeld et al. [27], the toxicity of the monomer disappears after 4 h. In our study of cement fragments which were harvested at the time of prosthetic revisions 48–78 months after implantation, there was no apparent toxic effect of the cement on the fibroblasts (L929) and human osteoblasts [28]. However, there may be variable reactions to PMMA depending of the cells involved.

PMMA is not cytotoxic with regard to human fibroblasts *in vitro*. However, it can stimulate proliferation and protein synthetic activity [29]. The increased proliferation of fibroblasts in response to PMMA exposure can be associated with an increased production of collagen and chemical mediators at the bone-cement interface [30, 31]. Chemical mediators, such as prostaglandin E2 (PGE2) and other cytokines (interleukine-1), have been shown to mediate inflammation, as well as induce cell division and differentiation [32, 33]. Fibroblasts have previously been implicated in the inflammatory response. Therefore, it is possible that they are responsible for the recruitment of inflammatory cells at the bone-cement interface via release of chemical mediators such as PGE2.

Monocytes and macrophages are significant agents of the inflammatory reaction. The principal function of the tissue macrophage is phagocytosis and the secretion of cytokines and

growth promoters. PMMA particles induce macrophages to secrete protein and to express mRNA of the proinflammatory cytokines, interleukin-1β (IL-1β), interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α), PGE2, proteinases, collagenases and oxygen metabolites. Other factors expressed include chemokines such as macrophage-activating and chemotactic protein 1 (MCP-1) as well as macrophage inflammatory protein (MIP) which may be linked to osteolysis [34–43]. Horowitz et al. described a dose-dependent release of arachidonic acid metabolites by murine macrophages induced by PMMA particles [44].

The osteoclast is a multinucleated cell which carries out the unique and highly specialized function of lacunar bone resorption. The osteoclast belongs to the mononuclear phagocyte system which consists of various cell types including monocytes, macrophages, Kupffer cells and microglia. A common feature of all these cells is their avid and efficient ability to carry out phagocytosis. Most studies have focused on the effect of biomaterial particle phagocytosis on the function of these cells and the observation that specific types of particle enhance the release of mediators thus stimulating osteoclastic bone resorption [45–47]. In addition, it has been shown that macrophages after having phagocytosed these particulates are capable of osteoclast differentiation [48]. Wang et al. [49] found that osteoclasts having phagocytosed PMMA wear particles exhibit normal lacunar bone resorption. As well, the phagocytosis of PMMA particles does not appear to compromise the response of osteoclasts to calcitonin or to the ability to carry out lacunar resorption, an observation that remains controversial. PMMA particles can inhibit osteoblast activities causing a decrease in cellular proliferation and collagen synthesis.

Local Tissue Reactions

PMMA bone cement is generally well tolerated and bony tissue, generally, flourishes on it's surface [29, 43]. However, there is evidence of the inflammatory potential of bone cement [50]. The tissue reaction around bone cement has several phases. Initially, there is a necrosis of the bone tissue and marrow to a depth of 5 mm depth related to the surgical wound and polymerisation. Next, there is a phase of cicatrisation lasting up to 6 months followed by a tissue granulation which develops over a period of 2 years. This tissue granulation is a characteristic of the chronic inflammation. The cement is then surrounded by a layer of fibrous tissue [51–54] and occasionally by a varying thickness of fibrocartilage [55, 56],.. Albrektsson [57] reported a 59 % reduction in the in growth of cortical bone into titanium bone chambers 1 month after cement application. Morberg et al. [58, 59] reported as well a decreased bone formation around cemented tibias, being 21 and 31 % lower than the non-cemented contralateral tibias after 3–11 and 32–55 weeks, respectively.

Osteonecrosis

Cell necrosis may occur because of the following: (1) monomer toxicity; (2) the high temperature of cement polymerisation; (3) pressure necrosis; (4) osteolysis caused by wear debris generation; or (5) the impairment of blood circulation in the bone caused by reaming and by the presence of cement [4]. Bone cement has been shown to decrease bone metabolism possibly causing a lower revascularisation [60, 61].

The production of heat at the bone-cement interface during the cement polymerisation *in vitro* is between 60 and 90 °C [62–64] and *in vivo* between 40 and 50 °C [65, 66], both depending on the thickness of the cement. The effect of this heat generation on bone was studied by Lundskog [67] who concluded that the exothermic polymerisation did not add to the surgical trauma and had no influence on bone generation. Lee et al. [68] found that the leakage of monomer was very low after the curing. Likewise, Sund and Rosensuist [69] stated "the effect of polymerisation heat and monomer toxicity are probably much less important than the trauma effected by blocking of the normal medullar blood supply". Rhinelander et al. [66] who noted a maximal temperature of 55 °C with the placement of thermometers at the bone-cement interface, concluded that thermal necrosis from cement polymerisation is not a

significant factor. Furthermore, after direct contact with acrylic cement, the delicate trabeculae of cancellous in the metaphysis contained healthy appearing osteocytes after 6 weeks.

Osteolysis

Bone surrounding an implant may undergo osteolysis leading to loosening and a decrease in cancellous bone strength. This may result in a weakening of the cement fixation or the formation of a gap between the cement and bone. Acrylic cement fragments are engulfed by eosinophilic histocytes which stimulated enzymatic release leading to bone resorption [70, 71]. In addition, bone cement particles could accelerate foreign body deterioration of articulating polyethylene inserts [72, 73]. The initial event can be either disintegration of bone cement or deterioration of the articulating surface. Phagocytosis and the development of foreign-body granulomas lead to osteolysis of the anchoring bone; thus disintegration or deterioration are enhanced accelerating the progress of osteolysis [51].

Formation of Fibrous Membrane

The formation of fibrous tissue is caused by the toxicity of the monomer release as well as the heat production of the polymerisation causing a chronic inflammation and eventual osteonecrosis and an osteolysis. It is a significant factor which induces the micromovements and the loosening of surgical implants. The thickness of the fibrous membrane around PMMA cement was of 40 μm and 60–70 μm after 1 and 4 weeks respectively in the tibiae diaphysis [53, 74]. In the human femur, the thickness was measured at 20–300 μm at 11 months to 7 years [55] and at 3–5 mm long-term. [54]

Implant Loosening

Revision of a cemented orthopaedic prosthesis may be necessary when pain occurs due to either the movement of the prosthesis, a bone fracture, bone cement fracture or prosthesis fracture. More specifically, these complications may result from prosthesis-cement, or cement-bone interfacial loosening or micromotion due to cement fracture or cement creep. Loosening of the prosthesis and fracture of the cement may lead to increased wear and bone cement particle formation. Those particles approximately less than 5 μm in size are phagocytosised by macrophages which become activated and directly or indirectly cause bone remodelling and osteolysis [14, 75–78]. However, PMMA particles ingested by macrophages cannot be degraded by lysosomal enzymes [45]. The final result is cell death leading to tissue necrosis and chronic inflammation [79]. For the femoral stem, the lower viscosity bone cement had a revision rate 2,5 times greater when compared to the use of higher viscosity cements. Additionally, a lower modulus cement had a revision rate that was 8.7 greater than the higher viscosity cements [80]. In general, revisions are required between 3.6 and 22.8 years following a total hip prosthesis. The most frequent periods of revision are either during the first 3 years or after 8 years postoperatively [81]. The aseptic loosening of the prosthesis is the principal cause of revision, implicated in: 73–74 % of the total cases [82, 83]. Subcritical debonding associated with mechanisms of cyclic fatigue crack growth are particularly relevant considering that these systems will experience over 1,000,000 physiological loading cycles per year, and are expected to survive a minimum of 10–15 years. In these terms, it is critical to understand the progressive debonding of prosthesis-PMMA cement interface [84].

Secondary Reactions

Systemic and Cardiovascular Reactions

Methylmethacrylate (MMA) is very volatile and is rapidly cleared from body through the lungs resulting in a local concentration that remains very low [85, 86]. MMA monomers escaping from the implanted polymerising cement have been associated with a decrease in both systolic blood pressure and arterial oxygen tension [87] and possibly cardiac arrest. [88] However, many studies have not confirmed this direct correlation between the concentration of MMA and blood pressure, heart depression or vasodilatation [86, 89, 90]. Circulatory disturbance during hip implantation may be primarily due to either the “implantation syndrome” or to the

blockage of pulmonary circulation by fat, bone marrow and entrapped air rather than MMA monomer. Release of MMA could cause a drop in the partial pressure of arterial oxygen leading to an increased heart rate [91, 92]. The possible metabolic pathway of MMA monomer is that the residual monomer is converted to methylacrylic acid rather than methylester. The methylacrylic acid, as a coenzyme A ester, is a normal intermediate in the catabolism of valine and the existence of an enzyme system would permit methylacrylic acid to enter a normal pathway, leading to carbon dioxide formation. Over 80 % of an administered dose of MMA is expired as carbon dioxide within 5–6 h [90].

Sensitising

While MMA is considered to be relatively immunologically inert, it can induce phagocytosis, the activation of macrophages and giant cells as well as the migration of inflammatory mononuclear cells [13, 14, 52, 74, 78]. Jensen et al. [52, 74] showed that MMA is extremely active in a guinea-pig maximisation test. The hospital personnel who repeatedly handle coring acrylic bone cement are potentially at risk of developing a delayed sensitivity [93]. Bengston et al. [94] reported that patients having received a cemented hip prosthesis had increased levels of anaphylatoxines which can contribute towards circulatory and respiratory disturbances. In contrast, Kanerva et al. [95] have found allergies to MMA to be rare in a study of patients between 1974 to 1992 (4 patients: a orthodontist, 3 dental technicians).

Improvement of the PMMA

The objective of the development of PMMA bone cement is to improve the biocompatibility, to diminish the temperature of polymerisation, to eliminate the generation of wear debris and fatigue fractures, as well as to increase the elastic modulus. Therefore, efforts to improve PMMA bone cement have proceeded in two main directions: (1) to change the composition and (2) to improve preparative techniques.

Tertiary aromatic amines are used as accelerators for the benzoyl peroxide (BPO) initiated MMA polymerisation. A complex series of reactions occurs between BPO and the amine, and free radicals are produced that initiate the polymerisation process [96, 97]. Several types of amine accelerators, such as dimethyl aniline and its derivatives, have been used in the polymerisation of MMA by the amines/BPO initiator system. Their relative efficiency as accelerators and their activating effects on the rate of polymerisation have been reported [96, 97]. Several workers have studied bone cement properties using a number of N,N-dimethyl-p-toluidine derivatives, such as, 4-dimethylaminobenzyl methacrylate, and 4-dimethylamino phenethyl alcohol [96–99]. Bone cement products containing residual monomer and amine have been reported in preparation where the amines/BPO molar ratio is outside the equimolar range [11]. Other study showed that MMA polymerisation in the presence of tir-*n*-butylborane used as the cure initiator does not occur too rapidly, and the high temperature during polymerisation is lower than that of conventional bone cement. The application time is short enough for clinical use, namely, within 10 min. As for the physical properties, it has a 3 % lower elastic modulus and greater ductility than the conventional cement [100].

Several workers have added particles or fibres to PMMA bone cement to improve the biocompatibility et the mechanical properties. The fibre reinforced bone cement possessed significantly greater stiffness and displayed poor intrusion characteristics [101–103]. A number of attempts have been made at filling a PMMA matrix with hydroxyapatite and tricalcium phosphate particles, and with bioactive glass [104–106]. The short-term results obtained are encouraging and suggest that the chemical nature of the bone/bioactive materials interface is very important relative to osteoconductivity [107]. For instant, PMMA bone cement can be used only to effectuate mechanical fixation for prosthesis or to physically fill bone defects. It however, does not exhibit the functions of osteointegration, biofixation, nor bioresorption.

Calcium Phosphate Cement (CPC)

Chemical Compositions and Crystallisation of the CPC

Calcium phosphate cements can be handled in paste form and set in a wet medium after precipitation of calcium phosphate crystals in the implantation site. Depending on the products involved in the chemical reaction leading to the precipitation of calcium phosphate, different phases can be obtained with different mechanical properties, setting times and injectability. Numerous components can enter the chemical reaction leading to calcium phosphate precipitation. More than 100 different of calcium orthophosphate cements were used to determine the compressive strength and the diametric tensile strength after storage. The setting was carried out on more than 15 formulations. These cements could be divided into four classes: dicalcium phosphate dihydrate, calcium and magnesium phosphates, octocalcium phosphate, and nonstoichiometric apatite cements [108, 109]. The calcium and phosphate compounds in Table 10.3 were often used to make the CPC. Moreover, adjuvants such as chitosan, lactic acid and glycerol are added to improve the injectability of the cement, and accelerators such as Na_2HPO_4, sodium phosphate, sodium succinate, and sodium chondroitin sulphate to accelerate its setting time.

The hardening process of CPC is complex and involves the dissolution of solid particles in the liquid, precipitation of HAP from the solution, and the reaction and diffusion on the particle surface. Under ideal conditions, continuing dissolution of the reactions supplies calcium and phosphate ions to the solution, while HAP formation depletes these ions. This process drives the solution composition to an invariant point, which is the intersection of the solubility curves for these two reactants. The pH is about 7.8, but this process is affected by many parameters, such as the component and the particle sizes of the solid phase, presence of HAP seed and properties, aqueous liquid, etc.

Physical and Mechanical Properties of the CPC

All CPC are formulated as solid and liquid components that, when mixed in predetermined proportions, react to form HAP. This final reactant is important because it determines whether the end product will be nonresorbable, minimally resorbable, or completely resorbable. The powder component usually consists of 2 or more calcium phosphate compounds, whereas the liquid component is either water, saline, or sodium phosphate (Table 10.4). Some of the calcium and phosphate compounds involved in bone and mineral formation, or as implants, are listed in Table 10.3. These materials have been well characterised chemically and have not been reported to cause foreign body reactions or other forms of chronic inflammatory response [110].

Table 10.3 Calcium and phosphate compounds

Name	Abbreviation	Formula	Ca/P	Solubility	Acidity	Stability
Monocalcium phosphate monohydrate	MCPM	$Ca(H_2PO_4)_2 \cdot H_2O$	0.5			
Dicalcium phosphate anhydrous	DCPA	$CaHPO_4$	1.0	+++++	+++++	+
Dicalcium phosphate dihydrate	DCPD	$CaHPO_4 \cdot 2H_2O$	1.0	+++++	+++++	+
Octacalcium phosphate	OCP	$Ca_4H(PO_4)_3$	1.33	++++	++++	++
Amorphous calcium phosphate	ACP	$Ca_9H(PO_4)_6$	1.3–1.5	+++	+++	+++
Tricalcium phosphate	TCP	$Ca_3(PO_4)_2$	1.5	++	++	++++
Hydroxyapatite	HAP	$Ca_{10}(PO_4)_6(OH)_2$	1.67	+	+	+++++
Tetracalcium phosphate	TTCP	$Ca_4(PO_4)_2O$	2.0			

Table 10.4 Properties of the CPC

Authors	Powders	Liquid	Setting (min)	Strength (MPa)	Resorption
Brown and Chow [5]	DCPD/DCP/TTCP/HA	H_2O	30–60	10	Minimally
Lemaitre et al. [6]	β-TCP/MCPM	H_3PO_4	10	25–35	Completely
BoneSource [110]	TTCP/DCPD	H_2O	10–15	36	Minimally
Norian [110]	MCPM/α-TCP/$CaCO_3$	$CaHPO_4$	10	55	Completely
Fernandez et al. [10]	DCPA/α-TCP	H_2O	–	30–40	Yes
Kurashina et al. [8]	α-TCP/DCPD/TTCP	Sodium succinate Sodium Chondroitin Sulphate	–	–	Yes
Liu et al. [9]	TTCP/DCPD/DCPA	H_2O	11	70	Yes
Ginebra et al. [7]	α-TCP/β-TCP	Na_2HPO_4	5–12	40	Yes

The physicochemical reaction that occurs during mixing of the solid and liquid compounds of CPC is complex. Briefly, when different calcium phosphate salts are mixed in an aqueous environment, dissolution of the solid compounds, then a precipitation or a nucleation, and finally a phase transformation occurs. The process leading to final phase transformation of the different forms of calcium phosphate salts is dependent on their solubility, product constant and pH. It is important to realise that water is not a reactant in the setting reaction of the cement, but it allows dissolution of the solids and precipitation of the products. The nature of the apatite makes the final form biocompatible and promotes a chemical bond to the host bone.

There is a possibility to transform the cement into an injectable paste by addition of adjuvants without fundamentally modifying the chemical reactions occurring during setting and hardening of the CPC. Leroux et al. [111] found that glycerol greatly improved the injectability and increased the setting time, but decreased the mechanical properties. Lactic acid reduced the setting time, increased the material toughness, but limited the dissolution rate. After injection, the cement did not present any disintegration. The effects of lactic acid were correlated with the formation of calcium complex. Its association with sodium glycerophosphate is particularly important. Chitosan alone improved the injectability, increased the setting time, and limited the evolution of the cement by maintaining the CPC phase.

The CPC have an inherent compressive strength at the final set that can govern their utility. Varying the crystallinity of the HAP or the particle size of materials used in the solid phase may alter the compressive strength. Because CPC are relatively insoluble at neutral and alkaline pHs, their porosity is related to the ratios of powder to liquid used in the starting mixture. Obviously, a cement with a high porosity would be expected to be of low compressive strength. Cements with a high compressive strength would be expected to find utility where they would stabilise nondisplaced bone fractures and comminutions, or repair large bone defects, or fixes surgical prosthesis. Cements with a low compressive strength would limit their utility and only fill small bone defects.

Biological Properties of the CPC

The calcium and phosphate compounds of the CPC have attracted considerable attention because they set like a dental cement and form hydroxyapatite as the end product which is the major mineral components of teeth and bone. A number of studies *in vitro* and *in vivo* have shown that CPC had no toxicity, negative mutagenicity and potential carcinogenicity [112, 113], no or slight inflammatory reactions, good osteoconductivity and bioresorption [114] as well as light exothermic temperature (<40 °C) during CPC hardening. However, CPC particles could be harmful for

osteoblasts with a decrease of viability, proliferation and production of extracellular matrix, especially when their size was smaller than 10 µm. A dose effect was present, ratio of 50 CPC particles per osteoblast could be considered as the maximum of what an osteoblast supported. The acidification of the medium due to the dissolution of the CPC could not be responsible for the decrease of osteoblast functions because the control of the pH value of the medium have shown that it did not change. It was then the direct interaction of osteoblasts with particles which was involved in the decrease of osteoblast functions [115]. Some adjuvants of the CPC can induce acidification and release some elements to modify the biological properties. We have cultivated osteoblasts on the CPC surface, cell proliferation increased after the first 7 days followed by a decrease afterwards and an absence of cells noted by the 21st day. This result indicated that the acidification of the medium and disaggregation of the CPC, are the two important factors: directly influencing cellular attachment and proliferation *in vitro* at cement surface. But, these cements are generally the product of an acid-base reaction which did not seem to induce any necrosis as no visible zone of dead tissue *in vivo* due to the system of the acid-base equilibrium in the organism.

The tissue reactions to the CPC are different in different tissues. When CPC was implanted in the cutaneous tissue, a slight inflammatory reaction with numerous macrophages and few foreign-body giant-cells were observed in the connective tissue adjacent to the cement implant. However, when CPC was implanted in the bone tissue, new bone was formed around the implant from 1 to 2 weeks, cements were resorbed and replaced by bone tissue from 4 to 8 weeks, then an bone remodelling occurred in the implanted zone, and no inflammatory reaction nor osteonecrosis at all phases [114, 116, 117]. From this difference, it could be hypothesised that micromovements persist in the materials implanted in the soft tissue which stimulate the tissue around implant to cause inflammatory reaction. On the contrary, the materials implanted in the bone tissue are immobilised by bone tissue which may explain the absence of this reaction.

There is controversy as to the resorption and replacement of CPC by bone tissue. Ikenaga et al. [118] reported that a CPC resorption was about 8 % at 2 weeks and 92 % at 12 weeks, and new bone formation was about 1 % at 2 weeks and 35 % at 12 weeks in the femoral condyle of rabbit. When CPC was implanted in same site, Frayssinet et al. [119] found a resorption of 54 %, 68 % and 89 %, and new bone formation of 25 %, 32 % and 23 % at 2, 6 and 18 weeks respectively. Our study have shown that the new bone formation increased from 2 to 24 weeks, and the material resorption was about 10 %, 15 %, 30 % and 60 % at 2, 4, 12, and 24 weeks respectively in the tibiae condyle of rabbit [114]. In contrast, Costantino et al. [120] made 2.5 cm in diameter full-thickness parietal skull defects in cats and reconstructed them with CPC. By 6 months, the CPC was replaced by new bone and soft tissue 7.2 mm in depth from the cement surface. Of the replacement tissue, 77.3 % was new bone and the remaining portion was soft tissue. Friedman et al. [121] found very little resorption of CPC or new bone deposition at months when the frontal sinus in the cat was obliterated and reconstructed with CPC. These differences are thought to be caused by many factors, including differences in species and age among the experimental animals, anatomical site, method and duration of implantation, composition of the CPC, etc.

CPC is only an osteoconductor without osteoinduction, and is in direct contact with osteoid or/and bone, but osteoblasts are rarely in direct contact with CPC surface. This maybe due to that the space formed rapidly by the material degradation at bone/cement interface, or/and products of the dissolution influence cellular adhesion. The biodegradation of the CPC respects the mechanisms of biomaterial which are resorption by phagocytic cells and dissolution by a physicochemical process. However, the degradation at the beginning is performed by the dissolution with the weak cellular process because of the presence of few osteoclasts, macrophages and foreign-body giant cells. From the 2nd week, numerous macrophages, few foreign-body giant cells and rare osteoclasts are found around cement, and CPC particles form at the interface and inside the cells.

We consider that the process of biodegradation is directly influenced by the type of crystallisation of the calcium phosphate material. For example, the sintered calcium phosphate bioceramics processed at a high temperature, exhibit good crystallisation and are primarily degraded by a process dependent on interstitial liquids. However, the phosphocalcic bone cement is formed by physicochemical crystallisation and is primarily degraded through a cellular process.

The mechanical properties of the CPC (compressive strength from 20 to 60 MPa) is less strong than that of PMMA cement (>70 MPa). Biodegrdation and new bone formation during implantation modify their properties. Yamamoto et al. [122] tested the CPC showed that a compressive strength increased at 3 days and 1 week, and decreased at 4 weeks *in vitro*; and *in vivo*, it increased at 3 days and 1, 2 weeks and decreased at 4 weeks *in vitro*. The values of these results *in vivo* was only 50–70 % of that *in vitro*. Our study revealed a strong decrease of the compressive strength after 2 weeks due to biodegradation, followed by a slight increase from 4 weeks due to new bone formation. There was a general decrease in the elastic modulus with time [114]. This change of the mechanical strength is supposed to be related to the kinetics of recrystallisation where the mechanical strength increased according to the progress of recrystallisation, but degradation of resorption subsequently starts after the crystallisation. This change also suggests that the calcium phosphate cement would be remodelled or resorbed in long term. This is the same as hydroxyapatite used as a bone substitute material, which is also the expected characteristic of calcium phosphate cement to be used for enhancing the initial fixation of implants and promote biological fixation in long term.

Clinical Application of the CPC

The CPC are a resorbable material with osteoconduction, which are not toxic, not exothermic and excellently biocompatible, but their mechanical properties are not ideal which limits their clinical utilisation. They are only used to fill small bone defect or to augment bone volume as bone substitute. Shindo et al. [123] reported that CPC has been used to augment the supraorbital ridge in dogs, as well as in a variety of skull base defects. It was also used in 24 patients, to augment or obliterate the frontal and ethmoid sinus regions and mastoid cavities. When these patients were observed for 2 years, it was necessary to remove the material in only a patient. Kveton et al. [124, 125] reported on the 2-year follow-up of 15 patients who underwent CPC reconstruction for translabyrinthine, middle cranial fosse, and suboccipital craniectomy; no complication were shown. Stankewich et al. [126] and Goodman et al. [127] showed augmentation of femoral neck fracture with CPC, which significantly improved the initial stability and failure strength of the fractures. The cement has also been used to stabilise distal radius fracture in 6 patients and appeared to promote healing and permit early mobilisation of the wrist. [128] Kopylov et al. [129] used an injectable calcium phosphate bone cement, with external fixation in the treatment of redisplaced distal radial fractures by a prospective randomised study in 40 patients. The chosen primary effect variable was grip strength at 7 weeks. Patients treated by injection of CPC had better grip strength, wrist extension and forearm supination at 7 weeks. There was no difference in functional parameters at 3 months or later. None of the methods could fully stabilise the fracture: radiographs showed a progressive redislocation over time.

Development of the CPC

The rational of using CPC is that this material will be completely resorbed and replaced by new bone. Two processes are simultaneously involved: (1) the degradation of CPC performed by osteoclasts and macrophagtes, and (2) the creation of new bone performed by osteoblasts. The presence of CPC particles could disturb the osteoblasts ability to make new bone. An unstable mechanical situation could result if the bone formation is delayed by the particles resulting from the CPC degradation. It would then be important

for future CPC development to minimise the generation of particles smaller than 10 μm.

Since the mechanical properties limit the clinical utilisation of the CPC, its composition or the adjuvants may be modified to maximise crystallisation to improved the mechanical properties. On the other hand, the equilibrium between osteogenesis and biodegradation is attentively thought. When CPC is rapidly resorbed during implantation and new bone formation is insufficient in the implanted site, or slowly resorbed to prevent the new bone formation and CPC loose its initial properties, the mechanical properties are decreased.

In orthopaedic surgery, PMMA cements are frequently used to fix prosthesis until today due to strong mechanical fixation, but this fixation presents loosening, especially in long term, because of the absence of biological fixation by bone tissue. For the fixation of surgical prosthesis, there is ideal to obtain the mechanical fixation in short time (during 1–3 months) and the biological fixation in long time (starting after 1 month). The mechanism of this fixation supposes that prosthesis are placed with a fixation by bone cement or by bone tissue, then the cement is resorbed and conducts new bone formation till the surface of prosthesis with excellent osteointegration to obtain the biological fixation. We think that when non-cemented prosthesis is combined with CPC, there is: (1) a mechanical fixation due to non-cemented prosthesis with a blockage between the prosthesis and bone tissue, and (2) the cement can fill the residual cavity around prosthesis. Ostoegenesis and an osteoconduction will lead to the fixation of the prosthesis by new bone formation.

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